ORGANIZATION

The 9th international conference of
the International Mesothelioma Interest Group
25-27 September 2008

Amsterdam, The Netherlands

FINAL PROGRAM
AND
ABSTRACT BOOK

AMSTERDAM, 25-27 SEPTEMBER, 2008

DE MEERVAART, AMSTERDAM

ORGANIZATION

Organized by:
I.M.I.G. – International Mesothelioma Interest Group

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M. van de Vijver
M. van der Woude
N. Vogelzang
N. van Zandwijk

GENERAL INFORMATION

CONFERENCE VENUE 'DE MEERVAART'.

de Meervaart
Meer en Vaart 300
1068 LE Amsterdam

PHONE +31 (0)20 - 410 77 20

www.meervaart.nl

De Meervaart is a well-known conference building and theater in Amsterdam West. It is located near a shopping mall.

PARKING
Q-Park parking garage Osdorpplein. Coming from the Lelylaan you take a right at the T crossing. At the second stoplight you take a left and you will see the garage on your left hand side (place for 500 cars, 2 minute walk). At the Meervaart you can buy an exit coin at a reduced rate. With this coin you can exit up to 2 hours after the show. The exit coin also serves to open the entrance door to the garage. The parking garage is also open on Sunday starting at 1 hour before the show. The garage can be exited 24 hours per day.

PUBLIC TRANSPORTATION to 'DE MEERVAART'.
Train
From Amsterdam Central Station or Station Cornelis Lelylaan take tram 1 or 17.
From Station Zuid WTC take bus 63.
From Station Sloterdijk take bus 192.

Tram/bus
Tram 17 towards Osdorp from Amsterdam Central Station stops in front of de Meervaart, stop 'Ruimzicht'.
Tram 1 towards Osdorp/de Aker from Amsterdam Central Station stops a 5 minute walk away from de Meervaart, stop 'Meer en Vaart'.
Buses 19, 63 and 192 towards Osdorp, stop 'Ruimzicht'.

Night bus 353 towards Amsterdam Central Station stop 'Ruimzicht'.

WALKING FROM TULIP INN AMSTERDAM CITY WEST
Tulip Inn Amsterdam City West is located at a 10 minutes' walk from the conference venue 'De Meervaart'. Turn left when you leave the hotel. At the end of the street turn left on the 'Osdorper Ban'. Turn right immediately across the bridge : 'Hoekenes'. Take the third turn to the left : 'Tussen Meer', this is a street with lots of shops and a covered sidewalk. Where the main street 'Tussen Meer' turns left and right, you cross the street and walk straight on into the shopping mall. Follow the passageway through the mall until you reaches the road 'Meer en Vaart'. The main entrance of the conference centre 'De Meervaart' is located at your right hand side facing the lake.

BUSES FROM HOTEL ARTEMIS
Conference Buses are available every morning at 07.00, 07.20, 07.45 and 08.000 hrs to bring you to the conference site. The transfer will take about 15 minutes.
Transfer back to the hotel Artemis: Thursday buses will be available to bring you to the hotel at 17.30, 19.30, 20.00 and 20.30 hrs**.** Friday bus transfers to hotel Artemis are planned at 17.30 hrs to the hotel Artemis and at 17.45 hrs to the social event. On Saturday buses are available to the hotel Artemis at 12.45 hrs and 13.30 hrs.
PUBLIC TRANSPORTATION FROM HOTEL ARTEMIS TO THE CONFERENCE SITE.
Bus 195 will bring you from hotel Artemis to 'Station Lelylaan'. At the North side of this station (1 minute walk) is the bus stop no 63 direction 'Osdorp-De Aker'. Get off at the 6st stop 'Ruimzicht' just before 'De Meervaart'. This ride will cost 3 'strippen'.
TAXIS:
Can be ordered at the hotel desk.

TICKETS FOR PUBLIC TRANSPORTATION
Tickets for public transportation will be available at the registration desk. This will be for a reduced price of € 5,= (normal price € 6,95). Tickets can be used on all buses and trams. A fare to Amsterdam Central Station costs 3 'strippen', whereas the 'strippenkaart' contains 15 'strippen'. Tickets will be valid throughout your stay in Amsterdam.

LANGUAGE
The official language of the congress is English. All lectures and presentations will be held in English.

REGISTRATION
The registration desk is located in the entrance hall of the conference centre. The desk will be open on Thursday and Friday from 7.15 AM until 17.00 PM.
Onsite registration is possible at the desk.
At the desk 'strippenkaarten' (bus and trams cards) are available at a reduced price of € 5,=.
Tickets for the special lunch seminars on Thursday and Friday will be available at the desk. The tickets are free.

All fees include:
- participation in the scientific sessions
- certificate of attendance
- abstract book
- congress bag
- breakfast, coffee breaks and lunch
- welcome reception

CASHPOINT
A cash point is located at the left hand side of the entrance of 'De Meervaart'.

BREAKFAST
On Thursday, Friday and Saturday breakfast will be served at the conference from 7.00 until 9.30 AM for all registrants.

LUNCH
Free lunch will be served at the conference in the foyer at the first floor for all registrants. Simultaneously, a special *LUNCH SEMINAR* will be held in the foyer on the second floor on Thursday and Friday. These luxury lunches are sponsored by *Fujirebio* and *Morphotek*, respectively.

One hundred free tickets are available for each seminar, and can be obtained for free at the registration desk at the conference hall and at the booths of Fujirebio and Morphotek. The program of these seminars is made under the responsibility of the sponsors.

COFFEE AND TEA BREAK
Free coffee, tea and refreshments will be available from 10.00 to 17.00 h.

INFORMATION FOR PRESENTERS
The speaker's room is located near the entrance of the 'Blue Room' at the second floor. We kindly ask the presenters of poster discussions, oral presentations and invited lectures to upload the presentations before the start of the session. The time schedule of the sessions is too tight to upload the presentations during the sessions.

TIME SCHEDULE
Every effort should be made to adhere strictly to the time allotted for each presentation.

POSTERS
The posters can be viewed during the whole conference. They will be exposed in three poster view rooms. The posters will be divided in two groups which will each be discussed on Thursday and Friday evening by experts. The winner of the poster award of that day will be announced.
We ask you to put the posters on the poster boards on Thursday morning between 7.00 and 10.00 AM, and remove the posters on Friday afternoon between 16.00 and 18.00 PM.

AWARDS
WAGNER MEDAL
The Wagner Medal award, found in honor of Dr. Chris Wagner, who first identified the association between asbestos exposure and mesothelioma, will be assigned also during this edition of the Meeting. The award will be presented to an individual who, in the opinion of the IMIG committee, has made a major contribution to mesothelioma research, either clinical or laboratory, over a number of years. The winner will be announced during the reception on Thursday evening September 25th.

YOUNG INVESTIGATOR'S AWARD
During the Poster Discussion session on Friday evening, the *Young Investigator Awards* will be presented by the respective sponsors, *International Ban Asbestos Secretariat (IBAS)* and *the Asbestos Disease Awareness Organization (ADOA).*
The abstracts were selected in three steps: first you should have indicated to younger than 40 years of age, when submitting the abstract. Next, the meeting chairs should have nominated your abstract. And finally, a selection of the finest iMig board members have chosen the awards winning abstracts from the nominated preselection.

POSTER AWARD
All abstracts which are presented either as poster presentation or as a poster are candidates for the *Poster Award.* The abstracts will be rated by the chairs of the poster discussion sessions Thursday and Friday afternoon. Each day one price is to be given away: five hundred euro and a brand new 2nd edition of the famous "TEXTBOOK OF PLEURAL DISEASES" by Richard W Light and YC Gary Lee.

SOCIAL PROGRAM

For the *Social Program* on Friday night, only 120 tickets are available: please check at the registration desk in the conference hall. Buses will be ready at the entrance of the Meervaart Friday 17.45 h.

You will be transported to the inner city of Amsterdam where we first have drinks and tapas, (offered by the Asbestslachtoffer Vereniging Nederland) followed by a canal boat tour which will take us to one of the older Indonesian restaurants on the Rembrandt square for an Indonesian rice table.

We expect to end around 22.15 and will return to the hotels by bus.

Special thanks to the Audiovisual Center of the Netherlands Cancer Institute for providing the pictures on the cover.

LIST OF SPONSORS

We are truly indebted to the sponsors who made it possible to organize this meeting.

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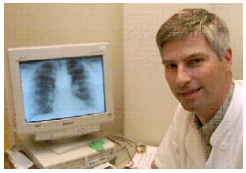
WELCOME FROM THE IMIG CHAIR

I am delighted to welcome you to Amsterdam, site of the 9th Meeting of the International Mesothelioma Interest Group. As the leading international organization for physicians and scientists dedicated to mesothelioma research, IMIG is proud to sponsor this conference every two years. This trans-disciplinary meeting will gather investigators from around the globe to present scientific information of the highest caliber. It is my hope that this IMIG meeting, like the others that have preceded it, will foster international collaboration, inspire young investigators, generate new ideas, and establish benchmark standards for the diagnosis and treatment of this disease.

Hedy Lee Kindler, MD

Chicago, USA

WELCOME FROM THE IMIG ORGANIZERS



Dear participant,

A warm welcome to you all in Amsterdam. We are honoured to be your hosts on the iMig 2009 meeting.

Mesothelioma remains a global problem. The incidence of this asbestos related disease is still rising. In the foreseeable future the fatality rate might drop in the developed countries but it is steeply rising in the third world. This is one of the most important reasons for us to organize this meeting every other year.

The format of the congress will include didactic lectures from internationally renowned leaders, debates and discussions on controversial topics. We hope to inform you on all aspects of malignant mesothelioma; epidemiology, biology, molecular genetics, diagnosis and treatment. Specialists have been asked to prepare sessions summarizing the hottest topics, the ongoing research and new developments. We look forwards to stimulating, open discussions during the sessions and hope that this will lead to fruitful collaborations.

During the preparation of this meeting, the European Association of Cardio-Thoracic Surgery approached us with the request to have a joined meeting during this conference. We were more than happy to include the special meeting where clinicians and researchers of all sorts can discuss the direction we should take for combined therapy approaches. The previous meetings have been a stimulus for us to prepare a program that fits best. In this congress book the sessions are presented for each subject by day, followed by the submitted abstracts for your convenience.

Finally, we are indebted to our sponsors who have made this event possible and hope that in the near future, together we will be able to achieve our goal: the eradication of this disease and finding a cure!

We hope that you will enjoy the meeting in Amsterdam.

Paul Baas, MD, PhD

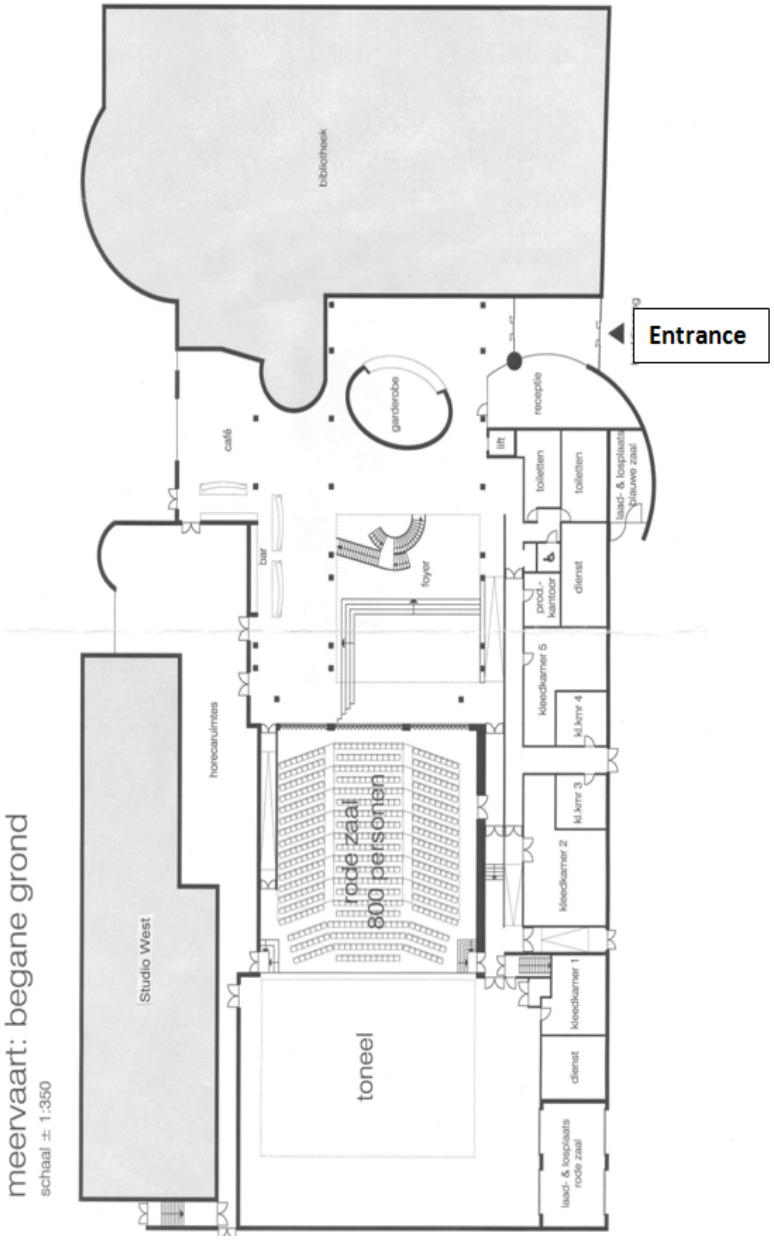
Sjaak Burgers, MD, PhD

The Netherlands Cancer Institute

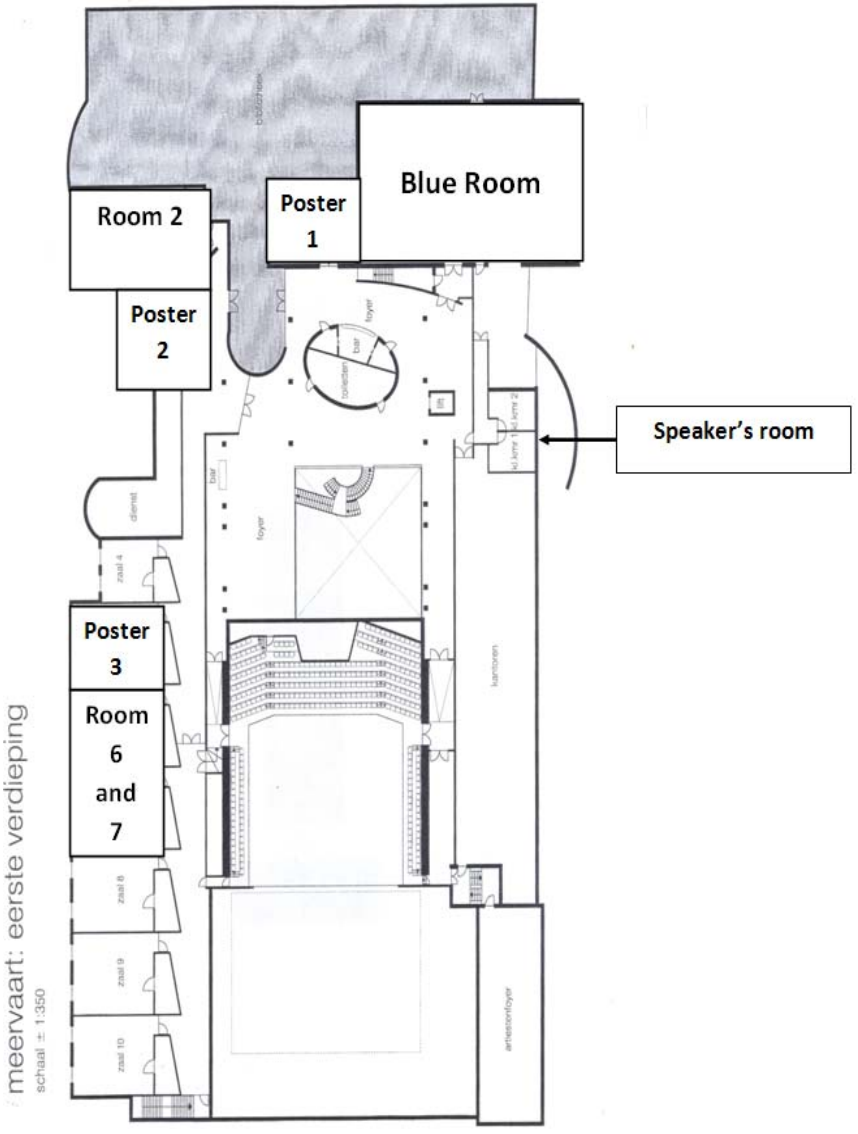
Amsterdam, The Netherlands

FIRST FLOOR

FLOOR MAP



SECOND FLOOR FLOOR MAP



THURSDAY 25 SEPTEMBER

Thursday Sept, 25	Blue room	Room 2	Room 6-7	Poster room
08.00	Welcome: Paul Baas	Chairs Blue Room: Sjaak Burgers Nick Pavlakis		**POSTERS** *Poster viewing* *Rooms 1, 2 and 3*
08.10	Presidents Address Hedy Kindler			
08.30	General session: Bruce Robinson Julian Peto Anton Berns Joseph Testa Lauri Kazan			
10.20	Break			
10.50 12.30	Chemotherapy 1 Chairs: Hedy Kindler Dean Fennell	Imaging Chairs: Sam Armato Anna Nowak	Animal Models Chairs: Anton Berns Joseph Testa	
12.40	LUNCH	*Special Lunch Seminar:* Fujirebio		
14.00	Radiotherapy Chairs: Rick Haas Craigh Stevens	Pathology 1 Chairs: Marc van de Vijver Brooke Mossman	Novel Targets Chairs: Raffit Hassan Oluf Dimitri Roe	
17.00- 17.30	Poster discussion with 5 top rated poster presenters and Highlight of the day Chairs: Dean Fennell Nico van Zandwijk MARF presentation M. Hesdorffer			
WELCOME RECEPTION Wagner Prize				

FRIDAY 26 SEPTEMBER

Friday, Sept 26	Blue room	Room 2	Room 6-7	Room 1
08.15	**IMIG and EACTS joint meeting** See additional Program			
10.20	Break			
10.50	**IMIG and EACTS joint meeting** See additional Program	**Early Diagnosis** Chairs: Steve Mutsears Jenette Creaney	**Asbestos victims: epidemiology, surveillance, compensation and awareness.** Chairs: Machiel van der Woude James teWaterNaude	
12.40	LUNCH	*Special Lunch Seminar:* *Morphotek*		
14.00	**IMIG and EACTS joint meeting** Chairs: See additional Program	**Immuno Therapy** Chairs: Courtney Broaddus Joost Hegmans	**Epidemiology and Causation** Chairs: Muzaffer Metintas Michele Carbone	**POSTERS** *viewing* *Room 1, 2 and 3*
17.00-17.30	Poster discussion with 5 top rated poster presenter and Highlight of the day Chairs: Bruce Robinson Ed van Hezik ADAO Poster Award, IBAS Poster Award			
SPECIAL EVENING TRIP AND BANQUET				

SATURDAY 27 SEPTEMBER

Saturday, Sept 27	Blue room	Room 2	Room 6-7
08.00	**Surgery and Multimodality Treatment** Chairs: Rolf Stahel Masahiro Tsuboi	**Future trends** Chairs: Rabab Gaafar Daniel Sterman	**Molecular Genetics** Chairs: Marc Ladanyi Marie-Claude Jaurand
10.10			
10.20	***Break***		
10.50	**Palliation – Pleurodesis** Chairs: Jeremy Steele Gary Lee	**Chemotherapy 2** Chairs: Nick Vogelzang Jan van Meerbeeck	**Molecular Pathology** Chairs: Lucio Mutti Sakari Knuuttila
	12.30 LUNCH AND FAREWELL		

LUNCH SESSION PROGRAM

Simultaneously to the free lunches, a special *LUNCH SEMINAR* will be held in the foyer on the second floor on Thursday and Friday. These luxury lunches are sponsored by *Fujirebio* and *Morphotek*, respectively.
One hundred free tickets are available for each seminar, and can be obtained for free at the registration desk at the conference hall and at the booths of Fujirebio and Morphotek. The program of these seminars is made under the responsibility of the sponsors.

Lunch session sponsored by Fujirebio, Thursday September 25

Time	Speaker	Title
12.40	Lee	Introduction
	Pass	Mesomark and treatment monitoring: the discovery phase
	Scherpereel	Soluble mesothelin and malignant pleural mesothelioma management: a French group five years experience
	Lee	Questions – comments

Lunch session sponsored by Morphotek, Friday September 26

Time	Speaker	Title
12.40	Hassan	Introduction
12.45	Robinson	Value of mesothelin-SMRP as a diagnostic marker in mesothelioma
13.00	Hassan	Targeting mesothelin using MORab-009, preclinical studies and results of phase I study
13.20	Morphotek	Phase II clinical trial of MORab-009 as front-line therapy for mesothelioma

GENERAL SESSION

CHAIRS: Nick Pavlakis and Sjaak Burgers

TIME	TITLE ABSTRACT	TYPE	abstract number
08.00	Welcome *Paul Baas*		
08.10	Presidential Address *Hedy Lee Kindler*		
08.30	INTERNATIONAL MORTALITY TRENDS *Julian Peto*	Invited speaker	1
08.50	CURRENT STATUS AND FUTURE DEVELOPMENTS OF TUMOR MARKERS IN MESOTHELIOMA *Bruce Robinson*	Invited speaker	2
09.10	MODEL SYSTEMS FOR HUMAN MALIGNANT MESOTHELIOMA *Anton Berns*	Invited speaker	3
09.30	TUMOR SUPPRESSION IN MESOTHELIOMA *Joseph Testa*	Invited speaker	4
09.50	INDIA'S ASBESTOS TIME BOMB *Laurie Kazan-Allen*	Invited speaker	5
10.20	Break		

CHEMOTHERAPY I

CHAIRS: Hedy Lee Kindler and Dean Fennell

TIME	TITLE ABSTRACT	TYPE	abstract number
10.50	GUIDELINES FOR THE MANAGEMENT OF MALIGNANT PLEURAL MESOTHELIOMA FROM THE 2007-2008 ERS/ESTS TASKFORCE *Arnaud Scherpereel*	Invited speaker	6
11.10	LATEST DEVELOPMENTS - APOPTOSIS AND MESOTHELIOMA *Courtney Broaddus*	Invited speaker	7
11.30	IN VITRO EXTREME CHEMOTHERAPY RESISTANCE ASSAY CONFIRMS UTILITY OF CISPLATIN IN THE TREATMENT OF MALIGNANT PLEURAL MESOTHELIOMA *Aneil Mujoomdar*	Oral presentation	8
11.40	INHIBITION OF TRANSLESION SYNTHESIS SENSITIZES MALIGNANT PLEURAL MESOTHELIOMA CELLS TO CISPLATIN TREATMENT *Philip Alexander Knobel*	Oral presentation	9
11,50	NGR-HTNF, A NOVEL VASCULAR TARGETING AGENT (VTA), AS SECOND-LINE THERAPY IN MALIGNANT PLEURAL MESOTHELIOMA (MPM): PRELIMINARY RESULTS OF A MULTICENTER PHASE II TRIAL *Paolo Zucali*	Oral presentation	10
12.05	PHASE II STUDY OF THE COMBINATION OF BEVACIZUMAB PLUS PEMETREXED AND CARBOPLATIN AS FIRST-LINE THERAPY IN PATIENTS WITH MALIGNANT PLEURAL MESOTHELIOMA (MPM) *Giovanni Luca Ceresoli*	Oral presentation	11
12.20	NEW DEVELOPMENTS IN MESOTHELIOMA *Hedy Lee Kindler*	Invited speaker	12
12.40	Lunch		

CHAIRS: Rick Haas and Craig Stevens

TIME	TITLE ABSTRACT	TYPE	abstract number
14.00	INDICATIONS AND LIMITATIONS OF RT IN MPM, SETTING THE SCENE *Craig Stevens*	Chair person	13
14.20	HYPERTHEMIA AND RT IN MPM: RATIONALE, TECHNIQUE AND CLINICAL RESULTS *J. van der Zee*	Invited speaker	14
14.40	FATAL PNEUMONITIS ASSOCIATED WITH IMRT IN MPM *Aaron Allen*	Invited speaker	15
15.00	Discussion	Chairs	
15.15	Break		
15.30	EXTRAPLEURAL PNEUMONECTOMY (EPP) AND HEMITHORACIC RADIATION THERAPY (RT) FOR MPM *Kenneth Rosenzweig*	Oral presentation	16
15.45	PLEURAL INTENSITY MODULATED RADIATION THERAPY IN PATIENTS WITH MPM *Kenneth Rosenzweig*	Oral presentation	17
16.00	ADJUVANT HEMITHORACIC RADIOTHERAPY FOLLOWING EPP FOR MPM IMPROVES LOCAL CONTROL *John Cho*	Oral presentation	18
16.15	PULMONARY TOXICITY FOLLOWING INTENSITY-MODULATED RADIOTHERAPY (IMRT) AFTER EXTRAPLEURAL PNEUMONECTOMY FOR MPM *Jens Benn Sørensen*	Oral presentation	19
16.30	IMRT AFTER EXTRAPLEURAL PNEUMONECTOMY (EPP) IN PATIENTS WITH MPM: DOES NODAL STATUS MAKE THE DIFFERENCE? *Marta Scorsetti*	Oral presentation	20
16.45	BORON NEUTRON CAPTURE THERAPY FOR MALIGNANT MESOTHELIOMA *Chunman Lee*	Poster discussion	22
16.50	SUMMARY	Chairs	

IMAGING

CHAIRS: Samuel Armato and Anna Nowak

TIME	TITLE ABSTRACT	TYPE	abstract number
10.50	ASSESSING PROGNOSIS OF MPM BY INCORPORATING FDG-PET PARAMETERS ADDS INCREMENTAL VALUE TO PROGNOSTIC MODELS INCORPORATING CLINICAL INFORMATION *Anna Nowak*	Oral presentation	23
11.05	EARLY RESPONSE EVALUATION IN MPM BY TOTAL GLYCOLYTIC VOLUME (TGV) ANALYSIS OF SERIAL FDG-PET SCANS *Giovanni Luca Ceresoli*	Oral presentation	24
11.20	DIFFERENTIATION BETWEEN MALIGNANT MESOTHELIOMA AND ASBESTOS-RELATED BENIGN PLEURAL DISEASE *Huseyin Yildirim*	Oral presentation	25
11.35	THICKNESS AND AREA IN THE CT-BASED ASSESSMENT OF MESOTHELIOMA TUMOR RESPONSE *Samuel Armato*	Oral presentation	26
11.50	ROLE OF 18FDG-PET-CT IN PATIENTS SURVEILLANCE AFTER MULTIMODALITY THERAPY OF MALIGNANT PLEURAL MESOTHELIOMA *Carol Tan*	Oral presentation	27
12.00	PRACTICAL AND REPRODUCIBLE VOLUME MEASUREMENT OF MALIGNANT PLEURAL MESOTHELIOMA FROM STANDARD CT IMAGES *Shin Matsuoka*	Oral presentation	28
12.10	THE INFLUENCE OF TALC PLEURODESIS ON FDG PET IMAGING FOR MPM. *Agatha van der Schaaf*	Oral presentation	29
12.20	CONTINUED PERMETREXED AND PLATIN-BASED CHEMOTHERAPY IN PATIENTS WITH MPM: VALUE OF 18F-FDG-PET/CT PARAMETERS *N.G. Schaefer*	Oral presentation	30
12.30	SUMMING UP	Chairs	
12.40	LUNCH		

PATHOLOGY

CHAIRS: Marc van de Vijver and Brooke Mossman

TIME	TITLE ABSTRACT	TYPE	abstract number
14.00	OPPORTUNITIES FOR OBTAINING HUMAN MESOTHELIOMA TISSUES TO CONFIRM THE RELEVANCE OF IN VITRO AND ANIMAL STUDIES *Brooke Mossman*	Chair person	31
14.15	THE DUTCH MESOTHELIOMA REGISTRY *Marc van de Vijver*	Chair person	32
14.30	EVIDENCE OF STAT1 ACTIVATION IN MPM IN FORMALIN-FIXED AND PARAFFIN-EMBEDDED TISSUE USING PROTEIN LYSATE MICROARRAYS *Hannelore Kothmaier*	Oral presentation	33
14.45	THE VALUE OF ERCC1 AS PROGNOSTIC MARKER FOR MPM *Isabelle Opitz*	Oral presentation	34
15.00	EPIGENETIC PROFILES DISTINGUISH PLEURAL MESOTHELIOMA FROM ADENOCARCINOMA OF THE LUNG *Brock Christensen*	Oral presentation	35
15.15	DISCUSSION		
15.30	BREAK		
15.45	DNA METHYLATION IN TUMORS AND MATCHED NORMAL TISSUES OF MPM IN THE EGYPTIAN POPULATION *Abeer Bahnassy*	Oral presentation	36
16.00	E-PATHOLOGY AND ATYPICAL MESOTHELIAL HYPERPLASIA (MESODIAG-AMH): THE EXPERIENCE OF THE INTERNATIONAL MESOTHELIOMA PANEL *Françoise Galateau Sallé*	Oral presentation	37
16.15	CRITICAL ANALYSIS OF NUCLEAR SIZE AS A HISTOLOGIC ASSESSMENT OF PROGNOSIS IN DIFFUSE MALIGNANT PERITONEAL MESOTHELIOMA *Paul Sugarbaker*	Oral presentation	38
16.30	DELIBERATELY PROVOKING LOCAL INFLAMMATION DRIVES TUMORS TO BECOME THEIR OWN PROTECTIVE VACCINE SITE *Delia Nelson*	Oral presentation	39
16.45	DISCUSSION		

ANIMAL MODELS

CHAIRS: Anton Berns and Joseph Testa

TIME	TITLE ABSTRACT	TYPE	abstract number
10.50	THE HETEROGENOUS MICROENVIRONMENT OF MURINE MALIGNANT MESOTHELIOMA DURING TUMOR IMPLANTATION *Bonnie Lau*	Oral presentation	40
11.05	HUMAN AND MURINE MESOTHELIOMA SHARE SIMILAR GENOMIC ALTERATIONS *Elodie Manié*	Oral presentation	41
11.20	EXTRACELLULAR SIGNAL-REGULATED KINASES (ERKS) HAVE DISPARATE ROLES IN GROWTH AND CHEMORESISTANCE OF HUMAN MESOTHELIOMAS IN VITRO AND IN A MOUSE XENOGRAFT MODEL *Arti Shukla*	Oral presentation	42
11.35	MALIGNANT MESOTHELIOMA MOUSE MODEL FOR IN VIVO AND IN VITRO THERAPEUTIC STRATEGIES *Johan Jongsma*	Oral presentation	43
11.50	RNA INTERFERENCE-BASED STRATEGIES DIRECTED AGAINST BCL-XL AND MCL-1 FOR THE TREATMENT OF MALIGNANT PLEURAL MESOTHELIOMA *Emilie Varin*	Oral presentation	44
12.00	DEPLETION OF ICOS- AND TNFR2-EXPRESSING EFFECTOR-SUPPRESSOR T CELLS PROMOTES THE ERADICATION OF SUBCUTANEOUS MESOTHELIOMAS IN MICE *Robbert van der Most-Richard Lake*	Oral presentation	45
12.10	HIGH FIDELITY PRE-CLINICAL MODELING IN MEXTAG TRANSGENIC MICE *Richard Lake*	Invited speaker	46
12.30	SUMMING UP	Chairs	
12.40	LUNCH		

NOVEL TARGETS

CHAIRS: Raffit Hassan and Oluf Dimitri Roe

TIME	TITLE ABSTRACT	TYPE	abstract number
14.00	WT-1 VACCINE IN MESOTHELIOMA; AN OVERVIEW *Lee Krug*	Invited speaker	47
14.20	IDENTIFICATION OF NEW TARGETS BY GENOME-WIDE PROFILING *Oluf Dimitri Røe*	Chair person	48
14.40	REVERSAL OF BORTEZOMIB RESISTANCE IN MESOTHELIOMA BY A MCL-1/A1 TARGETING BH3 PEPTIDOMIMETIC *Alex Chacko*	Oral presentation	49
14.55	IDENTIFICATION OF INTERNALIZING HUMAN ANTIBODIES TARGETING TUMOR CELL SURFACE ANTIGENS COMMONLY EXPRESSED BY ALL TYPES OF MESOTHELIOMA *Scott Bidlingmaier*	Oral presentation	50
15.10	MESOTHELIN AS TARGET FOR MESOTHELIOMA-IMMUNOTHERAPY *Raffit Hassan*	Chair person	51
15.30	BREAK		
15.45	FREQUENT CO-ACTIVATION OF MET AND EGFR IN MALIGNANT MESOTHELIOMA AS A RATIONALE FOR COMBINATION TARGETED THERAPY *Shigeki Shimizu*	Oral presentation	52
16.00	PAXILLIN IS A NOVEL POTENTIAL MOLECULAR THERAPEUTIC TARGET AGAINST MESOTHELIOMA *Ramasamy Jagadeeswaran*	Oral presentation	53
16.15	MESOTHELIOMA SPHEROIDS, mTOR, MITOCHONDRIA AND MULTICELLULAR RESISTANCE *Dario Barbone*	Oral presentation	54
16.30	TRANSDUCTION OF THE WILD-TYPE P53 GENE IN COMBINATION WITH ANTI-CANCER AGENTS PRODUCED ANTI-TUMOR EFFECTS ON MESOTHELIOMA *Yuji Tada*	Poster discussion	55
16.35	NOVEL THERAPY FOR MPM BASED ON ANTI-ENERGETIC EFFECT: AN EXPERIMENTAL STUDY USING 3-BROMOPYRUVATE IN NUDE MICE *Xiadong Zhang*	Poster discussion	56
16.40	RAPAMYCIN INTENSIFIES CISPLATIN CYTOTOXICTY IN MESOTHELIOMA CELL LINES *Mor-Li Hartman*	Poster discussion	57
16.45	SUMMARY		
17.00	The End		

IMIG EACTS JOINT SESSION

CHAIRS: Hedy Kindler, Bruce Case and Harvey Pass

TIME	**GENERAL SESSION: THE SURGICAL TRIALS**	abstract number
08.15	WELCOME. *Chairs*	
08.30	EORTC *Paul van Schil*	140
08.50	MARS *Julian Peto*	141
09.10	MesoVATS *Robert Rintoul*	142
09.30	STATISTICS IN 'difficult to do' MESOTHELIOMA TRIALS *Richard Stephens*	143
10.00	DISCUSSION	
10.30	BREAK	

CHAIRS: David Waller and Houke Klomp

TIME	**CURRENT PRACTICE: SURGEONS and SYMPTOM CONTROL**	abstract number
10.50	BEST PALLIATION OF BREATHLESSNES DUE TO FLUID. *Gary Lee*	144
11.10	PORT SITE RADIOTHERAPY. *Craig Stevens*	145
11.30	DECORTICATION AS A MEAN OF SYMPTOM RELIEF. *David Waller*	146
11.50	A PHYSICIAN'S PERSPECTIVE ON SURGICAL OPTIONS FOR MESOTHELIOMA. *Robert Rintoul*	147
12.10	OVERVIEW AND PANEL DISCUSSION. *Houke Klomp*	
12.30	LUNCH	

IMIG EACTS JOINT SESSION

CHAIRS: Tom Treasure and Jan van Meerbeeck

TIME	**MESOTHELIOMA: WHERE ARE WE AND WHERE ARE WE GOING?**	abstract number
14.00	A HISTORICAL PERSPECTIVE. *Eric Butchart*	148
14.20	AN ADVOCATE'S PERSPECTIVE: A CALL FOR A DATA-BASED APPROACH. *Roger Worthington*	149
14.40	WHO OWES WHAT TO WHOM IN CLINICAL AND SURGICAL RESEARCH? *Martyn Evans*	150
15.00	PROPOSAL FOR BETTER SURGICAL/PATHOLOGICAL STAGING. *John Edwards*	151

TIME	**MINI DEBATE: SHOULD SURGERY BE AIMING AT COMPLETE RESECTION?**	abstract number
15.20	PRO. *Tom Treasure* CON: *David Waller*	152 153
15.50	DOES RADIOTHERAPY ADD ANYTHING TO EPP? *Reza Mehran*	154
16.10	ESTIMATING THE SURVIVAL BENEFIT ASSICIATED WITH RADICAL SURGERY.*Tom Treasure*	155
16.30	WHAT MIGHT MARS-2 LOOK LIKE? *David Waller*	156
16.50	DIRECTIONS FOR FUTURE SURGICAL RESEARCH. *Panel*	

EARLY DIAGNOSIS

CHAIRS: Steve Mutsears and Jenette Creaney

TIME	TITLE ABSTRACT	TYPE	abstract number
10.50	THE FIBRINOLYTIC SYSTEM AND GROWTH OF MALIGNANT PLEURAL MESOTHELIOMA *Steven Idell*	Invited speaker	58
11.15	CYTOLOGICAL DIAGNOSIS OF MALIGNANT PLEURAL MESOTHELIOMA *Amanda Segal*	Invited speaker	59
11.35	BIOMARKERS FOR MALIGNANT PLEURAL MESOTHELIOMA: CURRENT STATUS *Laurent Greillier*	Invited speaker	60
11.45	THE DIAGNOSTIC ACCURACY AND REPRODUCIBILITY OF PLEURAL FLUID LEVELS OF MESOTHELIN IN UNSELECTED PATIENTS WITH PLEURAL EFFUSIONS *H.E. Davies*	Oral presentation	61
11.55	THE USE OF MESOTHELIN FOR MONITORING PATIENTS WITH MESOTHELIOMA *Jenette Creaney*	Oral presentation	62
12.05	EARLY CHANGE IN SERUM VEGF AND OSTEOPONTIN DURING TREATMENT FOR MESOTHELIOMA IS PREDICTIVE FOR SURVIVAL. *Rozelle Harvie*	Oral presentation	63
12.15	GENERAL DISCUSSION, including POSTER DISCUSSION	Chairs	
12.40	Lunch		

IMMUNOTHERAPY

CHAIRS: Courtney Broaddus and Joost Hegmans

TIME	TITLE ABSTRACT	TYPE	abstract number
14.00	ONCOLYTIC TYPE 5 ADENOVIRUSES WITH TYPE 35 FIBER-KNOB STRUCTURE PRODUCE BETTER CYTOTOXIC EFFECTS TO MESOTHELIOMA CELLS THAT EXPRESS THE TYPE 5 CELLULAR RECEPTORS AT A LOW LEVEL *Masatoshi Tagawa*	Oral presentation	64
14.15	IMMUNOLOGICAL CHANGES IN MESOTHELIOMA PATIENTS AND THEIR EXPERIMENTAL DETECTION *Takemi Otsuki*	Oral presentation	65
14.30	DENDRITIC CELL-BASED IMMUNOTHERAPY FOR MPM *Joachim Aerts*	Oral presentation	66
14.45	LOW-DOSE CYCLOPHOSPHAMIDE SYNERGIZES WITH DENDRITIC CELL IMMUNOTHERAPY IN ANTITUMORAL RESPONSES IN A MOUSE MODEL FOR MESOTHELIOMA *Joost Hegmans*	Oral presentation	67
15.00	5T4 AS A TUMOUR-ASSOCIATED ANTIGEN IN MPM *Saly Al-Taei*	Oral presentation	68
15.15	WILMS TUMOR-1 (WT1) PEPTIDE VACCINE CAN ELICIT IMMUNE RESPONSES IN PATIENTS WITH MPM *Andrew Brown*	Oral presentation	47
15.30	BREAK		
15.45	IMMUNOCHEMOTHERAPY REDUCES RECURRENCE OF MALIGNANT PLEURAL MESOTHELIOMA *Luca Ampollini*	Oral presentation	69
16.00	THE EFFECT OF CHEMOTHERAPY ON THE IMMUNE SYSTEM IN PATIENTS WITH MALIGNANT MESOTHELIOMA *Melanie McCoy*	Oral presentation	70
16.15	MODULATION OF TRANSLESION SYNTHESIS: IMPACT ON CHEMOTHERAPY RESISTANCE IN MPM? *Philip Alexander Knobel*	Oral presentation	71
16.30	NONSPECIFIC ACTIVE IMMUNOTHERAPY INCREASED SURVIVAL IN MALIGNANT MESOTHELIOMA *Marie-Marthe Philippeaux*	Oral presentation	72
16.45	SUMMING UP	Chairs	
16.50	THE END		

ASBESTOS VICTIMS: EPIDEMIOLOGY, SURVEILLANCE, COMPENSATION AND AWARENESS

CHAIRS: Machiel van der Woude and James teWaterNaude

TIME	TITLE ABSTRACT	TYPE	abstract number
10.50	INTRODUCTION	Chairs	
10.55	INTERNATIONAL MORTALITY TENDS *Peto*	Invited speaker	73
11.20	THE LATROBE VALLEY POWER INDUSTRY COHORT STUDY: A MULTI-DISCIPLINARY APPROACH TO STUDYING ASBESTOS RELATED DISEASES *Anthony LaMontagne*	Oral presentation	74
11.30	DISCUSSION		
11.35	THE FRENCH NATIONAL PROGRAM FOR POST-OCCUPATIONAL SURVEILLANCE OF SUBJECTS EXPOSED TO ASBESTOS *Patrick Rolland*	Oral presentation	75
11.45	DISCUSSION		
11.50	A PUBLIC HEALTH CRITIQUE OF SOUTH AFRICAN MESOTHELIOMA COMPENSATION. *James teWaterNaude*	Oral presentation	76
12.00	DISCUSSION		
12.05	DUTCH ASBESTOS VICTIMS INSTITUTE: A SOCIAL RESPONSIBLE SOLUTION FOR A COMPLEX HISTORICAL PROBLEM *Bas de Mol*	Invited speaker	77
12.15	DISCUSSION		
12.20	DEADLY DUST: MITIGATING THE IMPACT OF ASBESTOS THROUGH EDUCATION AND PREVENTION, EARLY DETECTION AND INCREASED FUNDING FOR RESEARCH *Linda Reinstein*	Invited speaker	78
12.35	DISCUSSION		
12.40	MESOTHELIOMA IN JAPAN AFTER THE ENACTMENT OF ASBESTOS-RELATED HEALTH DAMAGE RELIEF LAW *Kenji Morinaga*	Oral presentation	79

EPIDEMIOLOGY and CAUSATION

CHAIRS: Muzaffer Metintas and Michele Carbone

TIME	TITLE ABSTRACT	TYPE	abstract number
14.00	MESOTHELIOMA: CLINICAL CHALLENGES TO ADDRESS THE EPIDEMIOLOGY OF THIS CANCER WORLDWIDE *Muzaffer Metintas*	Chair person	80
14.20	CRITERIA TO ESTABLISH CAUSATION IN HUMAN CANCER AND MESOTHELIOMA *Michele Carbone*	Chair person	81
14.40	REVIEW OF THE PUBLISHED EPIDEMIOLOGY LINKING MINERAL FIBERS TO MESOTHELIOMA *Gunnar Hillerdal*	Invited speaker	82
15.00	ROUND TABLE DISCUSSION: CAUSATION, EPIDEMIOLOGY AND MESOTHELIOMA		
15.30	BREAK		
15.40	A CASE-CONTROL STUDY OF MALIGNANT MESOTHELIOMA IN SUBJECTS WITH NO KNOWN EXPOSURE TO ASBESTOS *Nicholas de Klerk*	Oral presentation	83
15.50	ONCONASE INHIBITS MESOTHELIOMA CELLS INVASION INDUCED BY TNF-ALPHA. *Haining Yang*	Oral presentation	84
16.00	PLEURAL MESOTHELIOMA AS A SECOND PRIMARY CANCER POST THERAPEUTIC RADIATION FOR HODGKIN'S AND NON HODGKIN'S DISEASE *David Sugarbaker*	Oral presentation	85
16.10	A POPULATION-BASED STUDY ON RADIOTHERAPY (RT) AS A RISK FACTOR FOR MALIGNANT MESOTHELIOMA *Enzo Merler*	Oral presentation	86
16.20	MESOTHELIOMA DIAGNOSIS IN QUÉBEC: PATHOLOGY, EPIDEMIOLOGY AND COMPENSATION. *Bruce Case*	Oral presentation	87
16.30	WITTENOOM, WOMEN AND MESOTHELIOMA *Alison Reid*	Oral presentation	88
16.40	FRENCH NATIONAL MESOTHELIOMA REGISTRY [MESONAT]: THE CONTRIBUTION OF PATHOLOGY *Nolwenn Le Stang*	Oral presentation	89
16.50	THE FRENCH NATIONAL MESOTHELIOMA SURVEILLANCE PROGRAM: ESTIMATES OF THE NATIONAL MESOTHELIOMA INCIDENCE – PERIOD 1998-2005 *Anabelle Gilg Soit Ilg*	Oral presentation	90
17.00	INDIVIDUAL COMPARISON OF INCIDENT CASES OF PLEURAL MESOTHELIOMA RECORDED BY THE FRENCH NATIONAL MESOTHELIOMA SURVEILLANCE PROGRAM AND THE RECORDED CAUSE OF DEATH FOR ESTIMATING THE NATIONAL INCIDENCE *Anabelle Gilg Soit Ilg*	Oral presentation	91
17.10	MESOTHELIOMA SURVIVAL: EFFECTS OF MANAGEMENT AND HISTOLOGICAL TYPE *William Musk*	Oral presentation	92

SURGERY and MULTIMODALITY TREATMENT

CHAIRS: Rolf Stahel and Masahiro Tsuboi

TIME	TITLE ABSTRACT	TYPE	abstract number
8.00	EVIDENCE-BASED ADJUSTMENTS TO PATHOLOGIC STAGING OF EPITHELIAL MPM *David Sugarbaker*	Oral Presentation	101
8.20	MULTIMODALITY TREATMENT *Masahiro Tsuboi*	Invited speaker	94
8.40	RECENT EXPERIENCE WITH A MODIFIED CLAGETT'S PROCEDURE IN PATIENTS WITH EMPYEMA AND BRONCHOPLEURAL FISTULA FOLLOWING EPP FOR MPM *John Pilling*	Oral Presentation	102
9.00	PREOPERATIVE STAGING BY 18F-FDG-PET-COMPUTED TOMOGRAPHY FUSED IMAGING AND MEDIASTINOSCOPY COMPARED TO PATHOLOGICAL FINDINGS AFTER EPP *Jens Benn Sørensen*	Oral Presentation	95
9.15	DETECTION OF N2 ADENOPATHY BY CERVICAL MEDIASTINOSCOPY IN 175 CONSECUTIVE PLEURAL MESOTHELIOMA PATIENTS *Tamara Tilleman*	Oral Presentation	96
9.25	REDUCED LUNG VOLUME MEASURED BY CT PREDICTS UNRESECTABILITY IN MESOTHELIOMA PATIENTS *Aneil Mujoomdar*	Oral Presentation	97
9.35	TRIMODALITY TREATMENT FOR MPM: THE HEIDELBERG EXPERIENCE *Hans Hoffmann*	Oral Presentation	98
9.45	CYTOREDUCTIVE SURGERY AND HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY IN THE TREATMENT OF DIFFUSE MALIGNANT PERITONEAL MESOTHELIOMA *Marcello Deraco*	Oral Presentation	99
9.55	CLINICAL AND PHARMACOLOGIC INFORMATION CONTROLLING A COMPREHENSIVE MANAGEMENT OF DIFFUSE MALIGNANT PERITONEAL MESOTHELIOMA *Paul Sugarbaker*	Oral Presentation	100
10.05	POSTER SUMMARY	Chairs	

PALLIATION AND PLEURODESIS

CHAIRS: Jeremy Steele and Gary Lee

TIME	TITLE ABSTRACT	TYPE	abstract number
10.50	WELCOME and INTRODUCTION *Chairs*		
10.55	PALLIATIVE CARE ISSUES SPECIFIC FOR MESOTHELIOMA *Jeremy Steele*	Chair person	103
11.10	PRO-CON DEBATE: SURGICAL PLEURODESIS IS THE REFERRED MANAGEMENT FOR MALIGNANT EFFUSIONS IN MESOTHELIOMA		
	PRO *Loïc Lang-Lazdunski*	Invited speaker	
	CON *Gary Lee*	Chair person	
11.40	NOVEL MANAGEMENT APPROACH FOR MALIGNANT EFFUSIONS: TARGETING FLUID FORMATION *Ioannis Kalomenidis*	Invited speaker	104
11.55	UNDERSTANDING THE PSYCHOLOGICAL ISSUES; THE NEGLECTED ASPECT OF MESOTHELIOMA CARE *Helen Clayson*	Invited speaker	105
12.15	THE END		

FUTURE TRENDS

CHAIRS: Rabab Gaafar and Daniel Sterman

TIME	TITLE ABSTRACT	TYPE	abstract number
8.00	INTRODUCTION *Rabab Gaafar*	Chair person	
8.15	TARGETING CD44 WITH HYALURONAN FOR BNCT:A NOVEL STRATEGY FOR MALIGNANT PLEURAL MESOTHELIOMA *Chunman Lee*	Oral presentation	21
8.35	TARGETING SURVIVAL AND CHEMORESISTANCE IN MALIGNANT MESOTHELIOMA *Giovanni Gaudino*	Oral presentation	106
8.50	TARGETING OF HUMAN MESOTHELIOMA CELLS AFTER BIFUNCTIONALIZATION OF THE SURFACE OF AMORPHOUS SILICA SPHERES WITH TETRAETHYLENE GLYCOL (TEG) AND AN ANTIBODY TO MESOTHELIN *Kai Cheng*	Oral presentation	107
9.05	CHEMOPREVENTION OF ASBESTOS INDUCED GENETIC INSTABILITY *Monica Neri*	Oral presentation	108
9.20	FUTURE TRENDS: CANADA *Chris Lee*	Invited speaker	109
9.40	FUTURE TRENDS: JAPAN *Takashi Nakano*	Invited speaker	110
09.55	SUMMING UP *Daniel Sterman*	Chair person	
10.20	BREAK		

CHEMOTHERAPY 2

CHAIRS: Nick Vogelzang and Jan van Meerbeeck

TIME	TITLE ABSTRACT	TYPE	abstract number
10.50	RESPONSE TO INDUCTION CHEMOTHERAPY IS THE STRONGEST PREDICTOR OF SURVIVAL IN A MULTICENTER U.S. TRIAL OF TRIMODALITY THERAPY FOR RESECTABLE MALIGNANT PLEURAL MESOTHELIOMA *Lee Krug*	Oral presentation	111
11.05	RISK FACTORS FOR ACUTE KIDNEY INJURY (AKI) IN PATIENTS UNDERGOING EXTRAPLEURAL PNEUMONECTOMY *Annette Mizugushi*	Oral presentation	112
11.20	URINARY KIDNEY INJURY MOLECULE-1 FOR THE EARLY DETECTION OF KIDNEY INJURY WITH FOLLOWING CYTOREDUCTIVE SURGERY AND INTRACAVITARY CISPLATIN LAVAGE FOR MESOTHELIOMA *Sushrut Waikar*	Oral presentation	113
11.35	NEW CHEMOTHERAPEUTIC DRUGS IN THE TREATMENT OF ADVANCED MALIGNANT PLEURAL MESOTHELIOMA IN EGYPT *Rabab Gaafar*	Oral presentation	114
11.50	CISPLATIN AND VINORELBINE FIRST LINE CHEMOTHERAPY IN NON-RESECTABLE MPM. *Jens Benn Sørensen*	Oral presentation	115
12.05	PHASE II STUDY OF SUNITINIB AS SECOND-LINE THERAPY IN MPM *Anna Nowak*	Oral presentation	116
12.20	SUMMING UP	Chairs	
12.40	THE END		

MOLECULAR GENETICS

CHAIRS: Marc Ladanyi and Marie-Claude Jaurand

TIME	TITLE ABSTRACT	TYPE	abstract number
8.00	INTEGRATED GENOMIC CHARACTERIZATION OF MESOTHELIOMA TUMORS AND CELL LINES *Marc Ladanyi*	Chair person	117
8.20	DISCOVERY OF DIFFERENTIALLY EXPRESSED ALTERNATIVE SPLICING TRANSCRIPT VARIANTS IN MPM USING NEXT GENERATION TRANSCRIPTOME SEQUENCING *Lingsheng Dong*	Oral presentation	118
8.30	MICRORNA ALTERATIONS IN MALIGNANT PLEURAL MESOTHELIOMA AS BIOMARKERS OF DISEASE *Brock Christensen*	Oral presentation	119
8.40	CELL SURFACE PROTEOMICS REVEALS NEW PROTEIN MARKERS FOR THE DISCRIMINATION OF MPM FROM LUNG ADENOCARCINOMA *Annemarie Ziegler*	Poster discussion	120
8.45	GENOME-WIDE PROFILE OF MESOTHELIOMA VERSUS PARIETAL PLEURA MAY EXPLAIN ITS CHEMO- AND RADIO-RESISTANCE AND INDICATE NEW TARGETS *Oluf Dimitri Røe*	Poster discussion	121
8.50	REDOX REGULATION OF FOXM1 IN MESOTHELIOMA *Nicholas Heintz*	Poster discussion	122
8.55	DISCUSSION		
9.10	IDENTIFICATION OF DNA METHYLATION MARKERS FOR MESOTHELIOMA *Janice Galler*	Oral presentation	123
9.20	ARGININOSUCCINATE SYNTHETASE EXPRESSION AND SURVIVAL OUTCOME IN PATIENTS WITH MALIGNANT MESOTHELIOMA: MOLECULAR ANALYSIS AND THERAPEUTIC IMPLICATIONS *Barbara Delage*	Oral presentation	124
9.30	CHROMOSOME XQ27 HARBORS A MESOTHELIOMA SUSCEPTIBILITY LOCUS ASSOCIATED WITH PATIENT SURVIVAL. *Heather Nelson*	Oral presentation	125
9.40	ASSOCIATION STUDY OF THE XRCC1 GENE WITH ASBESTOS-RELATED MALIGNANT MESOTHELIOMA (MM) *Marta Betti*	Poster discussion	126
9.50	POOLED ANALYSIS OF NAT2 GENOTYPES AS RISK FACTORS FOR ASBESTOS-RELATED MALIGNANT MESOTHELIOMA *Marta Betti*	Poster discussion	127
10.00	POSTER DISCUSSION	Chairs	

MOLECULAR PATHOLOGY

CHAIRS: Luciano Mutti and Sakari Knuutila

TIME	TITLE ABSTRACT	TYPE	abstract number
10.50	DETECTION OF CIRCULATING TUMOR CELLS (CTCS) IN MALIGNANT PLEURAL MESOTHELIOMA (MPM) *Fumihiro Tanaka*	Poster discussion	128
10.55	CIRCULATING ENDOTHELIAL CELLS (CECS) IN THE DIAGNOSIS OF MALIGNANT PLEURAL MESOTHELIOMA *Fumihiro Tanaka*	Poster discussion	129
11.00	PROGNOSTIC MARKER FOR MALIGNANT PLEURAL MESOTHELIOMA *Alexandra Schramm*	Poster discussion	130
11.05	THE ROLE OF PLEURAL EFFUSION CYTOLOGY IN THE DIAGNOSIS OF MALIGNANT MESOTHELIOMA IN 2008 *Françoise Galateau-Salle*.	Oral presentation	131
11.20	ROLE OF THE MESOTHELIN-CA125 INTERACTION IN MESOTHELIOMA *Mitchell Ho*	Oral presentation	132
11.35	A NOVEL MECHANISM OF LATE GENE SILENCING DRIVES SV40 TRANSFORMATION OF HUMAN MESOTHELIAL CELLS *Michele Carbone*	Oral presentation	133
11.50	IDENTIFICATION OF CELLS WITH STEM CELL/SELF RENEWAL PROPERTIES INMPM. *Emanuela Felly-Bosco*	Oral presentation	134
12.00	THE SV40 LARGE T ANTIGEN-P53 COMPLEXES BIND AND ACTIVATE THE IGF-1 PROMOTER STIMULATING CELL GROWTH *Maurizio Bocchetta*	Poster discussion	135
12.05	INCREASED uPAR EXPRESSION AND VIRULENCE OF REN HUMAN MPM CELLS. *Torry Tucker*	Poster discussion	136
12.10	MECHANISM OF ANOIKIS RESISTANCE IN MESOTHELIOMA CELLS. *Julien Daubriac*	Poster discussion	137
12.15	GENOMIC AND FUNCTIONAL PROFILING OF MALIGNANT MESOTHELIOMA *Sakari Knuutila*	Chair person	138
12.30	NOVEL MOLECULAR THERAPEUTICAL TARGETS FOR MESOTHELIOMA *Giovanni Gaudino*	Invited speaker	139

abstract number **TITEL – *presenter***

160. VALPROATE SYNERGIZES WITH CISPLATIN AND PEMETREXED TO INDUCE APOPTOSIS IN MALIGNANT PLEURAL MESOTHELIOMA CELLS
Fabian Vandermeers

161. INHIBITION OF TRANSLESION SYNTHESIS SENSITIZES MALIGNANT PLEURAL MESOTHELIOMA CELLS TO CISPLATIN TREATMENT
Philip Alexander Knobel

162. MULTIMODALITY TREATMENT VERSUS CHEMOTHERAPY IN MALIGNANT PLEURAL MESOTHELIOMA.
Guntulu Ak

163. RE-TREATMENT WITH PEMETREXED-BASED CHEMOTHERAPY IN PATIENTS WITH MALIGNANT PLEURAL MESOTHELIOMA (MPM): AN OBSERVATIONAL STUDY.
Fabio De Vincenzo

164. IMAGING FINDINGS OF MALIGNANT PLEURAL MESOTHELIOMA IN JAPAN.
Katsuya Kato

165. LOCALIZED MALIGNANT MESOTHELIOMA. 2 NEW CASES.
Alicia Morresi-Hauf

166. 18FDG PET: A NEW PREDICTIVE AND PROGNOSTIC TOOL IN PATIENTS WITH MALIGNANT PLEURAL MESOTHELIOMA.
Arnaud Scherpereel

167. THORACOSCOPY USING NARROW BAND IMAGING (NBI) AND AUTOFLURORESCENCE IMAGING (AFI) SYSTEMS IS A NOVEL MODALITY FOR THE DETECTION OF EARLY MESOTHELIOMA.
Takashi Nakano

168. A PROGNOSTIC INDEX FOR PREOPERATIVE EVALUATION OF PATIENTS WITH RESECTABLE EPITHELIAL MESOTHELIOMA.
William Richards

169. EFFECT OF AURORA KINASE INHIBITION IN MESOTHELIOMA CELL LINES.
Shigeki Shimizu

170. ENZASTAURIN, A PROTEIN KINASE C BETA (PKCβ) INHIBITOR IN MALIGNANT PLEURAL MESOTHELIOMA.
Leonardo Faoro

171. EXTRAPLEURAL PNEUMONECTOMY WITH ADJUVANT CHEMO-RADIOTHERAPY FOR TREATMENT OF MALIGNANT PLEURAL MESOTHELIOMA.
Abdel Rahman

172. TRIMODAL INITIAL VIDEOTHORACOSCOPY, INTRAPLEURAL CHEMOTHERAPY AND P-32 RADIATION FOR LUNG-SPARING TREATMENT OF PLEURAL MESOTHELIOMA: THE COLUMBIA PROTOCOL.
Robert Taub

173. IMPROVED SAFETY WITH EXTRAPLEURAL PNEUMONECTOMY IN MALIGNANT PLEURAL MESOTHELIOMA PERFORMED AT HIGH-VOLUME HOSPITAL WITH HIGH-VOLUME SURGEONS.
Jesper Bohsen Ravn

174. PROGNOSTIC FACTORS ACCORDING TO TREATMENT SCHEDULE IN MALIGNANT PLEURAL MESOTHELIOMA.
Guntulu Ak

175. INDUCTION CHEMOTHERAPY CONSISTING OF PEMETREXED PLUS CISPLATIN FOLLOWED BY EXTRAPLEURAL PNEUMONECTOMY FOR MALIGNANT PLEURAL MESOTHELIOMA.
Kazuya Fukuoka

176. MALIGNANT MESOTHELIOMA OF THE PLEURA IN THE PROVINCE OF TRIESTE, ITALY, 2001-2007.
Claudio Bianchi

177. GEOGRAPHY OF MESOTHELIOMA. RELIABLE DATA?
Claudio Bianchi

178. CLINICAL INVESTIGATION OF MALIGNANT PLEURAL MESOTHELIOMA: A NATIONWIDE SURVEY OF 502 DEATH CASES IN JAPAN.
Kenichi Gemba

179. IMMUNOHISTOCHEMISTRY IN DISTINGUISHING MALIGNANT MESOTHELIOMA FROM LUNG ADENOCARCINOMA: COMPARISON OF NEW MESOTHELIAL AND LUNG ADENOCARCINOMA MARKERS AND CONVENTIONAL MARKERS IN MALIGNANT MESOTHELIOMA.
Yasufumi Kato

180. CAVEOLIN-1 IS A NOVEL IMMUNOHISTOCHEMICAL MARKER OF MALIGNANT MESOTHELIOMA AND DIFFERENTIATES EPITHELIOID MESOTHELIOMA FROM LUNG ADENOCARCINOMA.
Vishwa Jeet Amatya

181. IMPACT OF OESTROGEN RECEPTOR BETA ON PROGNOSIS OF HUMAN MALIGNANT PLEURAL MESOTHELIOMA.
Giulia Pinton

182. MESOTHELIOMA PREVENTION BY AN ANTIOXIDANT FOOD SUPPORTS AN INVOLVEMENT OF REACTIVE OXYGEN SPECIES IN ASBESTOS CARCINOGENESIS.
Shuichi Adachi

183. ASBESTOS-INDUCED MURINE MESOTHELIOMA IN DIFFERENT GENETIC BACKGROUND.
Annie Renier

184. C. ELEGANS AS A MODEL SYSTEM TO EVALUATE GENETIC ALTERATIONS IN MPM, AND THE GENETIC-ENVIRONMENTAL INTERACTIONS/EFFECTS OF ASBESTOS.
Sivakumar Loganathan

185. IDENTIFICATION OF GENES RELEVANT FOR THE DEVELOPMENT OF MURINE MALIGNANT MESOTHELIOMA.
Erwin van Montfort

186. DIETARY VITAMIN A OR E SUPPLEMENTATION DOES NOT ALTER THE RATE OF DEVELOPMENT OF ASBESTOS INDUCED TUMORS IN AN ACCELERATED MODEL OF MESOTHELIOMA.
Cleo Robinson

187. ADENOVIRUS-MEDIATED NK4 GENE THERAPY FOR MALIGNANT MESOTHELIOMA.
Li Xiao

188. MEASLES VIRUS INDUCES ONCOLYSIS OF MESOTHELIOMA CELLS AND ALLOWS DENDRITIC CELLS TO CROSS-PRIME TUMOR-SPECIFIC CD8 RESPONSE.
Anne Gauvrit

189. CHEMOIMMUNOTHERAPY IN MESOTHELIOMA
Anna Nowak

190. MALIGNANT MESOTHELIOMA IN JAPAN IN RELATIONSHIP TO ASBESTOS EXPOSURE.
Takumi Kishimoto

191. TOTAL ANTIOXIDANT CAPACITY IN ASBESTOS-RELATED DISEASES IN PEOPLE EXPOSED TO CROCIDOLITE IN WITTENOOM.
Alfonso Helman

192. ASBESTOS FIBER CONCENTRATION IN LUNG TISSUES RESECTED FOR MALIGNANT PLEURAL MESOTHELIOMA.
Noriyasu Usami

193. CLINICAL OUTCOME, LUNG ASBESTOS BURDEN, AND DISEASE ARE PREDICTED BY EPIGENETIC PROFILES IN PLEURAL MESOTHELIOMA.
Brock Christensen

194. AN ANATOMO-PATHOLOGICAL STUDY OF SPONTANEOUS MALIGNANT MESOTELIOMA (MM) IN DOMESTIC ANIMALS. ITS POSSIBLE USEFULNESS IN ENVIRONMENTAL MONITORING FOR THE PROTECTION OF HUMAN HEALTH IN ASBESTOS-POLLUTED.
Narciso Mariani

195. HIGH PREVALENCE OF ASBESTOSIS ASSOCIATED WITH OCCUPATIONAL ASBESTOS EXPOSURE IN WESTERN AUSTRALIA.
Svein van Oyen

196. PANEL OF TUMOR MARKERS FOR THE DIAGNOSIS OF MALIGNANT PLEURAL MESOTHELIOMA.
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ABSTRACTS

Number: 1

Abstract title:
International mortality trends

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Keywords:
UK, Australia, mesothelioma, amosite, case-control

Abstract content:

By 1970 the UK had stopped using crocidolite and led the world in asbestos regulation, yet it now has over 2,000 mesothelioma deaths per year, the highest rate in the world and five times that in the US in men born between 1940 and 1955.
We conducted the first UK population-based study of mesothelioma and the largest worldwide, interviewing 612 mesothelioma patients and 1420 controls. We also compared death-rates, asbestos imports and male:female mortality ratios of mesothelioma in other countries to assess the contribution of different asbestos types on mesothelioma rates and to estimate the background rate in the absence of asbestos use.
Our main conclusion is that end-user exposure to amosite was a major cause of the extraordinary mesothelioma rate in British men born in the 1940s. The UK was the main importer of amosite, which carried the same control limit as chrysotile until 1983. Current mesothelioma mortality and historical patterns of amosite use in Australia are similar to those in the UK.
Other findings include: (1) about 1 in 17 of British carpenters and 1 in 50 of plumbers, electricians and painters born between 1940 and 1950 will die of mesothelioma; (2) only about 1% of mesotheliomas were caused by work in asbestos factories; (3) there appears to be a worldwide background rate unrelated to asbestos producing a lifetime risk of approximately 1 per 5,000 in both sexes; (4) the excess rate above this background in women throughout the world is approximately one tenth of the male rate; and (5) the lifetime risk in British men and women who report no potential asbestos exposure is four times this background (almost 1 per 1,000), suggesting that mesotheliomas were caused by unsuspected asbestos exposure in a wide range of occupational and non-occupational settings.

Number: 3

Abstract title:
Mesothelioma mouse models: ready for testing intervention strategies?

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Abstract content:

Malignant Mesothelioma (MM) is a devastating disease with poor prognosis due to its refractoriness to chemotherapy. Therefore, there is an urgent need for model systems that closely mimic human malignant mesothelioma in which new therapeutic interventions can be explored. We have generated mouse models that fulfill this requirement by the (conditional) inactivation of conbination of genes acting in pathways that are also frequently disrupted in human mesothelioma. These include the Nf2 tumor suppressor gene, p19Arf and Ink4a/b. The latter 2 act in the Rb and p53 pathway, respectively. We have generated single and compound (conditional) knockouts of these genes in the mesothelial lining of the thoracic cavity of mice by infection with adeno-Cre viruses and monitored the development of mesotheliomas. Murine MM developed in a very high percentage of compound Nf2F/F;p53F/F, Nf2F/F;Ink4aArfF/F and Ink4a;Ink4b;p19Arf mutant mice with a relatively short latency period, whereas single knockouts were refractory to mesothelioma development. Loss of Ink4a in combination with loss of Nf2 and p53 resulted in overall more invasive tumors suggesting that besides loss of Nf2 also loss of Ink4a might augment invasive disease. We have derived cell lines and established conditions in which these models can be efficiently used for testing intervention strategies using cytotoxic drugs and targeted therapies. In spite of the genetic uniformity of these models, tumor cell lines showed a significant variation in response to the various drugs. The utility of these models for designing new intervention studies will be discussed.

Number: 5

Abstract title:
India's Asbestos Time Bomb

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Keywords:
India, asbestos, illness, politics, ban

Abstract content:

India's Asbestos Time Bomb

"Historically the burden of industrial pollution has reached the developing world much faster than the fruits of industrial growth," writes Dr. Sanjay Chaturvedi. This statement is well illustrated by the evolution of the asbestos industry in India. In the frantic rush for economic development, there has been a pervasive lack of concern for the health of workers and the contamination of the environment. Sacrificing the lives of the few for the "good" of the many, the Indian Government has knowingly colluded in this sad state of affairs.

\"It cannot be disputed that no development is possible without some adverse effect on the ecology and environment … The comparative hardships have to be balanced and the convenience and benefit to a larger section of the people has to get primacy over comparatively lesser hardship.\"

Cumulative asbestos consumption in India between 1960-2008 was in excess of 7 million tonnes. As there is no safe level of exposure to asbestos and as even minimal precautions have been lacking, phenomenal numbers of workers have received hazardous exposures. In India, neither mesothelioma nor asbestos-related lung cancer are recognized. Although there are some regional cancer registries, cancer is not a notifiable disease in India; a grand total of 56 mesotheliomas were recorded during 1993-1997. National and state governments in India maintain a stony silence on the collateral damage caused by the widespread use of asbestos; virtually nothing has been done to quantify the effects of environmental pollution in the wider community.

This paper will explore the state of India's asbestos markets, the political favouritism the industry enjoys, the consequences of hazardous exposure to workers, the public and the environment and the attempts by grass-roots activists to support the asbestos-injured and impact on the national asbestos debate.

Number: 6

Abstract title:
Guidelines for the management of Malignant Pleural Mesothelioma from the 2007-2008 ERS/ESTS Taskforce

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Keywords:
mesothelioma, guidelines, management, european, taskforce

Abstract content:

Previously considered as a rare tumor with a poor survival, malignant pleural mesothelioma (MPM) has become a very important public health issue. MPM incidence is expected to continue to increase for at least the next ten years, linked to previous asbestos exposure, the main etiologic factor of MPM. Between September 2007 and June 2008, the European Respiratory Society (ERS) and the European Society of Thoracic Surgeons (ESTS) brought together experts on mesothelioma to draw up recommendations in order to provide clinicians with clear, concise, up-to-date guidelines on management of MPM.
To obtain an earlier and reliable diagnosis of MPM is a crucial issue. We recommend, except in case of preoperative contraindication or pleural symphysis, to perform thoracoscopy for the diagnosis of MPM. Standard staining procedures in Pathology are insufficient in 7-15% of cases. Therefore we propose a set of other staining methods and immunological markers and prefer multiple histological biopsies. Staging: in the absence of a uniform, robust and validated staging system, we advice to use of the most recent TNM based classification, and we propose a three steps pre-treatment assessment. Monitoring: Performance status of the patient and histopathological subtype are currently the only prognostic factors of clinical importance in management of MPM. Other potential prognostic parameters should be recorded at baseline and reported in clinical trials. Treatment: MPM exhibits a high resistance to chemotherapy; and only few patients are candidate for radical surgery. New therapeutic tools or strategies such as targeted therapies, gene or cell therapies, and multimodal treatment have been reviewed and commented. Because of limited data available on the best combination treatment, we emphasize that patients who are considered candidates for a multimodal approach should be included in a prospective trial in specialized centers. The highlights of the ERS/ESTS guidelines will be presented during the meeting.

Number: 8

Abstract title:
In Vitro Extreme Chemotherapy Resistance Assay Confirms Utility of Cisplatin in the Treatment of Malignant Pleural Mesothelioma

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Keywords:
Extreme Drug Resistance, Chemotherapy, cisplatin, chemoresistance

Abstract content:

Objective: In clinical trials, cisplatin has been shown to be the most effective singe agent chemotherapy agent in the treatment of malignant pleural mesothelioma (MPM). The incidence of in vitro drug resistance to cisplatin, gemcitabine, or vinorelbine in tumors in patients with MPM was prospectively evaluated.
Methods: Extreme Drug Resistance Assays (EDR®-Assay, Oncotech, Tustin, California) were performed on specimens from 126 patients from January 2006 until May 2008. Fresh tumor specimens in transport solution were couriered overnight to the Oncotech laboratories in Tustin, California. Tumor cells were plated on agar dishes and specific chemotherapeutic agents added. Tritiated thymidine was used to measure cell proliferation. Treated cells were compared to untreated controls. Assay results are divided into three categories. Extreme drug resistance is defined as tumor cell growth greater than one standard deviation above the median. Intermediate drug resistance is defined as tumor cell growth above the median but less than one standard deviation. Low drug resistance is defined as tumor cell growth less than the median. Drug resistance to cisplatin, gemcitabine, and vinorelbine was characterized.
Results: The EDR®-Assay was performed on 126 MPM tumor specimens from 85 extrapleural pneumonectomies, 27 pleurectomies, 11 thoracotomies, and 3 chest wall resections. Seventy eight (62%) were epitheliod type and 30 (24%) had received chemotherapy prior to the assay. Assay results were available for 105 specimens (83%); 21 had no assay result due to insufficient tumor growth. EDR to cisplatin was found in 11%, gemcitabine in 18% and navelbine 30%. IDR to cisplatin was found in 17%, gemcitabine in 15% and navelbine in 31%. LDR to cisplatin was found in 72%, gemcitabine in 66% and navelbine in 38%. In those patients who had received chemotherapy, incidence of EDR to cisplatin was 22% versus 8% in those patients who had not.
Conclusions: An in vitro assessment of tumor chemoresistance can be performed on a majority of mesothelioma tumor specimens. Cisplatin had the lowest incidence of EDR compared to gemcitabine and vinorelbine. Chemotherapy naïve patients also had a lower incidence of EDR to cisplatin. Correlation with survival will be required in order to validate the prognostic significance.

Number: 9

Abstract title:
Inhibition of translesion synthesis sensitizes malignant pleural mesothelioma cells to cisplatin treatment

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Keywords:
translesion synthesis, rev3, malignant pleural mesothelioma, siRNA, shRNA, cisplatin

Abstract content:

Background:
Malignant pleural mesothelioma (MPM) is most commonly treated with a multimodality therapy including treatment with cisplatin or cisplatin-analogues, which lead to the formation of inter- or intrastrand DNA adducts. Cisplatin adducts can be repaired or, if not repaired, induce replication fork stalling which can by overcome by specific translesion polymerases.
Translesion polymerase ζ consists of two subunits, Rev3 is the catalytic- and Rev7 the structural subunit. The translesion polymerase ζ is responsible for the translesion synthesis (TLS) of cisplatin based adducts and the repair of DNA interstrand crosslinks. Rev3 deficient vertebrate cell lines show the highest sensitivity to cisplatin compared to other repair-deficient cell lines. Rev3 inhibition by antisense treatment confers higher cisplatin sensitivity and lower mutagenicity in immortal human fibroblasts.
Working hypothesis:
Down-regulation of Rev 3 sensitizes MPM cells to cisplatin treatment and reduces the formation of cisplatin resistance.
Results:
We showed that the expression of Rev3 in human MPM cells is dependent on cell culture confluency and is also affected by cisplatin treatment in a time-dependent manner. Functional inhibition of REV3 by siRNA increased replication fork breakdown as indicated by enhanced H2AX phosphorylation. REV3 expression in rat and human MPM cells was successfully inhibited by transient transfection with plasmids containing short hairpin constructs targeting REV3.
We generated stable HEK293 and human lung fibroblast (Wi38-SV40) cell lines with decreased REV3 expression. Functional inhibition of REV3 in the HEK293 and Wi38-SV40 cell lines resulted in increased genotoxic stress as indicated by increased p53 expression, a slower growth rate and increased cisplatin sensitivity.
Conclusions:
We showed that functional inhibition of translesion polymerase ζ by shRNA against REV3 increased replicative stress in MPM cell lines and increased cisplatin sensitivity in human cells.

Number: 10

Abstract title:
NGR-hTNF, a novel vascular targeting agent (VTA), as second-line therapy in malignant pleural mesothelioma (MPM): Preliminary results of a multicenter phase II trial.

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Keywords:
NGR-hTNF, Vascular Targeting Agent, Second-line therapy

Abstract content:

Background: NGR-hTNF is a VTA exploiting a tumor-homing peptide (NGR) that selectively binds to aminopeptidase N/CD13 highly expressed on tumor blood vessels. NGR-hTNF combines activity on tumour vascular permeability and direct anticancer activity.
Methods: Patients (pts) with advanced MPM were treated with low-dose NGR-hTNF given at 0.8 µg/sqm as 1-hour intravenous infusion every 3 weeks (q3w). This dose was previously selected in a phase I trial based on dynamic imaging changes and preliminary clinical activity. The trial had a 2-stage design with 16 and 27 pts to be enrolled. Progression-free survival (PFS) was the primary endpoint with restaging performed q6w according to MPM-modified RECIST criteria.
Results: From May 2007 to January 2008, forty-three pts with documented progressive disease after pemetrexed/platinum-based regimens were enrolled. Globally, 41 pts received 151 cycles (median, 2; range, 1-16). Pts characteristics were: median age 64 years (range, 34-80); M/F 27/14; histology epithelial/non-epithelial (E/NE) 32/9; PS 0/1/2 24/10/7; EORTC prognostic score (EPS) good/poor 32/9. To date, 5 pts (12%) remain on treatment (range, 4.6 to 11.7 months). 18 pts (44%; 95% CI, 30-59%) had stable disease (SD) as best response. Median and 3-month PFS were 2.8 months (95% CI, 2.0-3.6) and 43% (95% CI, 26-59%), respectively. In an exploratory analysis, there were no differences in PFS between pts with good/poor EPS, E/NE histology, PS 0-1/2 and age </≥70 years. For pts achieving SD at their first restaging (n=18), the median and 6-month PFS were 5 months and 44%, respectively. PFS durations of 11.7 and 9.5 months were observed in a 70-year-old male pt with PS 2 and in a chemo-refractory male pt with biphasic histology, respectively. With a median follow-up of 6.1 months (95% CI, 5.3-6.8), 31 pts (76%) are still alive. Neither grade 4 treatment-related adverse events nor toxicity-related death were observed. Most common grade 1-2 toxicities per patient were transient infusion-related symptoms, including chills (63%) and fatigue (24%). Currently, an additional cohort of 12 pts is treated with a weekly schedule.
Conclusion: NGR-hTNF is well tolerated and shows evidence of disease control in chemo-pretreated MPM patients. The drug will be further developed in advanced MPM.

Number: 11

Abstract title:
PHASE II STUDY OF THE COMBINATION OF BEVACIZUMAB PLUS PEMETREXED AND CARBOPLATIN AS FIRST-LINE THERAPY IN PATIENTS WITH MALIGNANT PLEURAL MESOTHELIOMA (MPM)

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Keywords:
chemotherapy, bevacizumab, pemetrexed, carboplatin

Abstract content:

Background: The combination of pemetrexed and carboplatin was found to be active and well tolerated in MPM patients (pts) in phase II trials. Vascular endothelial growth factor (VEGF) is highly expressed in MPM; in pre-clinical models, anti-VEGF antibodies were shown to decrease MPM cells growth. The humanized anti-VEGF monoclonal antibody bevacizumab has shown a synergistic effect when combined with a number of chemotherapeutics. Aim of this trial is to assess the activity of bevacizumab in combination with pemetrexed and carboplatin (BPC regimen) as first-line therapy in MPM pts.
Patients and Methods: Chemotherapy-naive pts with measurable disease and adequate organ function, not candidates for curative surgery, are eligible to receive pemetrexed 500 mg/m2 and carboplatin area under the plasma concentration-time curve of 5 mg/mL/min, followed by bevacizumab 15 mg/Kg, administered intravenously every 21 days. All patients receive folic acid and vitamin B12 supplementation. Main endpoint of the study is time to disease progression. Response is evaluated according to modified RECIST criteria.
Results: This ongoing, multicenter, open label phase II study was designed to include up to 77 pts. Until May 2008, 19 pts have been enrolled, and data of 16 are available for a preliminary analysis. Pts characteristics are: M/F 11/5, median age 68 yrs (range 47-77), EORTC prognostic score good/poor 5/11.Histology was epithelial in all pts. A partial response was achieved in 6 patients, for a response rate of 37.5%. Ten patients had stable disease. With a median follow-up of 6 months (range 1-8 months) 6 pts had disease progression; the others are still on treatment. No severe hematological or non-hematological toxicity was observed, except for one case of bowel perforation possibly related to treatment. A mild, asymptomatic proteinuria was observed in 6 pts. Grade 2 anemia and fatigue were registered in 3 and 4 pts, respectively.
Conclusion: First-line treatment with BPC regimen in MPM pts seems feasible, with acceptable toxicity. Bevacizumab-related adverse effects should be strictly monitored. In spite of the limited number of enrolled pts and the short follow-up time, preliminary activity results are promising. The study is ongoing and updated results will be presented at this meeting.

Number: 14

Abstract title:

Hyperthermia and radiotherapy in malignant pleural mesothelioma: rationale, technique and clinical results.

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Symptomatic recurrences of malignant mesothelioma are often painful and could cause mechanical obstruction. Although for intervention site recurrences radiotherapy (RT) is the most effective treatment, both objective and subjective response rates are disappointing. In an attempt to improve the results of radiotherapy, we explored the combination of radiotherapy and hyperthermia (HT) in these patients. HT, an increase in tissue temperature to 40-45°C for some time has a tumour specific cell killing effect complementary to that of RT, and is a strong radiosensitiser. Tissue heating can be achieved by microwave radiation.

The outcome in 18 patients treated by RT in combination with HT was compared to that in a historical control group of 24 patients treated with RT alone. The results are shown in the table. All patients presented with a painful chest-wall tumour, had a performance status of ECOG ≤ 2, and were treated with a 4 Gy per fraction scheme, 3 fractions weekly, tot a total dose of median 40 Gy. HT was applied once weekly during the period of RT. The relatively large number of patients with unknown outcome reflects the poor short-term survival of this patient population.

	RT + HT	RT alone
Reduction in pain		
Yes	15	13
None	1	9
Unknown	2	2
Recurrence of pain (in responders)		
None	1	0
Within RT field	3	8
Outside RT field	7	1
Unknown	4	4

Tumour response		
Complete response	4	2
Partial response (>50%)	13	5
No change	0	3
Progressive disease	0	3
Unknown	1	11
Tumour progression (after initial response)		
Within RT field	1	8
Outside RT field	12	2
Unknown	5	14

No patient developed >grade 2 toxicity (RTOG/EORTC radiation morbidity score). The comparison suggests that the addition of HT improved pain control (94 vs 59%) and objective tumour response (100 vs 54%). Further the occurrence of subjective (pain) or objective (tumour) progression within the RT field was less frequent in the combined-modality group.

In our institute, the combination of RT and HT is therefore offered as palliative treatment to those patients in a relatively good condition with a symptomatic recurrence at an intervention site.

Number: 16

Abstract title:
EXTRAPLEURAL PNEUMONECTOMY (EPP) AND HEMITHORACIC RADIATION THERAPY (RT) FOR MALIGNANT PLEURAL MESOTHELIOMA (MPM)

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Keywords:
hemithoracic radiotherapy

Abstract content:

Purpose: The treatment of MPM remains a therapeutic challenge. Even after resection with EPP there is a large risk of tumor recurrence. We have therefore treated patients with post-operative hemithoracic RT in an effort to improve local control. The purpose of this study is to evaluate the effectiveness of EPP and RT for the treatment of MPM.
Methods: Between 1994 and 2006, 89 patients with MPM were treated with EPP followed by hemithoracic radiation therapy. EPP was defined as en bloc resection of the entire pleura, lung, and diaphragm, with or without resection of the pericardium. The radiation therapy target volume was the entire hemithorax, including the pleural folds and the thoracotomy and chest tube incision sites.
Results: A total of 89 patients underwent RT after EPP. Patient characteristics were: age (median 61 years), sex (male 74%), laterality (right-sided disease 52%), histology (epithelial in 71% and mixed or sarcomatoid 29%), stage (I: 7%, II:35%, III:55%, IV: 3%). Median dose was 5400 cGy (range 2160 cGy – 5400 cGy). The median follow-up was 13 months (range, 0-99) and 28 months in survivors (range, 2-99 months). The median overall survival was 17.4 months. The 2-year and 5-year overall survival was 36% and 14% respectively. The 2-year and 5-year local control was 59% and 41% respectively. On multi-variate analysis only total dose was significant for improvement in local control (p=0.004). Grade 2 or worse toxicity was: esophagitis (25%), pneumonitis (8%), dyspnea (22%), arrythmia (2%), pericarditis (1%), nausea (44%), vomiting (28%), fatigue (47%).
Conclusions: Extrapleural pneumonectomy followed by hemithoracic radiation therapy is tolerable and has favorable survival and local control in this aggressive disease. Higher doses of radiation therapy appear to improve local control

Number: 17

Abstract title:
Pleural Intensity Modulated Radiation Therapy in Patients with Malignant Pleural Mesothlioma

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Keywords:
radiation therapy, IMRT, unrectable

Abstract content:

Purpose: In patients with malignant pleural mesothelioma (MPM) who are unable to undergo a pneumonectomy, it is difficult to deliver tumoricidal doses to the pleura without significant toxicity. We have implemented a technique of using intensity-modulated radiotherapy (IMRT) to treat these patients. This report assesses the feasibility and toxicity of treating patients with MPM using pleural IMRT in patients who have not had a pneumonectomy.
Methods and Materials: Between 2005 and 2008, 18 patients with MPM were treated with pleural IMRT to the hemithorax without pneumonectomy (median dose: 50.4 Gy, range: 45-50.4 Gy) at Memorial Sloan-Kettering Cancer Center.
Results: Patient characteristics were: right sided (61%), histology (epithelial – 72%, sarcomatoid – 11%, mixed – 16%), stage (I – 11%, II – 33%, III – 22%, IV – 33%). Fifteen patients (83%) received induction chemotherapy (mostly cisplatin and pemetrexed). Surgery was: pleurectomy/decortication – 8 patients (44%), pleurectomy alone – 2 patients (11%), unresectable – 8 patients (44%). Of the 18 patients, there were 2 cases of acute grade 3 dyspnea requiring steroids or oxygen and 1 case of acute grade 3 fatigue. There were no cases of acute grade 4 or 5 toxicity. Of the 12 patients with adequate follow-up to assess late toxicity, there was one case of continuing grade 3 dyspnea. With a median follow-up of 9 months, the 1-year and 2-year overall survival rates were 92% and 52% respectively with a median overall survival of 25.7 months. There was no difference in survival between patients undergoing surgery (pleurectomy/decortication or pleurectomy only) versus patients with unresectable disease (p=0.56).
Conclusions: Treating the intact lung with pleural IMRT in patients with MPM is a safe and feasible treatment option to a dose of 50.4 Gy. We have initiated a phase II trial of induction chemotherapy with pemetrexed and cisplatin followed by pleural IMRT in patients with unresectable disease.

Number: 18

Abstract title:
Adjuvant hemithoracic radiotherapy following EPP for MPM improves local control

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Keywords:
mesothelioma; radiotherapy; extrapleural pneumonectomy; local control

Abstract content:

Objective: To examine the outcome of aggressive multimodality therapy for malignant pleural mesothelioma and the impact of adjuvant hemithoracic radiotherapy (RT) following extrapleural pneumonectomy (EPP).
Methods: We reviewed 50 consecutive patients undergoing extrapleural pneumonectomy for malignant pleural mesothelioma in our institution between January 1993 and March 2005. EPP consisted of en bloc removal of the parietal pleura and lung with excision of the ipsilateral hemidiaphragm and pericardium. Induction chemotherapy, if given, consisted of 2 to 3 cycles of platinum-based regimens. Adjuvant hemithoracic RT was given to 29 patients and consisted of 50-54 Gy in 25-30 fractions.
Results: The median survival was 11 months, with a 3-year survival of 24%. Patient sex, histologic cell type, stage, and N2 disease had significant impacts on survival according to univariate analysis. In a multivariate analysis, however, only the presence of N2 disease remained a significant predictor of mortality. The presence of N2 disease had no impact on the site of recurrence. Adjuvant hemithoracic RT significantly decreased the risk of locoregional recurrence to 7% (2/29) (P=0.01) but did not influence survival. Patients managed with EPP without RT had a locoregional failure rate of 38% (8/21).
Conclusions: Aggressive tri-modality therapy is feasible in selected patient with malignant pleural mesothelioma. Adjuvant hemithoracic RT appears to significantly reduce the risk of locoregional recurrence. However, better systemic therapies are needed.

Number: 19

Abstract title:
Pulmonary Toxicity following Intensity-Modulated Radiotherapy (IMRT) after Extrapleural Pneumonectomy for Malignant Pleural Mesothelioma

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Keywords:
pneumonitis, IMRT, extrapleural pneumonectomy, dose constraints

Abstract content:

Introduction: The introduction of trimodality treatment combining chemotherapy, surgery, and radiotherapy has improved the prognosis for patients with malignant pleural mesothelioma (MPM). Several studies have indicated a radiation dose-response relationship, and IMRT has allowed for an increase in dose to the pleural cavity as well as a reduction in radiation doses to organs at risk. Even with IMRT, unexpected fatal pulmonary toxicity has been reported. The present study reports the incidence of fatal pulmonary toxicity in patients treated at Rigshospitalet, Copenhagen, and identifies lung dose parameters of importance for establishment of appropriate lung dose constraints for future radiotherapy planning.
Results: Twenty-six patients with stage T1-3N0M0 MPM were included from April 2003 to April 2006. Induction chemotherapy with three courses of platinum-based combination chemotherapy was administered preoperatively at the local oncology departments. Extrapleural pneumonectomy was subsequently performed and followed by IMRT at Rigshospitalet, Copenhagen. The entire pre-operative pleural surface area was treated to 50 Gy and areas with suspected residual disease or close surgical margins was treated to 60 Gy in 30 fractions. Organs at risk were contoured and the IMRT plans were calculated using CadPlan (Helios) or Eclipse/Aria.
The main toxicities were nausea, vomiting, esophagitis, dyspnea, and thrombocytopenia. Five out of 26 patients developed fatal toxicity. One patient died from an intracranial hemorrhage during severe thrombocytopenia. Four patients (15%) experienced grade 5 lung toxicity, i.e. pneumonitis with a radiographic diffuse interstitial infiltrate 19-40 days after completion of radiotherapy. Patients with pneumonitis had a significantly higher V10 (median: 60.3%, range 56.4%-83.2%) compared to patients without pneumonitis (median: 53.1%, range: 25.6%-83.2%) (p=0.02). Mean lung dose (MLD) was also significantly higher in patients who developed pneumonitis (median 13.9 Gy, range: 13.6-14.2 Gy) than in patients who did not (median = 12.4 Gy, range: 8.4 Gy-15.4 Gy) (p=0.04).
Conclusions: Significant differences in MLD and V10 for patients with fatal pulmonary toxicity compared to patients without fatal lung toxicity have been demonstrated. Based on the presented data we have modified our lung dose constraints in order to avoid unacceptable toxicity.

Number: 20

Abstract title:
INTENSITY-MODULATED RT (IMRT) AFTER EXTRAPLEURAL PNEUMONECTOMY (EPP) IN PATIENTS WITH MALIGNANT PLEURAL MESOTHELIOMA (MPM): DOES NODAL STATUS MAKE THE DIFFERENCE?

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Keywords:
radiotherapy, IMRT, extrapleural pneumonectomy, nodal status

Abstract content:

INTRODUCTION: Hemithoracic RT has been used after EPP to reduce the local recurrence rate. IMRT allows for significant improvements in dose delivery, but can increase radiation dose to contralateral lung. Aim of this dosimetric study was to compare target coverage and normal tissue sparing achieved with standard 3D conformal technique (3DCRT) and IMRT in MPM patients (pts) after EPP. Pts were analysed according to disease side and nodal status after surgery.
MATERIALS AND METHODS: Fifteen pts were included: 7 with left-sided and 8 with right-sided disease; 6 with pN0 and 9 with pN1-2 at pathological examination. 3DCRT was planned to deliver a total dose of 54Gy/27 fractions to the planning target volume (PTV) with 3-5 orthogonal photon beams of 6-18MV. Dose calculation was performed by Eclipse (Varian) treatment planning system. IMRT was planned to the same dosage scheme. Seven to nine coplanar beams were used for each patient. Dose calculation and optimisation were done using an inverse treatment planning system (HELIOS, Eclipse, Varian). Dose-volume constraints included, for contralateral lung, a mean lung dose (MLD) <9.5Gy, a volume receiving ≥ 20Gy (V20) <11%, and a V5 <60%; for heart V45 <30% and V50 <20%. Finally, for liver mean liver dose (MLiD) was <31Gy and V30 <33%.
RESULTS: In all cases, with both techniques, PTV coverage was excellent, with an average of 95% for target dose. IMRT was more efficient in heart and liver sparing. In left-sided MPM, a reduction of about 65% was observed for heart V45 (from 72.70+/- 14.92% to 22.58+/-10.79%), while V50 was improved of about 75% (from 65.04+/-15.94% to 11.91+/-8.56%). In right-sided MPM, liver V30 was reduced of more than 50% (from 67.40+/-22.90% to 31.40+/-2.24%),and MLiD of about 40% (from 38.41+/-10.36 to 22.89+/-4.06 Gy). For contralateral lung, V20 and MLD were comparable for both techniques; V20 was 2.8+/-2.9% and 2.3+/-3.2% for 3DCRT and IMRT, while MLD was 4.7+/-2.0Gy and 7.0+/-1.5Gy respectively. Major differences between the two techniques were found for V5 where, due to fields entering in contralateral lung in IMRT, 3DCRT had better results (55.9 +/-14.1 vs 19.9 +/- 21.1%). However, in IMRT plans all pts with pN0 stage fully respected dose constraints for contralateral lung. V5 was 47.7 +/-5.1% in pN0 compared with 61.3 +/-12.4 % in pN1-2 pts. Regarding contralateral kidney, spleen and oesophagus both irradiation methods respected the dose.

ABSTRACTS

However, in IMRT plans all pts with pN0 stage fully respected dose constraints for contralateral lung. V5 was 47.7 +/-5.1% in pN0 compared with 61.3 +/-12.4 % in pN1-2 pts. Regarding contralateral kidney, spleen and oesophagus both irradiation methods respected the dose constraints.

CONCLUSIONS: Local control remains an important endpoint in MPM pts after EPP. Dose to contralateral lung is critical, with high risk of severe pulmonary toxicity. Data from our dosimetric study confirm that IMRT provides superior dose distribution in comparison to 3DCRT in pts without nodal involvement. In pts with pN1-2 disease, IMRT should be used with caution, and modified techniques with restricted fields should be considered.

Number: 21

Abstract title:
Targeting CD44 with hyaluronan for BNCT:A novel strategy for malignant pleural mesothelioma

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Keywords:
BNCT, Hyaluronan, CD44

Abstract content:

Boron Neutron Capture Therapy (BNCT) is the tumor selective radiotherapy with the alpha particles produced by BNC Reaction that is due to a nuclear reaction between 10B and thermal neutrons. It is necessary for effective BNCT to accumulate 10B atoms in the tumor cells, but not normal cells. As a prerequisite for selectiveness, tumor selectivity of 10B compounds is absolutely imperative. We focused CD44 for the targeting therapy of MPM, because large amounts of CD44 is expressed on the MPM cells. We developed Hyaluronan (HA) - 10B conjugate for the targeting of BNCT. We also used the hemagglutinating virus of Japan envelope (HVJ-E) as a vehicle of 10B, because it possesses the immediate cell fusion ability and can induce antitumor immune responses. However, the application of HVJ-E is restricted to the local administration because of the hemagglutination. So we developed the novel HVJ-E compounds with biocompatible polymer to alleviate the side effect of HVJ-E. Finally we examined basic characteristics and antitumor efficacy of the following compounds, Cationized-HA HVJ-E conjugate with Sodium Borocaptate (BSH), Cationized Gelatin(CG) HA HVJ-E with BSH, and CG HVJ-E with BSH. 1) At first, we examined the hemagglutination with the above HVJ-E compounds. The hemagglutination of HVJ-E was inhibited by CG HA and other HVJ-E compounds. The MTD of HVJ-e, CG HVJ-e, CG HA HVJ-e for normal mice was 1,500, 2,000, 2,500 HAU (hemagglutination unit), respectively. These results suggested Polymer HVJ-E compounds could alleviate the side effect of HVJ-E. 2) We examined the biding ability of novel compounds to the MPM cells. CG HA HVJ-E with luciferase showed significant higher gene expression to the MPM cells comparing with CG HVJ-E, but not to the tumor cells expressing little CD44. The same result was confirmed in the fluorescence microscopy assay with the fluoresecence labeled HVJ-E compounds. These results suggested CG HA HVJ-E showed high affinity and high gene expression to the MPM cells. 3) We examined the cytotoxicity of each BSH compound to the MPM cells with BNC Reaction after only 30 minutes Contactof each BSH compound, so CG HA HVJ-E BSH showed the strongest cytotoxicity comparing with various BSH compounds. The cytotoxicity of the CG HA HVJ-E BSH corresponds with that of BSH left in the well during the BNCR. 4) We examined the anti-tumor efficacy of each BSH compound injected into the pleural cavity of the MPM pleural dissemination mouse model. CG HVJ-E BSH showed the most effective anti-tumor efficacy comparing with various BSH compounds. These results suggest that the targeting CD44 with CG HA HVJ-E is the effective method for the BNCT of MPM.

Number: 22

Abstract title:
Boron Neutron Capture Therapy for Malignant Mesothelioma

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Keywords:
BNCT, CD44, Hyaluronan

Abstract content:

The therapy of MM is required the multidisciplinary treatment. In other words, each monotherapy is incomplete for MM. For example, radiotherapy is limited utility because the extensiveness of the tumor requires large fields and it is impossible to administer tumoricidal doses without injuring the adjacent lung and mediastinal organs. Boron Neutron Capture Therapy (BNCT) is the tumor selective radiotherapy with the alpha particles produced by a nuclear reaction between 10B and thermal neutrons. BNCT is expected to be a breakthrough strategy for MM, because it is suitable for the therapy of diffuse and invasive tumor without injuring the normal tissues. However, the success of BNCT depends on the selective delivery of 10B–atoms to tumor cells to supplement the attenuation of thermal neutron for deep lesions. We focused CD44 for the targeting therapy of MM, because a large amount of CD44 is expressed on the MM cells. We developed Hyaluronan (HA) - 10B conjugate for the targeting of BNCT. We also used the Hemagglutinating Virus of Japan Envelope (HVJ-E) as a vehicle of 10B, because it possesses the high cell-fusion ability of 10B and keep the high concentration of 10B in tumor cells. So we developed the novel HA and HVJ-E conjugate (CZ-HA-HVJ-E) incorporating BSH to diminish the side effect of HVJ-E. We examined the characteristics and antitumor efficacy of CZ-HA-HVJ-E compound for MM. 1) Binding ability and gene transfer efficiency of CZ-HA-HVJ-E to MM cells; CZ-HA-HVJ-E with Quantum Dot 655 or with luciferase gene showed significant higher fluorescence or higher transfection efficiency than HVJ-E, despite only 30 min Contactwith MM cells. Furthermore, these preferences to the MM cells were diminished by the CD44 neutralizing mAb. 2) Cytotoxicity of CZ-HA-HVJ-E BSH to MM cells with BNCR; CZ-HA-HVJ-E BSH showed the higher cytotoxicity than BSH by BNCR after only 30 minutes Contactof each BSH compound. 3) Anti-tumor efficacy of CZ-HA-HVJ-E BSH for MM pleural dissemination model; CZ-HA-HVJ-E BSH efficiently suppressed the local growth of MM cells in vivo with BNCR. These results suggest that the novel BNCT with CD44-targeted delivery of 10B is a potentially useful modality for MM.

Number: 23

Abstract title:
Assessing prognosis of malignant pleural mesothelioma (MPM) by incorporating FDG-PET parameters adds incremental value to prognostic models incorporating clinical information

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Keywords:
Prognostic models; FDG-PET; pleuradesis; tumor volume; imaging

Abstract content:

Background: MPM has a poor prognosis. Prognostic information can be important for individual patients and as a stratification factor in clinical trials. Since previous scoring systems were developed, FDG-PET scanning has become available. FDG-PET can quantify metabolic activity and tumor volume, although prior pleuradesis may make interpretation difficult. We prospectively assessed whether FDG-PET scanning added information to clinical prognostic variables with or without prior pleuradesis.
Methods: Participants were all consenting, newly-referred, untreated patients with a confirmed diagnosis of MPM at a single tertiary referral centre. Patients were not excluded by age or performance status (PS). The study was approved by the institutional Human Research Ethics Committee. All patients were assessed at baseline for clinical and laboratory prognostic factors. Patients underwent helical CT scan of thorax and abdomen, and a whole-body FDG-PET scan within 28 days of study enrolment, with imaging tests within 14 days of each other. A semi-automated region-growing algorithm derived the Total Glycolytic Volume (TGV), a composite of tumour volume and SUV/metabolic activity (Francis et al, J Nucl Med (48) 1449-58; 2007). Patients were treated as clinically indicated and followed up for survival.
Results: 97 patients were accrued from 2003 to 2006. 4 were not assessable as they did not have a PET scan, 3 were ineligible, and 2 were excluded from survival analyses due to prolonged time from diagnosis to study entry. Of eligible, assessable patients, 82% were male, 87% had a history of asbestos exposure, and 76% had epithelioid mesothelioma. Most patients were symptomatic, and most had an ECOG PS of 0-1 (84%). 29 of 92 patients had undergone pleuradesis before study enrolment. On univariate analysis, significant prognostic factors were: TGV on FDG-PET in non-pleuradesed patients ($p=0.004$), sarcomatoid subtype ($p<0.0001$), forced vital capacity as % predicted ($p=0.03$), weight loss ($p=0.04$), and EORTC "good' prognostic score ($p=0.03$). Baseline high TGV was more predictive of survival than the EORTC prognostic score both with ($p=0.0005$) and without ($p=0.0008$) inclusion of sarcomatoid subtypes in the model.
Conclusion: FDG-PET-derived parameters can add prognostic information to standard clinical variables, even when the strongest clinical prognostic factor, sarcomatoid histology, is excluded.

Number: 24

Abstract title:
EARLY RESPONSE EVALUATION IN MALIGNANT PLEURAL MESOTHELIOMA (MPM) BY TOTAL GLYCOLYTIC VOLUME (TGV) ANALYSIS OF SERIAL FDG-PET SCANS

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Keywords:
PET, response evaluation, chemotherapy

Abstract content:

Background: Response evaluation with conventional criteria based on computed tomography (CT) is challenging in MPM due to its diffuse pattern of growth. Preliminary reports have suggested that therapy-induced changes in tumor fluorodeoxyglucose (FDG) uptake as measured by positron emission tomography (PET) may predict patient (pt) outcome early in the course of treatment.
Patients and Methods: A retrospective volume-based analysis of FDG-PET uptake was performed in a previously reported series of MPM patients (Ceresoli et al, J Clin Oncol 2006) using a semiautomated 3D volume-based region-growing algorithm (Francis et al., J Nucl Med 2007). Pts were not candidates to curative surgery, and received chemotherapy with a pemetrexed-based regimen. They were evaluated by FDG-PET and CT at baseline and after two cycles of therapy. Total glycolytic volume (TGV) was obtained from each scan. Survival outcomes were measured and analyzed according to TGV changes after chemotherapy; metabolic response (MR) was defined as any TGV reduction or as a decrease of  25% in maximum standardized uptake value (SUVmax).
Results: Twenty patients were included in the study, and 17 were assessable for TGV analysis. After two cycles of chemotherapy, 3 pts achieved a partial response at CT evaluation, and in 11 a stable disease was observed. TGV value fell in 11/17 pts (65%), with a median reduction of 36% of baseline (range, -100/+827%). Early MR was significantly correlated to time to tumor progression (TTP), with a median TTP for metabolic responders of 15,8 months versus 5,6 months for non responders (P = 0.04). A similar result was observed when MR was defined according to SUVmax variations (P = 0.06). Patients with a MR had a trend towards longer overall survival; median OS was 25.4 months in pts with any TGV reduction vs 17.5 months for non responders, but this difference did not reach statistical significance (P = 0.20).
Conclusion: Volume-based (TGV) FDG-PET assessment of response seems effective in predicting patient outcome in MPM. However, the sensitivity of this method in comparison to a single-pixel evaluation (SUVmax) should be evaluated in a larger prospective series.

Number: 25

Abstract title:
DIFFERENTIATION BETWEEN MALIGNANT MESOTHELIOMA AND ASBESTOS-RELATED BENIGN PLEURAL DISEASE:

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Keywords:
mesothelioma, asbestos related benign disease, PET/CT

Abstract content

INTRODUCTION: Several studies have already addressed the potential role of an increased fluorine 18 fluorodeoxyglucose (18 F FDG) uptake in identification of pleural malignancy.
AIM: We sought to define an accurate diagnostic approach for differentiating benign pleural disease from malignant mesothelioma on positron emission tomography (FDG-PET).
MATERIALS AND METHODS: The study population comprised 42 consecutive patients (18 malignant mesothelioma, 15 benign asbestos pleurisy, 9 diffuse pleural fibrosis; mean age, 59.8 years; age range, 39-82 years) who underwent combined whole-body PET/CT scanning for evaluation of known or suspected neoplasms between July 2005 and April 2008. PET images were first reviewed by nuclear medicine physicians who had no clinical information. Thoracoscopy or image-guided pleural needle biopsy were systematically performed to reveal pathological diagnosis, and/or clinical follow-up for at least 2 year for presence or absence of malignant pleural effusion. ROCs analyses for standardized uptake value adjusted to body weight (SUV) were calculated between benign and malignant pleural diseases.
RESULTS: FDG-PET imaging correctly detected the presence of malignancies in 17 of 18 patients for sensitivity, specificity, and accuracy of 94.4%, 91.7%, and 92.3%, respectively. FDG-PET imaging correctly identified 22 of 24 cases of benign pleural disease. Two patients with benign pleural effusions were read to be positive for pleural uptake on PET scans. Malignant lesions accumulated significantly more FDG than the benign ones. The mean SUV values were 7.8 +/- 3.3 and 0.4 +/- 0.8, respectively, (p = 0.000). When we compared the two groups of pleural disease, a cut-off value of 3.0 for SUV gave the best accuracy with 100% and 100%, respectively, for sensitivity and specificity.
CONCLUSION: FDG-PET imaging is a highly accurate and reliable noninvasive test to differentiate malignant from benign pleural disease.

Number: 26

Abstract title:
Thickness and Area in the CT-Based Assessment of Mesothelioma Tumor Response

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Keywords:
tumor response, RECIST, computed tomography (CT), tumor volume

Abstract content:

Background: The quantification of pleural mesothelioma tumor extent is required to evaluate the efficacy of clinical trials. The manual acquisition of linear tumor thickness measurements on each of three sections across a series of computed tomography (CT) scans is the current standard for tumor response assessment. The purpose of this study was to determine the correlation of response based on linear tumor thickness measurements and response based on a more complete (but tedious) analysis of tumor area.
Methods: 201 CT scans were collected from 42 mesothelioma patients enrolled in a clinical trial. These scans represented the complete on-study radiologic history of each patient beginning with the baseline scan. Linear measurements used for the clinical management of each patient were recorded along with tumor area as outlined in each section in which linear measurements had been acquired. Patient response was determined from changes in the summed linear measurements based on the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines, which dictate that an increase in summed linear measurements of at least 20% represents progressive disease. RECIST is based on a spherical tumor model, for which a 20% increase in the linear diameter corresponds to a 44% increase in the cross-sectional area. Accordingly, 44% was used as the criterion for area-based progressive disease.
Results: A comparison of the sum of tumor thickness measurements and tumor area yielded a correlation coefficient of 0.54 across all 201 scans. With regard to tumor response, of the 28 patients who were determined to have progressive disease based on a 20% or greater change in the sum of tumor thickness measurements, only 13 (46%) demonstrated a change in total tumor area that exceeded the mathematically expected 44% threshold required for an area-based designation of progressive disease; the remaining 15 patients would have been classified as stable disease based on measured changes in tumor area.
Conclusion: Changes in area-based measurements, a presumably more complete assessment of tumor burden, exhibited a 46% concordance rate with the current standard, changes in linear measurements. Tumor response assessment for mesothelioma is not consistent with spherical-model-based criteria.

Number: 27

Abstract title:
Role of 18FDG-PET-CT in patients surveillance after multimodality therapy of malignant pleural mesothelioma.

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Keywords:
PET-CT. Multimodality therapy. Extrapleural pneumonectomy. Pleurectomy. Mesothelioma.

Abstract content (maximal 350 words, no graphs)**:**

Objectives: To investigate the role of 18FDG-PET-CT in patients surveillance after multimodality treatment of malignant pleural mesothelioma.
Methods: Retrospective study of patients having had chemotherapy, radical surgery and radiotherapy for malignant pleural mesothelioma in our unit. Radical surgery included extrapleural pneumonectomy (EPP) or radical pleurectomy/decortication (P/D).
18FDG-PET-CT was performed at least 6 months postoperatively to evaluate response to treatment or when disease recurrence was suspected.
18FDG-PET scans were acquired from skull base to upper thighs together with low dose CT scans for attenuation correction and image fusion.
Results: Thirty five patients had EPP (21) or P/D (14) between January 2004 and November 2007.
Eight symptomatic patients had 18FDG-PET-CT done for suspicion of disease recurrence at a median of 9 months (6 to 16), postoperatively. In the meantime, 8 asymptomatic patients had a surveillance 18FDG-PET-CT done at a median of 11 months (6 to 26) postoperatively.
18FDG-PET-CT correctly diagnosed mesothelioma recurrence in 6 of 8 symptomatic patients and missed microscopic recurrence in one.
18FDG-PET-CT showed unsuspected recurrences in 5 out of 8 asymptomatic patients.
Recurrent mesotheliomas had a mean SUVmax measured at 11±5 (4 to 22).
Globally, 18FDG-PET-CT had a sensitivity of 91.6%, specificity of 100% and accuracy of 94%.
Eleven patients were started on a second-line chemotherapy based on 18FDG-PET-CT findings.
Conclusions: 18FDG-PET-CT is useful in diagnosing or ruling out disease recurrence in asymptomatic and symptomatic patients following multimodality therapy of malignant pleural mesothelioma.
We recommend that 18FDG-PET-CT is performed in all symptomatic patients and we suggest that asymptomatic patients have a surveillance 18FDG-PET-CT at 12 months postoperatively and then yearly.

Number: 28

Abstract title:
Practical and Reproducible Volume Measurement of Malignant Pleural Mesothelioma from Standard CT Images

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Keywords:
Tumor volume, CT

Abstract content:

Rationales/Purpose; CT Measurement of tumor volume of malignant pleural mesothelioma (MPM) is challenging. MPM grows rather diffusely encasing the lung, which is different from spherical growth of other solid tumors. We have developed a new method of segmentation and volume measurement of MPM using CT images. This method uses semi-automatic threshold technique to isolate the tumor lesion from other tissues and structures, and selects all pixels between 5 and 150 HU that are considered tumor lesion can be calculated in each CT slice. Tumor volume can be obtained as follows; tumor area ; CT slice thickness ; number of slices. However, this procedure takes time, so we hypothesized that tumor volume also can be obtained using every second or third images without significant error. Thus, this study was conducted to test our hypothesis, and also evaluate the reproducibility of this method.
Method; Randomly selected 9 patients with MRM who underwent CT scanning were analyzed. We calculated the tumor volume using all CT images (measurement #1), every second images (measurement #2), and every third images (measurement #3) in each patient. Correlations were assessed among those results of calculated tumor volume using liner regression analysis. Intraobserver error was also tested using the second measurement performed one month after the first session.
Results; There were strong correlations between measurement #1 and measurement #2 ($r2 = .994$, $p < 0.0001$), and between measurement #1 and measurement #3 ($r2 = .999$, $p < 0.0001$). The mean difference was 1.6% ; 2.1 of tumor volume between measurement #1 and measurement #2, and 1.2% ; 1.5 of tumor volume between measurement #1 and measurement #3. A strong correlation was also found between first and second session of tumor volume measurements ($r2 = .996$, $p < 0.0001$), and the mean difference was 2.4% ; 3.1 of tumor volume.
Conclusion; We have established practical and reproducible technique for MPM volume measurement using standard CT images.

Number: 29

Abstract title:
The influence of talc pleurodesis on FDG PET imaging for malignant pleural mesothelioma (MPM).

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Keywords:
FDG PET, Mesothelioma, Pleurodesis

Abstract content:

Aim: FDG PET is an emerging imaging modality in MPM. Pleurodesis may aid symptom control however resulting inflammatory effects may confound interpretation of FDG-PET scans. We aimed to describe the effect of pleurodesis on FDG-PET imaging in MPM.
Methods: Participants were consenting, newly-referred, untreated patients with a confirmed diagnosis of MPM at a single tertiary referral centre. Patients underwent a helical CT scan of the thorax/abdomen, and a whole-body FDG PET scan within 14 days of each other. Tumour stage was derived for FDG PET and CT scans using UICC TNM staging. FDG PET scans were analysed using a semi-automated 3D region-growing algorithm (J Nucl Med (48) 1449-58; 2007) to derive measures of total glycolytic volume (TGV) and SUVmax. Patients were treated as clinically indicated and followed up for survival.
Results: 97 patients were accrued from 2003 to 2006. 3 patients were ineligible and 4 were not assessable as they did not have a PET scan performed (n=92). 2 patients were excluded from survival analyses, due to prolonged time from diagnosis to study entry. 29 of 92 (32%) patients had undergone prior pleurodesis. The groups were similar in age, gender, pathology, performance status, FVC and overall survival (p>0.05). More pleurodesed patients reported chest pain (p=0.02). PET TNM stage did not differ between the groups (p=0.6). CT stage was significantly higher in pleurodesed patients (p=0.03), who were more likely to be CT-defined N2 or N3 (p=0.05). PET quantitative analysis: mean TGV (non-pleurodesed) 506 (95%CI 302-847) vs (pleurodesed) 1796 (95%CI 1133-2849), (p=0.003); mean SUVmax (non-pleurodesed) 6.7 (95%CI 5.8-7.8) vs (pleurodesed) 9.1 (95%CI 7.7-10.7), p=0.02. Cox proportional hazards regression shows that baseline TGV is a significant prognostic indicator for both non-pleurodesed (HR=1.25, p=0.004, C=62.3%) and pleurodesed (HR=1.54, p=0.010, C=70.3%) patients.
Conclusion: FDG PET tumour staging does not differ following pleurodesis, however CT nodal staging was higher in patients with previous pleurodesis. Quantitative PET parameters are significantly higher with prior pleurodesis, likely reflecting inflammatory effects. Despite the inflammatory effects of pleurodesis, baseline TGV remains a strong independent prognostic factor in both pleurodesed and non-pleurodesed patients.

Number: 30

Abstract title:
Continued Pemetrexed and Platin-based Chemotherapy in Patients with Malignant Pleural Mesothelioma (MPM): Value of 18F-FDG-PET/CT parameters

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Abstract content:

Purpose: To evaluate the response to Permetrexed and Platin based chemotherapy beyond the third cycle in patients with malignant pleural mesothelioma (MPM) using CT and PET-criteria.
Methods: Between Feb. 2002 and Jun. 2004 prospectively recruited patients with MPM were included in the study. Response to therapy using 18F-FDG-PET/CT (PET/CT) was assessed after every 3 cycles of Permetrexed and Cisplatin or Carboplatin. Patients with talc pleurodesis within 1 month prior to chemotherapy were excluded. PET therapy-response assessment used the maximum standardized uptake value (SUVmax) according to EORTC guidelines: Partial response (PR) <-25%; Stable disease (SD) -25% - +25%; Progressive disease (PD) >+25% compared to the previous examination. CT-based therapy response used modified RECIST criteria: PR <-30%; SD -30% - +20%; PD >+20% compared to the previous examination. Patients with PR and SD compared to the previous examination were defined as sequential responders (SR), patients with PD as non-sequential responders (NSR). The mean overall survival for all groups was calculated.
Results: 42 patients were included. Mean age 62 years (44 – 74 years). Median survival after the first PET/CT was 461 days. All patients but one died during observation. Survival after 6 cycles according to SR vs. NSR: 567d vs. 379d (PET) and 507d vs. N/A (CT). After 9 cycles: 637d vs. 312d (PET) and 502d vs. 603d (CT). After 12 cycles: 759d vs. 317d (PET) and 586d vs. 465d (CT). After 15 cycles: 875d vs. 135d (PET) and 606d vs. 608d (CT). After 18 cycles: 890d vs. 411d (PET) and 698 vs. N/A (CT). After 21 cycles: 1090d vs. 362d (PET) and 727 vs. 725d (CT). Detailed information is listed in table 1.
Conclusion:
Patients with MPM undergoing combined Permetrexed and Platin chemotherapy benefit from treatment beyond the third cycle if stated SR in the preceding PET according to the EORTC guidelines. No such correlation to survival can be found with CT if using modified RECIST criteria.

Table 1.

	6 cycles	9 cycles	12 cycles		15 cycles		18 cycles	21 cycles
PET (EORTC)	5 PR	6 PR	4 PR	1 PR	1 PR	1 PR		
	16 SD	12 SD	7 SD	6 SD	2 SD	1 SD		
	7 PD	9 PD	8 PD	4 PD	2 PD	2 PD		
CT(modified RECIST)	1 PR	3 PR	2 PR	1 PR	0 PR	2 PR		
	30 SD	20 SD	15 SD	8 SD	5 SD	1 SD		
	0 PD	5 PD	2 PD	2 PD	0 PD	1 PD		
SR PET	75%	67%	58%	64%	60%	50%		
SR CT	100%	82%	89%	82%	100%	75%		

Written by: Niklaus Schaefer

Number: 33

Abstract title:
EVIDENCE OF STAT1 ACTIVATION IN MALIGNANT PLEURAL MESOTHLIOMA IN FORMALIN-FIXED AND PARAFFIN-EMBEDDED TISSUE USING PROTEIN LYSATE MICROARRAYS

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Keywords:
STAT1, FFPE tissue, protein microarray, proteomics, cell signalling

Abstract content:

Background: STAT\'s (signal transducer and activators of transcription) are latent in the cytoplasm until they are activated. While STAT3 and STAT5 are referred as the oncogenic STAT's, STAT1 is regarded as tumour suppressor. Recently, we have shown that the tumour suppressor STAT1 in MPM patients acts similar to an oncogene. However, STAT1 overexpression confers some tumours resistance against radiation and cisplatin treatment. Resistance against cisplatin- and radiation-based therapies is also frequent in MPMs. The aim of our study is to examine STAT1 protein expression and activation status by comparing the phosphorylation pattern in MPM tissue.
Design. Routinely processed formalin-fixed and paraffin-embedded (FFPE) tissue from 14 epithelioid MPM patients were used for protein extraction and coupled with protein lysate microarray technology. After deparaffination tissues were manually microdissected from the slides. Proteins were extracted according manufactures protocol (Qproteome FFPE tissue Kit). Protein lysates were spotted with the MicroCaster (Whatman/Schleicher and Schuell) in four replicates onto nitrocellulose coated glass slides. STAT1 and phospho-specific STAT1 (pSTAT1) antibodies were detected by chemiluminiscence, and signal intensity from the antibody stained slide was used for quantitative protein analysis, normalized to the total protein amount as determined by Sypro Ruby stained slides.
Results: Up to 15-year old FFPE mesothelioma cases were used for protein extraction. We were able to extract immunoreactive STAT1 and pSTAT1 protein for analysis. STAT1 is highly expressed in 14/14 cases. Accordingly, we evaluated pSTAT1 and found STAT1 phosphorylated on serine 727 and tyrosine 701 in MPM. Measured phosphorylation pattern were also associated with survival and could be linked with poor patient outcome (survival< 3 years).
Conclusion: Our findings suggest that STAT1 signalling plays a critical role in the pathogenesis of MPM. In MPM STAT1 activation seems to be driven by post-translational modifications, such as phosphorylation on serine 727 and tyrosine 701. Proteomics in archived FFPE mesothelioma tissue is a new powerful way to analyse tissues whose pathological status has been determined but whose protein makeup regarding phosphorylation status of encoded proteins is largely unknown and has therefore a great impact on translational clinical research.

Number: 34

Abstract title:
The value of ERCC1 as prognostic marker for MPM

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Keywords:
ERCC1, EPP, induction chemotherapy, prognostic marker

Abstract content:

Background: Expression of the excision repair cross-complementation group 1 (ERCC1) protein predicts response to platinol-based chemotherapy and survival in lung cancer patients. The relevance of ERCC1 expression in MPM has not yet been studied.
Patients and Methods: Three tissue microarrays (TMA) with biopsies of 341 MPM patients without standardized treatment were used as training set for the assessment of immunohistochemical expression of ERCC1. Staining intensity was semi-quantitatively scored (0-3) and percentage of positive stained cells (0-100%) was measured. A final H-score was calculated and correlated to overall survival of this retrospective data.
One TMA with tumour of 93 MPM patients who underwent induction chemotherapy with cisplatin/gemcitabine (cis/gem) or cisplatin/pemetrexed (cis/pem) followed by extrapleural pneumonectomy (EPP) was constructed. It will be assessed for ERCC1 expression and correlated to prospectively documented data. The influence on overall survival, time to recurrence and response to chemotherapy will be evaluated.
Results:
ERCC1 was expressed in 80% of the cases in the training TMA set. Median survival of patients with ERCC1-H-score <0.26 was 8.8 (95% CI 7.1; 10.5) in comparison to patients with H-score < 0.26 15.5 months (95% CI 8.0; 22.9). Cox-regression analysis revealed that ERCC1 H-score was the only independent marker for overall survival.
From May 1999 to January 2008, 139 were intended to treat with induction chemotherapy followed by EPP (49% cis/gem; 51% cis/pem). Toxicity was significantly less frequent after chemotherapy with cis/pem (p=0.05). 90-day mortality was 6.5%. The median survival of these patients was 23 months (95% CI: 19.9; 26.0) in comparison to 9.5 months (95%CI: 8.1; 10.7) of the patients without EPP (p=0.0004). There was no difference in survival between both chemotherapy regimens applied.
Analysis of ERCC1 expression in the preoperative biopsies and EPP specimens and correlation to survival data is currently ongoing and will be reported at the meeting.
Conclusion: Loss of ERCC1 expression seems to be an independent prognostic marker for poor overall survival of mesothelioma patients as assessed in the retrospective data set. The exact predictive value of this marker especially in the context of platinol-based chemotherapy is currently analysed in the prospective TMA.

Number: 35

Abstract title:
Epigenetic profiles distinguish pleural mesothelioma from adenocarcinoma of the lung

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Keywords:
Epigenetics methylation diagnosis

Abstract content:

Alterations in the cellular epigenome are stable and clearly implicated in the genesis of human cancers, including pleural mesothelioma and lung adenocarcinoma. Epigenetic alteration, marked by promoter DNA methylation, can alter gene function leading to aberrant gene expression or silencing. In order to evaluate the potential for epigentic alteration profiling to assist in the differential diagnosis of mesothelioma we studied the methylation of 1505 CpG loci associated with 803 cancer-related genes using the Illumina GoldenGate® bead-array in 158 mesotheliomas, 18 non-tumor pleura, 113 non-small cell lung tumors, and 52 normal lung tissues. Applying an unsupervised mixture-modeling approach to classify all samples based upon CpG methylation profile, 29 distinct methylation profile classes resulted, significantly discriminating among mesothelioma, lung tumors, normal lung, and normal pleura (permutation $P < 0.0001$). To determine the ability of CpG methylation to predict sample type we used a random forests classification of all samples and the overall sample misclassification error was 7.3% ($P < 0.0001$). Four mesotheliomas (3%) were misclassified, and one lung tumor (<1%) was misclassified. Next, in a mixture model containing only non-sarcomatoid mesotheliomas (n=153) and lung adenocarcinomas (n=57), 14 distinct methylation profiles were highly significant predictors of tumor type (permutation $P < 0.0001$). To follow up, a supervised random forests classification was performed on these tumors only and the overall misclassification error was <1% with one misclassified lung adenocarcinoma (<2%), one misclassified mesothelioma (<1%), ($P < 0.0001$). Finally, comparing methylation on a locus-by-locus basis using generalized linear models, 776 CpG loci had increased methylation ($Q < 0.05$) in lung adenocarcinomas compared to mesotheliomas after false discovery rate correction, and 490 CpG loci had increased methylation ($Q < 0.05$) in mesotheliomas. Our results show that methylation profiles can differentiate mesothelioma from lung adenocarcinoma. Once validated in a separate set of tumors, this method would be a rapid, cost-effective complement to immunohistochemistry-based diagnostic techniques, accelerating and increasing specificity for discrimination of pleural mesothelioma from lung adenocarcinoma. In addition, these profiles may aid in identifying overlapping and distinct targets for novel treatments or preventative approaches for these diseases.

Number: 36

Abstract title:
DNA methylation in tumors and matched normal tissues of malignant pleural mesothelioma (MPM) in the Egyptian population

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Keywords:

DNA methylation, malignant pleural mesothelioma, early detection, prognosis

Abstract content:

Background: Epigenetic changes, particularly methylation are excellent candidates to explain how certain environmental factors may increase the risk of cancer. Malignant pleural mesothelioma (MPM) is an aggressive disease, which is closely linked to asbestos exposure and associated in some cases with SV-40 infection. It is asymptomatic in its early stages and therefore it is usually discovered late. It would be highly beneficial to have molecular markers for early detection of mesothelioma. Methylation signatures are a powerful tool by which specific kinds of cancer could be recognized.
Methods: We assessed DNA methylation status of 23 genes on 45 paired cancerous and noncancerous tissue samples obtained from Egyptian MPM patients. Twenty four of them were males and 21 were females (ratio 1:1.4), the median age was 47.6 years (range 20-70), 84.4% gave a history of asbestos exposure and 40% were positive for SV40 by PCR. Twenty four cases were epithelioid, 16 sarcomatoid and 5 mixed. Sixteen patients were of stage I, 12 stage II, 10 stage III and 7 stage IV. Methylation specific PCR was performed using DNA extracted from formalin fixed paraffin embedded tissues with a specific panel of selected genes that are frequently methylated in several tumor types.
Results: Methylation of APC, CCND2, DcR1, HIC1 and MLH1 was frequently detected in tumor and noncancerous tissues, suggesting that these genes may be early events in the pre-neoplastic stage of MPM and could therefore be related to asbestos exposure. Ten genes (p16, RARB, RASSF1, DcR1 and DcR2, CDKN2A, MGMT, RIZ1, HIC1, RRAD) were found to be significantly methylated more frequently in tumor than in non-cancerous tissue samples ($p< 0.001$). Methylation of RASSFIA, DcR1, TMS1, CRBP1, HIC-1, RRAD was significantly more frequent in SV40-positive cases ($p= 0.023$).
Conclusions: Aberrant methylation is a frequent event in MPM. Detection of APC, CCND2, DcR1, HIC1 and MLH1 methylation may help in the early detection of MPM. Moreover, detection of methylation of the affected genes in the blood of MPM patients should be investigated as it might help in follow up of patients for early detection of recurrence in early stage MPM.

Number: 37

Abstract title:
E-pathology and atypical mesothelial hyperplasia (MesoDiag-AMH): The experience of the international mesothelioma panel.

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Keywords:
Atypical mesothelial hyperplasia, mesothelioma, e-pathology

Abstract content:

Background: Use of virtual slides system and web based technologies in pathology is promising, but many pathologists remain septic regarding the feasibility of diagnosis based on analysis of digitally scanned slides. Sending slides from difficult and rare cases to a panel of experts worldwide is consuming time with a risk of damage or leakage of the slides. We conducted an evaluation on digital scanned slides of reactive mesothelial hyperplasia, atypical mesothelial hyperplasia of undetermined malignancy [AMH] and mesothelioma with minimal invasion[MM] to assess reproducibility of the diagnosis and if possible identify criteria that might predict malignancy.
Design: 55 cases of AMH were retrieved from the files of the Mesonat registry between 1995-2008 and reviewed by 5 pathologists from the International mesothelioma panel, and 4 senior pulmonary pathologists, plus one fellow. Each pathologist received an application with a MesoDiag-AMH user manual to download the system[CCITI company]. They enter in the system with a personal login and password. Digital images were retrieved on a server based in Dijon France. The expert blindly reviewed the virtual slides. Each expert has to fill a score sheet and to justify criteria on which they make their diagnosis by selecting region of interest (ROI) using a drawing tool. Inter-observers agreement on the diagnosis was calculated according to Kappa test. The diagnosis was then correlated to the survival.
Results: 570 analysis were performed. There was a general moderate agreement on the diagnosis between experts from the core panel and from those outside of the core panel. Total agreement was observed in 30/55 cases (21 MM/ 9 reactive) and disagreement in 25 cases (major in 18 and minimal in 7). AMH was observed in 11.7% of the cases. Problems encountered with the software and slides review system were discussed. The use of ROI for discussion was extremely useful to understand discrepancy between experts.
Conclusion: Our results show that e-web based pathology is extremely promising and a very useful tool for the interpretation of multiple diagnostic variables on the review of difficult cases providing a good start for the creation of virtual slides expertise center.

Number: 38

Abstract title:
Critical Analysis of Nuclear Size as a Histologic Assessment of Prognosis in Diffuse Malignant Peritoneal Mesothelioma

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Keywords:
Peritoneal mesothelioma, cytoreductive surgery, intraperitoneal chemotherapy, nuclear grading

Abstract content:

Aims: Nuclear size has been proposed as a significant prognostic indicator for survival after cytoreductive surgery and perioperative intraperitoneal chemotherapy for diffuse malignant peritoneal mesothelioma (DMPM). Additional histopathologic criteria useful in an assessment of prognosis have not been determined. This current study assessed the correlations between nuclear size and 12 other histopathologic parameters.
Methods: A review of the histopathological features of DMPM in 62 patients who underwent uniform management of cytoreductive surgery and perioperative intraperitoneal chemotherapy was performed. Nuclear size was categorized into two groups: ≤ 30 µm (n = 35) versus > 30 µm (n = 27). The correlations between nuclear size and 12 histopathologic parameters of DMPM were determined by univariate analysis.
Results: Patients with nuclear size > 30 µm had a less favorable prognosis, as compared to patients with nuclear size ≤ 30 µm (p < .001). Nuclear size was statistically correlated with histologic type (p = .012), nuclear/cytoplasmic ratio (p < .001), mitotic count (p = .001), atypical mitosis (p < .001), tumor necrosis (p < .001), chromatin pattern (p < .001) and nucleolar size (p < .001).
Conclusions: Histopathologic prognosticators in addition to nuclear size are histologic type, nuclear/cytoplasmic ratio, mitotic count, atypical mitosis, tumor necrosis, chromatin pattern and nucleolar size in patients undergoing cytoreductive surgery and perioperative intraperitoneal chemotherapy. The histopathologic features taken together may allow the best current assessment of prognosis.

Number:

39

Abstract title:

Deliberately provoking local inflammation drives tumors to become their own protective vaccine site

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Keywords:
Immunotherapy, memory, neutrophils

Abstract content:

Anti-cAnti-cancer immunotherapies aim to generate resolution of all existing tumors, including inaccessible ones, and provide long-term protection against recurrence. This is rarely achieved. Thus, we aimed to determine if the tumor microenvironment could be turned into a potent ‘self’ vaccine site. Our target was to eradicate larger tumor burdens. Our models respond to single-agent immunotherapies however, they fail at a precisely defined ‘cut-off’ tumor burden. Thus, this system was used to define the immune mechanisms required to mediate regression of larger tumors that are resistant to mono-immunotherapies. We report that direct injection of IL-2 with agonist anti-CD40 antibody into the tumor bed resulted in permanent resolution of treated and untreated distal tumors. Tumor-infiltrating CD8+ T cells and neutrophils collaborated to eradicate treated tumors, IFNγ was not critical, and protective memory was preserved. This approach relied only on tumor antigens expressed within the tumor microenvironment. It also avoided systemic toxicities, did not require chemotherapy or surgery, and is clinically useful because only one tumor site has to be accessible for treatment. We conclude that provoking intratumoral inflammation skews the tumor microenvironment from tumorigenic to immunogenic, resulting in the resolution of treated and untreated distal tumors, as well long-term protective memory.

Number: 40

Abstract title:
The heterogenous microenvironment of murine malignant mesothelioma during tumor implantation

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Keywords:
tumor microenvironment, immunocompetent murine model, host cell recruitment, chemokines, growth factors

Abstract content:

Immunocompetent murine models for malignant mesothelioma are valuable for studying the host response to tumor implantation. While the tumors from a murine model using intraperitoneal injection of mesothelioma cells has been previously described to recapitulate the histopathology and molecular alterations of the human disease, the dynamic time course of host cells being recruited to the tumors and the corresponding expression of chemokines and growth factors for recruitment of host cells, has not been evaluated. We hypothesize there are multiple cell types being recruited at different rates and times throughout the progression of malignant mesothelioma. We describe tumor progression as tumor spheroid growth and local invasion, and as solid tumor invasion and metastasis. Multiple cell types, including tumor-associated macrophages, endothelial cells, dendritic cells, myeloid-derived suppressor cells, T lymphocytes and stem/progenitor cells are identified in the stroma of both tumor spheroids and solid mesothelioma tumors. The dynamics and distribution of host-derived stromal cells change over time. This dynamic time course is also reflected by up- and down-regulation of genes involved in recruitment of stromal cells, as determined by real-time PCR arrays. Elucidating the dynamics of host cell recruitment to malignant mesothelioma can provide novel targets for therapy.
This work is funded by the National Institutes of Health NIEHS grant R01 ES03721 (Kane) and NRSA grant F30 ES013639 (Lau).

Number: 41

Abstract title:
Human and murine mesothelioma share similar genomic alterations

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Abstract content:

Mesothelioma is a severe disease, which frequency has dramatically increased due to the large use of asbestos fibers. To gain insight in its physiopathology, a model was developed in wildtype (WT) and hemizygous N*f*2KO3/+ mice exposed to fibers (asbestos and refractory ceramic fibers), which developed mesothelioma and tumoral ascites (TA) 9 to 24 months after exposure. Seventeen TA, 4 and 13 in WT and N*f*2KO3/+ backgrounds, respectively, were characterized by array-comparative genomic hybridization (CGHa) and compared to DNA profiling obtained from a series of 34 human mesotheliomas.
CGHa was performed on the genome-wide CIT M3 Mus musculus 1K BAC array and analyzed using the VAMP interface. A syntenic conversion tool was developed to visualize the "humanized" profile of murine tumors and to facilitate comparison with human profiles. The most frequent aberration was an interstitial deletion of murine chromosome 4 in 14/17 tumors, with frequent bi-allelic deletions (9/17). The minimal region of deletion contained the Cdkn2a/2b genes. Other alterations included recurrent gains of chromosomes 15, 19 and 6, and losses of chromosomes 7 and 14, most frequently implicating whole chromosomes. However, an interstitial deletion of chromosome 14 was defined in 12/17 tumors. Five high level gains were observed in 2 tumors, implicating regions containing Met, Myc and B-Raf as candidate target genes.
Genomic profile of human mesotheliomas is characterized by frequent gains of chromosomes 5p, 7p and 20, and losses of chromosomes 1p, 3p, 4, 6q, 9p, 13, 18 and 22. After "humanizing" murine tumor genomic profiles, similarities and differences were easily evidenced. Strikingly, the most frequent deletion in human disease and mouse models is the deletion of CDKN2A/2B, frequently by bi-allelic deletion. Other shared aberrations are the deletion of 1p, of chromosome 13 and gain of 5p. However, the frequent deletion of 3p in human tumors was not found in murine tumors.
Acknowlegements: Murine CGHa was performed at the CIT platform at Institut Curie by C Blanchard. Human CGHa was performed at the CIT platform at IGBMC. We are grateful to A Janin, F Galateau-Sallé, C Danel, I Abd Alsamad, P Astoul, I Monnet, JC Pairon, F Le Pimpec Barthes.
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Number: 42

Abstract title:

Extracellular Signal-Regulated Kinases (ERKs) have Disparate Roles in Growth and Chemoresistance of Human Mesotheliomas In Vitro and in a Mouse Xenograft Model

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Keywords:
Malignant Mesothelioma, Extracellular Signal-Regulated Kinases, Chemoresistance, Cell Growth

Abstract content:

Malignant mesothelioma (MM) is a fatal cancer associated historically with occupational exposures to asbestos. Extracellular signal-regulated kinases (ERKs) are deregulated in approximately one third of all human cancers and activated by asbestos; however, little is known regarding their role(s) in MM. Initially, we used several pleural MM cell lines (MO, ME12, ME26 and ME27) in vitro to assess the role of ERK1/2 in migration, invasion, and gene expression in the presence or absence of a MEK1/2 inhibitor, U0126 (10 and 20 μM) or its inactive analog, U0124 (20 μM). Cell migration and invasion were greatest in the only sarcomatoid MM line (MO) and inhibited by U0126 but not U0124. Addition of Doxorubicin (Dox) (LD50~25μM) caused loss of viability as well as ERK1/2 activation in all 4 MM cell lines. Use of U0126 inhibited Dox–induced ERK1/2 activation and modified cell viability, suggesting a prosurvival role for ERK1/2. To dissect the individual roles of ERK1, ERK2 and ERK5, a ERK family member recently linked to Fra-1 regulation and MM viability (Ramos-Nino et al., Am J Respir Cell Mol Biol. 38: 209-17, 2008), in MM growth and chemoresistance, we created stable shERK lines using a MM cell line (H-meso) giving rise to tumors after subcutaneous (sc) injection into SCID mice. Selective inhibition of approximately 80-90% of ERK1, ERK2 or ERK5 was achieved in individual clones without compensatory increases in other ERK family members. These clones, untransfected, and control vector transfected (shNC) lines were injected into mice (N= 4 sc injection site/ 4 mice/group) and assayed for their chemoresistance to Dox in vitro. In comparison to all other groups, mice injected with shERK2 cells showed decreased or no tumor development whereas shERK5 cells showed increased viability in response to Dox addition in vitro. These observations are presently being confirmed in other shERK-modified human MM cell lines. Data demonstrate that ERK2 plays an important role in MM cell growth whereas ERK5 governs Dox resistance. Supported by P01CA11407.

Number: 43

Abstract title:
Malignant mesothelioma mouse model for in vivo and in vitro therapeutic strategies

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Keywords:
mesothelioma model, tumorigenesis, therapy, in vitro, bioluminescence

Abstract content:

We have developed a murine model for human malignant mesothelioma where we induce site-specific loss of Nf2, Ink4a/Arf, and p53 by using the Cre-lox system in Nf2loxP/loxP, Ink4a/ArfloxP/loxP, p53loxP/loxP, Nf2loxP/loxP;Ink4a/ArfloxP/loxP, Nf2loxP/loxP;p53loxP/loxP, and Nf2loxP/loxP;Ink4a*/*; p53loxP/loxP. Murine mesotheliomas developed on either visceral pleura of lungs and heart and/or on parietal pleura of diaphragm and thoracic chest wall. We are able to follow tumor growth non-invasively with a conditional luciferase reporter. Next to our in vivo model, we also developed several in vitro cell lines with or without the luciferase reporter from murine mesotheliomas from different genetic backgrounds. From the luciferase reporter positive cell lines we have successfully derived orthotopic tranplantation models which gives us the opportunity to quickly set up large in vivo experiments.
A genetic approach by both expression/oligo and CGH Bac array technology to further validate the mouse model for human mesothelioma is ongoing in the murine tumors and cell lines as well as in patient material to search for parallel genetic aberrations. The results of this detailed genetic validation should yield us information as to which genetic aberrations occur most frequent, what expression profiles are concomitant with these specific genetic aberrations and to what extent we can interfere with pathways to stop tumor growth in relation to specific aberrations.
In this model we perform basic and pre-clinical research. The basic research consists on study of early events in murine mesothelioma development and the role of loss of Ink4a in murine mesothelioma development. The pre-clinical part focuses on comparative treatment in the mouse model, both in vivo and in vitro, with different therapeutic options ranging from use of cytostatics (e.g. cisplatinum, doxorubicin or gemcitabine), biological compounds (e.g. pemetrexed, thalidomide, or gefitinib), radiation and immunological intervention (e.g. IL2 or DC) or combinations of the above.

Number: 44

Abstract title:
RNA interference-based strategies directed against Bcl-xL and Mcl-1 for the treatment of malignant pleural mesothelioma

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Keywords:
Chemoresistance, RNA interference, Bcl-xL, Mcl-1

Abstract content:

Malignant pleural mesothelioma (MPM) is a highly aggressive tumour with poor prognosis and limited response to standard combined chemotherapy (i.e. pemetrexed plus cisplatin). Altered expression of anti-apoptotic proteins have been previously described to contribute to chemoresistance, and among them, Bcl-xL seems to play an important role in MPM. Different strategies have been developed to impede its activity (BH3-mimetics) or its expression (antisense oligonucleotides). Interestingly, since it based on the highly specific and efficient silencing of a target gene, RNA interference (RNAi) represents one of the most promising innovating approaches to be combined to conventional therapies. In our study, a Bcl-xL specific RNA interference approach (siXL1) was used to inhibit Bcl-xL expression in mesothelioma cell lines for evaluating both its antitumor effect and its potential to sensitize mesothelioma cells to standard chemotherapy. We showed that siXL1 induced a drastic inhibition of Bcl-xL expression both at the mRNA and protein levels in different MPM cell lines. We characterized the response of chemoresistant NCI H28 cells to siXL1, alone or associated to cisplatin. siXL1 alone caused death of a fraction of the population (about 20%), the majority of cells being only transiently arrested in the cell cycle for few days. Notably, the combination of siXL1 and cisplatin resulted in a supra-additive effect with nearly complete annihilation of the population, whereas neither cisplatin alone nor cisplatin associated to control siRNA induced cell death in these cells. Moreover, it was recently demonstrated that the neutralization of both Bcl-xL and Mcl-1 suffices for efficient Bak-mediated apoptosis. We thus evaluated the interest of the siXL1/siMCL1 combination and showed that this association is sufficient to induce a significant cell death. The interest of such siRNAs association combined to standard chemotherapy for the prevention of long term recurrence is under investigation. Finally, preclinical studies will be performed in nude mice to precise the therapeutic potential of such approaches for the treatment of MPM. In summary, these findings highlight that siRNA strategy aimed at down-regulating both Bcl-xL and Mcl-1 may be used as novel and highly effective tool, with the potential for future targeted therapy of malignant pleural mesothelioma.

Number: 45

Abstract title:

Depletion of ICOS- and TNFR2-expressing effector-suppressor T cells promotes the eradication of subcutaneous mesotheliomas in mice

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Abstract content:

Tumor growth is closely linked to immunosuppression and CD25+ regulatory T cells play a key role in this process. Here, we report that the chemotherapeutic drug cyclophosphamide eradicates established mesotheliomas in mice in a CD8 T cell dependent fashion and that depletion of an effector suppressor population of T cells is a necessary part of the process. Our study makes four points. First, cyclophosphamide depletes all cycling (Ki-67hi) T cells, but preferentially targets foxp3+ CD4 T cells. Second, cycling regulatory CD4 T cells express high levels of TNFR2 and ICOS consistent with this population including the maximally suppressive regulatory T cells. Third, reconstitution of cyclophosphamide-treated mice with CD4+ CD25+ T cells from untreated tumor-bearing mice resulted in rapid tumor growth, showing that depletion of regulatory T cells was essential for tumor eradication. However, depletion of regulatory T cells per se (by targeting the CD25+ population) had no effect on tumor growth. Fourth, combination of the cytotoxic drug gemcitabine, which as a single agent does not cure mice, with CD25-depletion cured 75% of mice. Thus, the interaction between tumor cell apoptosis and regulatory T cell depletion yields a significant benefit. Our data show that cyclophosphamide cures mice because it preferentially depletes effector-suppressor T cells. The synergy between gemcitabine and CD25+ CD4 regulatory T cell depletion suggests that combinations of therapies may offer benefit to patients with mesothelioma.

Number: 47

Abstract title:
Wilms tumor-1 (WT1) peptide vaccine can elicit immune responses in patients with malignant pleural mesothelioma

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Keywords:
Vaccines, Immunotherapy

Abstract content:

BACKGROUND: The transcription factor, WT1, is highly overexpressed in malignant pleural mesothelioma (MPM) such that immunohistochemical stains for WT-1 are routinely used to aid in its diagnosis. For this reason, WT-1 is an attractive target for immunotherapy. Using computer prediction analysis we designed analog peptides derived from WT-1 sequences by substituting amino acids at key HLA-A0201 binding positions. One peptide (WT-A1) was capable of stimulating CD8 T-cells for killing of HLA matched tumor cells. A modified version of the protein (WT1-122A1) created by adding flanking amino acids to the core sequence, generated CD4 responses as well. Two additional peptides were generated (WT1-427 & WT1-331) which were capable of recruiting CD4 T-cell response across multiple HLA-DR subtypes. These four peptides administered together with adjuvant Montanide and GM-CSF comprise the vaccine.
METHODS: We tested the safety, activity and immunogenicity of WT1 vaccine in patients with myeloid and thoracic neoplasms. Patients with MPM were required to have tumors expressing WT1 by immunohistochemistry and treated with no more than one prior chemotherapy regimen. Immune responses were evaluated by DTH, CD4 T-cell proliferation, CD4 and CD8 T-cell interferon release, and WT1 peptide tetramer staining.
RESULTS: Twenty patients have been enrolled including eight with MPM (4 with relapse after combined modality therapy, 3 with one prior chemotherapy regimen for advanced disease, and one previously untreated). Five MPM patients discontinued vaccines because of progression, two are active, and one has no progression 7 months after completion of 12 vaccinations. Preliminary results show CD4 response in 7/9 patients overall and 2/3 MPM patients, CD8 response in 5/6 overall and 1/2 MPM patients, and DTH responses in 4/14 overall and 1/3 MPM patients. In one MPM patient, WT1 peripheral blood level was undetectable after 3 vaccines. Toxicities were limited to mild injection site reactions and one grade 2 urticaria. CONCLUSIONS: This analog WT1 peptide vaccine is well tolerated and immune responses can be elicited in patients with MPM. A randomized trial testing this vaccine as adjuvant therapy in MPM is planned. Supported by NIH PO1 23766, Innovive Pharmaceuticals, MARF, The Experimental Therapeutics Center and the Baker Street Foundation.

Number: 49

Abstract title:
Reversal of Bortezomib Resistance in Mesothelioma by a MCL-1/A1 targeting BH3 Peptidomimetic

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Keywords:
apoptosis, BCL-2 family, proteasome inhibition, bortezomib, obatoclax,

Abstract content:

Based on promising pre-clinical data, bortezomib (bz) is currently under investigation in two phase II clinical trials in mesothelioma. However, the molecular determinants of sensitivity and resistance to bz are unknown, warranting analysis of its proapoptotic pharmacodynamics. Bz is known to modulate both pro- and antiapoptotic BCL-2 family proteins. Accordingly, their regulation was explored in mesothelioma cells. Bz upregulated the proapoptotic BH3-only protein and MCL-1/A1 antagonist NOXA, in sensitive REN cells and xenografts, but not in resistant MPP89 or REN spheroids. Knockdown of NOXA by siRNA inhibited bz-induced death of REN cells. Despite the lack of NOXA upregulation in MPP89 cells, direct targeting of MCL-1/A1 with either exogenous BH3NOXA or with obatoclax, a BH3 peptidomimetic targeting MCL1/A1, was sufficient to reduce MPP89 viability. Furthermore, combination of obatoclax and bz exhibited potent synergy in these cells. Bz efficacy is therefore characterized by NOXA upregulation, which is absent in resistant cells. Antagonism of MCL-1/A1 is sufficient to induce apoptosis irrespective of bz-sensitivity. The promising potency observed with bz plus obatoclax suggests a novel therapeutic strategy with potential to reverse bz resistance in mesothelioma.

Number: 50

Abstract title:
Identification of internalizing human antibodies targeting tumor cell surface antigens commonly expressed by all types of mesothelioma

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Keywords:
Internalizing human single chain antibodies. MCAM, all types of mesothelioma

Abstract content:

Mesothelioma is a deadly disease caused by malignant transformation of the mesothelium, the protective lining surrounding most of body's internal organs. There are three main types of mesothelioma: epithelioid, sarcomatoid, and mixed. Epithelioid mesothelioma is the most common form, comprising between 50-70% of mesothelioma cases, and is the most likely to respond to treatment. Sarcomatoid mesothelioma accounts for 10-20% of mesothelioma cases and rarely responds to treatment. Approximately 20-35% of mesothelioma cases are mixed type, which contains both epithelioid and sarcomatoid features and has an intermediate outlook. Currently, very few mesothelioma-associated cell surface antigens that are expressed by all types of this disease are known. For example, mesothelin, a cell surface glycoprotein, has been shown to be a useful marker for epithelioid mesothelioma, but it is not expressed by sarcomatous mesothelioma. To identify cell surface antigens that are expressed by all types of mesothelioma, we have probed the cell surface epitope space of various types of mesothelioma by monoclonal antibodies. We have selected a 500-million member phage antibody display library on epithelioid and sarcomatoid mesothelioma cell lines, and have identified a panel of internalizing human single chain antibodies that bind to both types of mesothelioma cells. We have further exploited the internalizing function of these antibodies to specifically deliver lethal doses of liposome-encapsulated small molecule drugs to both epithelioid and sarcomatous types of mesothelioma cells. To identify antigens bound by those novel tumor-targeting antibodies, we screened by flow cytometry the entire human proteome displayed on the surface of yeast. We have identified MCAM/MUC18/CD146 as one of the target antigens. Immunohistochemistry analysis of mesothelioma tissue microarrays confirmed that MCAM is widely expressed by epithelioid, sarcomatous and mixed types of mesothelioma tumor cells in situ but not by normal mesothelial cells. Thus, we have identified a cell surface antigen expressed by all types of mesothelioma, making MCAM a candidate for therapeutic targeting.

Number: 52

Abstract title:
Frequent Co-Activation Of MET And EGFR In Malignant Mesothelioma As A Rationale For Combination Targeted Therapy

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Abstract content:

Background: To identify new therapeutic targets in malignant mesothelioma (MM), we performed a screen for activated receptor tyrosine kinases (RTKs) in mesothelioma.
Experimental Design: We studied 14 MM cell lines and 70 primary tumors. Expression of phosphorylated RTKs was analyzed by western blotting and a membrane-based antibody array (Proteome Profiler, R&D Systems). Screening for mutations was performed by direct sequencing of exons encoding the kinase, semaphorin, and juxtamembrane domains of MET and the kinase domain of EGFR. MET, HGF, and EGFR expression were studied by western blotting, immunohistochemistry, ELISA (HGF), and at the transcript level in Affymetrix expression microarray data or by Q-RT-PCR. Cell proliferation was measured by MTT assays.
Results: Profiling of the phosphorylation status of 42 RTKs in MM cell lines showed prominent expression of both phospho-MET and phospho-EGFR in 8/14 (57%). Two MM cell lines showed nonsynonymous sequence alterations in MET (R988C, T1010I) and none showed EGFR mutations. No somatic mutations of MET were found in 70 primary tumors. Treatment with the MET inhibitor, PHA-665752 (gift of Pfizer), identified JMN as the most sensitive cell line and this was also the only line to show autocrine HGF production. Notably, MET inhibition by PHA-665752 in JMN and other MM lines inhibited not only the phosphorylation of MET but also that of EGFR. Knockdown of MET by RNA interference also reduced EGFR phosphorylation. Conversely, stimulation with HGF increased both phospho-MET and phospho-EGFR. Combination therapy with PHA-665752 and the EGFR inhibitor, erlotinib, suppressed cell growth more than either agent alone in 3/6 (50%) cell lines.
Conclusion: MM frequently coexpress phosphorylated MET and phosphorylated EGFR with evidence of cross-activation. Combination targeting of MET and EGFR may be more effective than either inhibitor alone in a subset of MM.

Number: 53

Abstract title:
Paxillin is a Novel potential Molecular therapeutic Target Against Mesothelioma

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Keywords:
Paxillin, mutation, gene amplification, Mesothelioma

Abstract content:

Malignant Pleural Mesothelioma (MPM) cells migrate along the pleural surface, are invasive, and can metastasize to lymph nodes. These mechanisms can potentially involve the cytoskeleton. We have recently identified that paxillin, a focal adhesion protein, is an important active cytoskeletal protein in MPM. We first found unique paxillin (PXN) gene mutations identified in between LD motifs and with in LIM domains in mesothelioma DNA samples. Paxillin is an important downstream target of receptor tyrosine kinases, such as c-Met. We examined the expression of paxillin and c-Met in mesothelioma cell lines using standard immunoblotting with the 5H11 paxillin monoclonal antibody and polyclonal anti-c-Met antibody. There was significant over expression of paxillin and c-Met in most of the MPM cell lines (4 out of 5) examined when compared to MeT-5A (normal mesothelial cells). We found overexpression of paxillin (2+ to 3+) in archival mesothelioma tumor tissues. A number of mesothelioma tissues had high expression of paxillin in MPM sub-types, in particular 89% of sarcomatoid (score 2+ to 3+) compared to epithelioid (54%) and mixed type/biphasic (60%). Statistically significant differences between epithelial and sarcomatoid tumors were observed for paxillin ($p<0.01$). Specific staining of the mesothelioma tumor tissue was evident with negative staining seen in the surrounding stromal tissues. Expression of paxillin in tumor tissues was identified as both nuclear and cytoplasmic in epithelioid type and predominantly membranous localization in sarcomatoid type of mesothelioma patients. Gene amplification of paxillin (PXN) and c-Met was analyzed by methods of QPCR and FISH in a panel of mesothelioma cell lines. There was increased copy numbers of the paxillin gene identified in H2461 and H2691 cells. A total genomic gain of PXN in mesothelioma cell lines was about 33% (3 out of 9). One of the most frequently occurring paxillin mutants (A127T) found in MPM was a gain-of-function mutant that conferred cell survival advantage, enhanced cell motility/migration, and angiogenesis. SiRNA inhibitory strategy was used to target against paxillin mRNA to test and validate the potential of therapeutic inhibition of paxillin. SiRNA duplexes targeting paxillin mRNA was transfected into cells to achieve paxillin gene silencing. Paxillin protein expression was successfully inhibited by 70-90% over 72h. SiRNA down-regulation of paxillin protein resulted in reduced cell viability. Therefore, paxillin would be an important therapeutic target in MPM, and rational inhibitory drug design should be considered against this important cytoskeletal molecule.

Number: 54

Abstract title:
Mesothelioma spheroids, mTOR, mitochondria and multicellular resistance

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Keywords:
Apoptosis, biomarker, TRAIL, S6K, three-dimensional

Abstract content:

Mesothelioma progresses from a two-dimensional (2D) layer of normal mesothelial cells into a three-dimensional (3D) thick tumor mass. This structural transition may itself account for some of the characteristic properties of the tumor such as chemoresistance. We found that, when grown as 3D spheroids (multicellular spheroids), mesothelioma cell lines acquire a pronounced resistance to a wide array of chemotherapeutics compared to their 2D monolayer counterparts, a property termed multicellular resistance. Pro-apoptotic treatments included combinations of TRAIL, gemcitabine, the proteasome inhibitor MG-132 and histone deacetylase inhibitors trichostatin A and sodium butyrate. We have investigated the mechanisms that drive multicellular resistance in 3D using both mutlicellular spheroids generated from mesothelioma cell lines and tumor fragment spheroids grown from human mesothelioma tumor. In both models, we have found that the PI3K/Akt/mTOR axis and particularly mTOR signaling contribute to multicellular resistance; in fact, inhibition of S6K, a downstream target of mTOR, effectively reduced by more than 40% the apoptotic resistance in the 3D spheroids but not in monolayers. Furthermore, tumor fragment spheroid responsiveness to mTOR/S6K inhibition correlated with positive staining for phospho-S6K, but not for phospho-Akt. Staining of tissue microarrays containing 37 mesotheliomas further demonstrated that phospho-S6K correlates only weakly with phospho-Akt, suggesting the existence of an Akt-independent regulation of mTOR. The actual targets of the mTOR/S6K signals that confer multicellular resistance are not yet identified but appear to converge at the mitochondria, where apoptotic signals are known to be integrated and amplified.
We propose that mTOR/S6K mediates survival signals in many mesothelioma tumors as revealed by its contribution to the acquired apoptotic resistance of mesothelioma cells in 3D but not in 2D cultures. We suggest that 3D spheroids reflect a more clinically relevant in vitro setting in which mTOR elicits anti-apoptotic properties, modeling the chemoresistance seen in vivo. Inhibition of mTOR may provide a non-toxic adjunct to therapy directed against malignant mesothelioma, especially in tumors with high baseline expression of phospho-S6K.
Research was supported by NIH RO1 CA95671 (VCB) and the Buzzi-UNICEM Foundation (GG and DB).

Number: 55

Abstract title:
Transduction of the wild-type p53 gene in combination with anti-cancer agents produced anti-tumor effects on mesothelioma

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Keywords:

gene therapy, adenovirus, p53, cell cycle, chemotherapy

Abstract content:

Malignant mesothelioma is one of the intractable diseases and the prognosis remains poor despite multimodal treatments. We examined a possible therapeutic strategy with adenovirus (Ad)-mediated transduction of the wild-type p53 gene in combination with anti-cancer agents, gemcitabine and pemetrexed. Most of mesothelioma cells are devoid of p14/p16 genes and subsequently the p53-mediated signal pathways are functionally inactivated. Restoration of the pathways could be a strategy to induce DNA damage-induced apoptosis and to increase the sensitivity to anti-cancer agents. Transduction of human mesothelioma cells with Ad bearing the cytomegalovirus promoter-linked the p53 gene (Ad-p53) suppressed the survival depending on the Ad amounts whereas the Ad expressing beta-galactosidase gene did not. The Ad-p53-mediated cytotoxicity was influenced by expression levels of type 5 Ad receptors, coxsackievirus and adenovirus receptor (CAR) molecules, on target cells. Cell cycle analyses showed that transduction with Ad-p53 induced G1 phase arrest whereas gemicitabine and pemetrexed did S phase arrest. Both Ad-p53 and the agents increased subG1 fractions thereafter. Combinatory treatments of Ad-p53 and either gemicitabine or pemetrexed produced additive cytotoxic effects in particular on mesothelioma expressing CAR at a high level. Cell cycle analyses suggested that a precedent treatment of mesothelioma cells with pemetrexed before Ad-p53 administration increased the subG1 population compared with other combination schedules. Cytotoxic assays also supported the schedule-dependent effects. These data collectively imply that transduction with Ad-p53 is a possible treatment modality for mesothelioma and enhanced cytotoxicity by combination of anti-cancer agents is another therapeutic option.

Number: 56

Abstract title:
Novel therapy for malignant pleural mesothelioma based on anti-energetic effect: an experimental study using 3-bromopyruvate in nude mice

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Keywords:
mesothelioma, nude mice, glycolysis, energetic metabolism, chemotherapy

Abstract content:

Purpose: Most cancer cells exhibit increased aerobic glycolysis and use this metabolic pathway for the generation of ATP as a main source of energy. This impaired metabolism of glucose, leading to the secretion of lactic acid even in the presence of oxygen, is named the “Warburg effect”. Because cancer cells are partly or mainly dependent on such pathway to generate ATP, inhibition of glycolysis may slow down the proliferation or kill cells.
Experimental design: We tested the effect of 3-Bromopyruvate (3-BrPA) alone or associated to cisplatin on nude mice presenting intraperitoneal carcinomatosis developed after intraperitoneal injection of human mesothelioma cells (MSTO-211H).
Results: 3-BrPA prolonged very significantly survival of animals. Combined with cisplatin, it demonstrated significant benefit on survival whereas cisplatin alone has no or mild effect.
Conclusions: 3-BrPA may thus constitute an interesting novel anticancer drug that could be tested in humans.

Number: 57

Abstract title:
Rapamycin intensifies cisplatin cytotoxicity in mesothelioma cell lines

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Keywords:
mTOR, Rapamycin, Cisplatin, dephosphorylation, PI3K/Akt pathway, cytotoxicty

Abstract content:

Malignant pleural mesothelioma (MPM) is an aggressive cancer that responds poorly to standard chemotherapeutic approaches, with five-year survival less than 1%. Cisplatin is the chemotherapeutic agent most commonly used; however, its moderate therapeutic impact justifies the search for additional agents to enhance its therapeutic effect. The phosphatidylinositol 3-kinase (PI3K)/Akt pathway, often activated in MPM, has been implicated in the aggressive behavior of this tumor, putatively by mediating cell survival and reducing sensitivity to chemotherapy. Rapamycin is an established inhibitor of the Akt/mTOR pathway. We sought to determine whether combined therapy with rapamycin+cisplatin would enhance cell death in MPM.
Human MPM cell lines were incubated with rapamycin or cisplatin alone or in combination and assayed for cell viability over time. Akt and downstream proteins of the mTOR pathway, p70 S6 kinase and 4E-BP1, were analyzed at different phosphorylation sites, to characterize the dephosphorylation effects of different treatment regimens.
MPM cells exhibited a range of sensitivity to each drug. Rapamycin+cisplatin significantly ($p=0.029$) increased cell death compared with either drug alone. Combined treatment caused greater dephosphorylation of 4E-BP1 than either drug alone. In addition, combined treatment caused dephosphorylation of Akt and p70 S6 kinase. In at least one cell line, H2052 (cisplatin-sensitive cell line), 24-hour pretreatment with rapamycin caused greater cell death compared with combined treatment alone. rapamycin+cisplatin.
Rapamycin appears to enhance the sensitivity of cisplatin in MPM cell lines via the mTOR pathway. The results provide a basis for clinical evaluation of combined rapamycin+cisplatin chemotherapy.

Number: 58

Abstract title:
The fibrinolytic system and growth of malignant pleural mesothelioma

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Abstract content:

Malignant mesothelioma (MM) is a lethal neoplasm for which current therapy is unsatisfactory, prompting the search for new therapeutic targets. The fibrinolytic system and the urokinase plasminogen activator receptor (uPAR) in particular are implicated in the pathogenesis of a number of solid neoplasms but their role in the propagation of MM is at present unclear. We found that REN human pleural MM cells expressed >10-fold more of the urokinase receptor than MS-1 or M9K cells or MeT5A human pleural mesothelial cells. Overexpression of uPAR relates to inability to internalize the receptor and REN cells lack LRP but uPAR mRNA is stabilized in these cells. In a new orthotopic murine model of pleural MM, the kinetics of REN cell tumorigenesis was accelerated versus MS-1 or M9K cells, that REN instillates generated larger tumors and caused earlier mortality. REN, MS-1 and M9K tumors are all associated with prominent extravascular fibrin deposition and excised REN tumor homogenates were characterized by markedly increased uPAR expression at both the mRNA and protein levels. Proliferative capacity of REN cells REN cells traversed three-dimensional fibrin gels while MS-1, M9K and MeT5A cells were immotile in this system. uPAR silencing or uPAR blocking antibodies decreased REN cell migration and invasion in this system and in chamber analyses, while uPA and serum augmented the effects. uPA was absent in cultured REN cells but was detectable in tumor homogenates and in the REN-derived tumors by immunohistochemistry. These observations link uPAR to the pathogenesis of malignant pleural mesothelioma and suggest that this receptor contributes to accelerated tumor growth in part through interactions with uPA.

Number: 59

Abstract title:
Cytological diagnosis of pleural malignant mesothelioma (MM)

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Abstract content:

BACKGROUND: Cytological examination of effusion specimens provides an opportunity to establish a diagnosis of MM sometimes at an early stage of disease prior to a detectable mass lesion. However cytological diagnosis is controversial (Churg AJSP 2000), and is not accepted by some pathologists and clinicians. To examine the role of cytology in this diagnostic setting we conducted an audit of pleural cytology specimens over a 20 year period (1988-2007).
MATERIALS AND METHODS: Pleural specimens received at PathWest QEII were extracted from the database and analysed to identify MM cases, and determine the number of cases diagnosed by cytology and the frequency with which cytology-based MM diagnosis was confirmed by additional pathology or by the WA Mesothelioma Registry.
RESULTS: 9985 pleural samples were received (1740 biopsy, 8245 cytology) from 6198 individuals. 801 individuals had a final diagnosis of MM. 544 of these had cytological material examined, and 425 (78%) received a cytological diagnosis of MM. Followup information was obtained in 404 (95%). In 318 cases the diagnosis was confirmed by biopsy, electron microscopy (EM), and/or necropsy. In 86 cases MM was confirmed by WA Mesothelioma Registry data. Twenty one cases had cytological diagnosis alone. There were two incorrect diagnoses of MM in patients with metastatic malignancy to the pleura; both occurred prior to availability of specific mesothelial markers. 119 patients with a biopsy diagnosis of MM had a cytology specimen which was not diagnostic of MM; 49 were diagnosed as atypical or suspicious and 70 as negative for malignancy. Of the cases not established by cytology, 40 (34%) were sarcomatoid on biopsy. Positive predictive value of a cytological diagnosis of MM was 99.8% and predictive value of a malignant diagnosis in MM cases was 100%. Absolute sensitivity was 78%; complete sensitivity 87%, and specificity 99.9%.
CONCLUSION: The value of cytology in the diagnosis of pleural epithelioid MM is unquestionable. Cytology provides a rapid, cheap and minimally invasive diagnostic modality, and may enable early diagnosis. Effusion cytology is rarely helpful in the diagnosis of sarcomatoid MM, and there are some cases of epithelioid/biphasic MM which require biopsy to establish a definitive diagnosis.

Number: 60

Abstract title:
Biomarkers for malignant pleural mesothelioma: current status

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Keywords:
Biological markers, Diagnostic biomarkers, Prognostic biomarkers, Predictive biomarkers, Malignant Pleural Mesothelioma

Abstract content:

Malignant pleural mesothelioma is an aggressive tumor, whose main etiology is the exposure to asbestos fibers. The incidence of malignant mesothelioma is anticipated to increase during the first half of this century, both in developed and developing countries. The prognosis of malignant pleural mesothelioma patients is poor, with a median overall survival without treatment of less than 12 months. For various reasons, malignant pleural mesothelioma is difficult to diagnose and this disease is notoriously refractory to most of treatments. However, two active chemotherapy regimens were recently demonstrated to significantly increase malignant pleural mesothelioma patients' survival, and several therapeutic agents and strategies are currently under evaluation.
For twenty years, there has been great enthusiasm in the search for molecules that may serve as biomarkers for malignant pleural mesothelioma. Indeed, biomarkers would be helpful in three different steps of clinical management of mesothelioma patients: early diagnosis, prognosis, and treatment outcome prediction. The aim of the present review was to summarize the published and recently presented data on malignant pleural mesothelioma biomarkers, to draw the current status of scientific knowledge in this domain and to identify perspectives for future translational research projects.

Number: 61

Abstract title:
The Diagnostic Accuracy and Reproducibility of Pleural Fluid Levels of Mesothelin in Unselected Patients with Pleural Effusions

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Keywords:
Mesothelioma, pleural effusion, pleural fluid mesothelin, diagnosis, pleural fluid cytology

Abstract content:

Pleural fluid mesothelin levels are elevated in effusions from mesothelioma. The value of pleural fluid mesothelin over existing diagnostic tests and the reproducibility of pleural fluid mesothelin levels have not been established.

Aim: To (i) assess the diagnostic value of pleural fluid mesothelin levels in patients with undiagnosed pleural effusions; and (ii) determine variation of pleural fluid mesothelin levels over time in patients with persistent effusions.

Methods: Mesothelin concentrations were determined in 306 pleural fluid samples by ELISA (CIS Bio, France). Pleural fluid was prospectively collected from 139 patients presenting to a tertiary pleural unit with a previously undiagnosed pleural effusion, including effusions from mesothelioma (n=18), metastatic carcinomas (n=57) and benign causes (n=64). Serial samples of pleural fluid were obtained from patients who received an indwelling pleural catheter (n=19) or repeated thoracentesis (n=15).

Results: Pleural fluid mesothelin concentrations were significantly higher [median (range) 42.8 (3.7-96.2) nM/L] in the mesothelioma group compared with metastatic carcinomas [5.95 (0-86.7) nM/L] and benign effusions [5.79 (0-82.0) nM/L], $p<0.0001$.

At the optimal cutoff of 20nM/L, the diagnostic sensitivity and specificity of pleural fluid mesothelin levels for mesothelioma were 78% and 87% respectively. All false negative cases were mesotheliomas of the sarcomatoid subtype.

Pleural fluid mesothelin measurement provided additional value over cytological analysis. In effusions negative for malignant cells on cytologic examination (86 of 125), measurement of pleural fluid mesothelin levels offered a sensitivity and specificity of 70% and 95% respectively for the diagnosis of mesothelioma. Importantly, pleural fluid mesothelin levels correctly identified all four cases of mesothelioma in pleural fluids 'suspicious' but not definite for malignant cells (n=7).

Intra-individual reproducibility was excellent. In paired pleural fluid samples obtained within seven days, mean (±SD) variation of mesothelin was -0.11 (± 8.42) nM/L in mesothelioma patients, and 0.76 (± 6.02) nM/L in non-mesothelioma cases. Pleural fluid mesothelin levels increased significantly with time ($r=0.595$, $p<0.0001$) in mesothelioma patients, reflecting disease progression.

Conclusion: Pleural fluid mesothelin provides additional diagnostic value for mesothelioma over cytologic examination. Mesothelin measurements are highly reproducible in the short term (<7 days) but increase over time in patients with mesothelioma.

Number: 62

Abstract title:
The use of mesothelin for monitoring patients with mesothelioma

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Keywords:
mesothelin

Abstract content:

Numerous studies have demonstrated the sensitivity and specificity of the biomarker mesothelin for diagnosing malignant mesothelioma both in serum and in effusion samples. The current study examined the utility of mesothelin for monitoring of patients, both during the course of natural disease progression and in response to therapy.

Longitudinal serum samples were collected from mesothelioma patients during the course of their routine standard care, and mesothelin concentrations were determined using the MESOMARK™ assay (Fujirebio Diagnostic Incorporated, Malvern PA).

There was good correlation between mesothelin level and tumour stage, as defined by the IMIG TNM staging system) ($r=0.579$; $p<0.05$). Furthermore, mesothelin levels were correlated in 41 patients with tumour burden as measured by Positron Emission Tomography (PET). Using baseline measures, there was a positive correlation of mesothelin levels with total glycolytic volume (TGV; $r=0.4$; $p=0.01$) and maximum standardized uptake value (SUVmax; $r=0.34$; $p<0.05$). Changes in mesothelin level also reflect reduction in tumour burden as evidenced by the finding that an average 50% reduction of pre-surgery mesothelin concentration was observed in 14 patients following extrapleural pneumonectomy. In 35 patients who underwent partial debulking surgery a reduction in mesothelin level was also observed though the average reduction was approximately 15% of baseline. In over 70% of 52 patients who received chemotherapy (various regimes) there was concordance between patient response, at specified time points, as defined by radiological measures and percent change in mesothelin concentration.

Further, more complex analyse of longitudinal changes in mesothelin levels is underway however, at present we are confident that the biomarker mesothelin has a valuable role to play in the clinical management of mesothelioma patients.

Number: 63

Abstract title:
Early change in serum VEGFand osteopontin during treatment for mesothelioma is predictive for survival.

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Keywords:
VEGF osteopontin serum predictive treatment survival

Abstract content:

We evaluated a panel of potential serum markers for their predictive value in a cohort of patients treated with thalidomide in 2 previously reported Phase II trials (N= 62). Serum levels of vascular endothelial growth factor (VEGF), osteopontin, C-reactive protein (CRP), mesothelin, interlukin-6 and soluble IL-6 receptor were measured pre-treatment and after 8 weeks using ELISA method. Survival correlations were made using univariate analyses with median levels used as cut-off. Only VEGF and CRP showed a significant relationship between pre-treatment (baseline) level and survival. Patients with VEGF < median had a mean survival of 70 weeks compared to 31 weeks for those with > median VEGF levels (P<0.05). Mean survival when CRP < median was 62 weeks compared to 31 weeks with CRP > median (P<0.05). The change between baseline and 8 week VEGF and osteopontin was also prognostic of survival. Decreasing VEGF was associated with a mean survival of 79 weeks compared to 39 weeks for increasing VEGF (P<0.05). Decreasing osteopontin was associated with a mean survival of 108 weeks compared to 47 weeks for increased levels (P<0.05). VEGF change on treatment (increasing or decreasing) was predictive regardless of baseline VEGF. Patients with high baseline VEGF and decreasing VEGF had a mean survival of 56 weeks compared to 26 weeks for those with increasing VEGF (P<0.05). Likewise, osteopontin change on treatment (increasing or decreasing) was predictive in patients with both high or low baseline VEGF: patients with high baseline VEGF and decreasing osteopontin had a mean survival of 92 weeks compared to 45 weeks for those with increasing osteopontin levels (P=0.05). Change in osteopontin level was also prognostic in the patient group with low pre-treatment VEGF: patients with decreasing osteopontin had a mean survival of 125 weeks compared to 62 weeks for those with increasing osteopontin (P<0.05). These findings suggest that the changes in VEGF and osteopontin during treatment may be more useful as predictive markers than their pre-treatment levels. Changes in VEGF and osteopontin may provide a means of monitoring treatment response in mesothelioma and should be evaluated prospectively.

Number: 64

Abstract title:
Oncolytic type 5 adenoviruses with type 35 fiber-knob structure produce better cytotoxic effects to mesothelioma cells that express the type 5 cellular receptors at a low level

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Keywords:
gene therapy, adenovirus, coxsackievirus and adenovirus receptor, CD46, E1A, tumor promoter

Abstract content:

We investigated a possible application of adenoviruses (Ad)-mediated cell death to mesothelioma treatments. The E1A gene of Ad encodes a transcriptional factor that regulates the viral replication and S phase entry of cell cycle in the infected cells. Ad in which the E1A expression is regulated with an exogenous promoter replicate depending on the promoter specificity and can produce cytotoxicity to the infected cells accordingly. Controlled E1A expression with tumor specificity thereby renders the Ad cytotoxic to the infected tumors. We examined transcriptional activities of regulatory regions of the midkine, surviving and cyclooxygenase-2 genes and found that these putative tumor promoters could activate a reporter gene in mesothelioma cells. We developed type 5 Ad (Ad5) by integrating the putative tumor promoters-linked with the E1A and E1B genes. These Ad powered by the promoters achieved cytotoxic effects to human mesothelioma cell lines and produced oncolytic activities with minimal toxicity to normal cells. These oncolytic Ad however did not produce significant anti-tumor effects in some cell lines. Infectivity of Ad5 to cells is primarily mediated by the interaction between the Ad fibers-knob region and the coxsackievirus and adenovirus receptor (CAR). Down-regulated CAR expression, often found in human tumors, hampered Ad5-mediated gene transfer. The CAR expression level of mesothelioma cells was variable and the infectivity of Ad5 to CAR-low expressing cells thereby diminished. The decreased anti-tumor effects with oncolytic Ad5 could be attributable to the down-regulated CAR expression. Type 35 Ad use CD46 molecules as their cellular receptors and expression levels of CD46 on tumors were not down-regulated. Chimeric Ad5 in which the fiber-knob structure was substituted with that of the type 35 (Ad5F35) would infect human cells in a different manner from Ad5. We found that Ad5F35 infected mesothelioma cells better than Ad5 and that oncolytic Ad5 with the fiber-knob replacement produced greater anti-tumor effects than unmodified Ad5 particularly to CAR-low expressing mesothelioma cells. These data suggest that the fiber-knob modified Ad5 powered by putative tumor promoters are a potential therapeutic modality to most of mesothelioma and could be a feasible strategy in combination with conventional chemotherapy.

Number: 65

Abstract title:
Immunological changes in mesothelioma patients and their experimental detection

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Keywords:
mesothelioma, immunology, tumor immunity, apoptosis, cytokine

Abstract content:

It is common knowledge that asbestos exposure causes asbestos-related diseases such as asbestosis, lung cancer and malignant mesothelioma (MM) not only in people who have handled asbestos in the work environment, but also in residents living near factories that handle asbestos. These facts have been an enormous medical and social problem in Japan since the summer of 2005. To analyze the possibility that immunological alteration in asbestos-related diseases (ARDs) such as asbestosis (ASB) and malignant mesothelioma (MM) may affect the progression of cancers, a human adult T cell leukemia virus-immortalized T cell line (MT-2Org) was continuously exposed to 10 g/ml of chrysotile-B (CB), an asbestos. After at least 8 months of exposure, the rate of apoptosis in the cells became very low and the resultant subline was designated MT-2Rst. The MT-2Rst cells were characterized by (i) enhanced expression of bcl-2, with regain of apoptosis-sensitivity by reduction of bcl-2 by siRNA, (ii) excess IL-10 secretion and expression, and (iii) activation of STAT3 that was inhibited by PP2, a specific inhibitor of Src family kinases. These results suggested that the Contactbetween cells and asbestos may affect the human immune system and trigger a cascade of biological events such as activation of Src family kinases, enhancement of IL-10 expression, STAT3 activation and Bcl-2 overexpression. This speculation was partially confirmed by the detection of elevated bcl-2 expression levels in CD4+ peripheral blood T cells from patients with MM compared with those from patients with ASB or healthy donors. Further studies will be required to verify the role of T cells with enhanced bcl-2 expression in tumor progression induced by asbestos exposure. In addition, high plasma concentrations of interleukin (IL)-10 and transforming growth factor (TGF) -ß, and multiple over-representation of T cell receptor (TcR)-Vß in peripheral CD3+ T cells found in MM patients. We also detail an experimental long-term exposure T-cell model. Analysis of the immunological effects of asbestos may help our understanding of the biological effects of asbestos.

Number: 66

Abstract title:
Dendritic cell-based immunotherapy for malignant pleural mesothelioma

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Keywords:
dendritic cells, immunotherapy, phase I study

Abstract content:

Introduction:
Dendritic cells (DCs) are extremely potent antigen presenting cells specialized for inducing activation and proliferation of CD8+ cytotoxic T lymphocytes and other lymphocytes. Exploiting these immunostimulatory capacities of DCs holds great promise for cancer immunotherapy. DCs can be generated in large amounts in vitro, in the absence of the suppressing tumor microenvironment, and subsequently injected in a mature state to induce anti-tumor responses. A phase I clinical trial was initiated to define the safety and toxicity of tumor lysate-pulsed DCs injected in patients with mesothelioma after chemotherapy. Secondary end-points include immune responses by skin delayed type hypersensitivity reactions on mesothelioma cell lysates and the control antigen keyhole limpet hemocyanin (KLH) both in vivo and in vitro.

Methods:
Patients with enough tumor cells (> 150x10e6 tumor cells) in their pleural effusion at time of diagnosis were included in the study. Tumor cell lysates were generated by repeated freeze-thaw cycles and irradiation. After chemotherapy, patients underwent leukapheresis. Monocytes were isolated by elutriation and DCs could be cultured in sufficient amount using GM-CSF and IL-4. After 5 days in culture, DC were pulsed with autologous tumor lysate and KLH. A cytokine cocktail induced the final maturation step at day 8. The morphology and phenotype of cultured cells was consistent with dendritic cells. Nine patients received the three planned DC vaccinations and are currently followed.

Results:
This study showed that injection of DCs was overall well tolerated without systemic toxicity, with the exception of a low-grade flu-like symptoms: fever, rigors, and a temporarily local skin reaction after DC injection (mild grade 1 or 2). Local accumulation of T cells were found at the vaccination sites. All participants thus far experienced no rash or lymphadenopathy or developed any clinical evidence of autoimmunity or rheumatoid disease. DTH and strong antibody immune responses (IgM and IgG) on KLH were seen in all patients indicating that immune responses were generated. It is important to emphasize that several laboratory tests need to be performed to allow firm conclusions (e.g. in vitro assays of lymphocyte function).

Discussion & conclusion:
First results from our phase I clinical trial indicate that DC-immunotherapy is safe and feasible for mesothelioma patients.

Number: 67

Abstract title:

Low-dose cyclophosphamide synergizes with dendritic cell immunotherapy in antitumoral responses in a mouse model for mesothelioma

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Keywords:
dendritic cells, immunotherapy, regulatory T cells, cyclophosphamide

Abstract content:

Introduction:
Malignant mesothelioma (MM) is a cancer with dismal prognosis. Currently we are investigating dendritic cell-based immunotherapy in patients with MM after chemotherapy. Further optimization in mice is recommended to exploit the full therapeutic potential of dendritic cells. It is known that tumor cells create an immunosuppressive environment that can lead to a down-regulation of the anti-tumor immunity. One type of suppressive cells, the regulatory T cells (Tregs) seems instrumental in allowing a growing cancer to evade immunological attack. These cells may contribute to the impaired T cell function frequently observed in mesothelioma patients. The goal of this study is to investigate measures that can overcome the suppressive function of regulatory T cells in combination with DC immunotherapy to increase the success rate of tumor eradication.
Materials & Methods:
At day 0, immunocompetent BALB/c mice were inoculated with a lethal dose of AB1 mesothelioma tumor cells. Tumor lysate-pulsed DCs were administrated intraperitoneally at day 10. CTX was added to the drinking water from day 3 till day 10 and / or from day 14 till day 21. Mice were killed if profoundly ill, and scored death in survival analysis. Tumors, blood and lymph nodes were excised and analyzed for Tregs using immunohistochemical stainings and flowcytometry.
Results:
Increased numbers of Tregs were found within the blood, draining lymph nodes, and tumors of mice with mesothelioma. Administration of low-dose CTX prevented the induction of Tregs leading to an increased survival. No toxic side effects were observed in mice receiving low-dose CTX.
Discussion & conclusion:
We demonstrate in a mouse model that immunotherapy using stimulated dendritic cells is a powerful tool to control MM outgrowth. We found that low-dose cyclophosphamide induced beneficial immunomodulatory effects by reducing the levels of Tregs. It improves DC-based immunotherapy leading to an increase in median and overall survival. Future studies will demonstrate the usefulness of this combination treatment in mesothelioma patients.

Number: 68

Abstract title:
5T4 as a tumour-associated antigen in malignant pleural mesothelioma

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Keywords:
Malignant Pleural Mesothelioma, Immunotherapy, 5T4

Abstract content:

Malignant pleural mesothelioma (MPM) is a malignancy of the lung mesothelium with late diagnosis and resistance to conventional treatments. Alternative strategies are needed to improve disease prognosis. Pre-clinical models of MPM have responded favourably to immunotherapeutic approaches but cancer vaccine design is hampered by the relative lack of MPM-associated tumour antigens. 5T4 is a 72 KDa oncofoetal antigen, highly expressed on a wide range of tumours; the cancer vaccine TroVax® (modified vaccinia virus Ankara encoding 5T4) is presently undergoing phase III clinical trials in renal cancer. The aim of our project was to assess if 5T4 may serve as an immunological target in MPM. We have studied the expression of 5T4 in mesothelioma cell lines and also in the cellular fraction of pleural fluid samples obtained from MPM patients. Varying levels of 5T4 cell surface expression was identified by flow cytometry in 19 out of 19 cell lines and in 6 out of 6 pleural fluid samples where tumour cells were identifiable in the cellular fraction by flow cytometry. The findings were confirmed by western blotting. 5T4-specific CD4+ memory T cell responses have been detected in a patient with 5 year disease-free survival following pneumonectomy. Ongoing work is focusing on screening MPM patients for 5T4 memory T cell responses and characterising T cells with the relevant specificities. Taken together, we report here for the first time the overexpression of 5T4 on mesothelioma cells, indicating that 5T4 is a potential new target antigen for the immunotherapy of MPM.

Number: 69

Abstract title:
Immunochemotherapy reduces recurrence of malignant pleural mesothelioma

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Keywords:
Immunotherapy - cisplatin - intrapleural - toll like receptors - CpG-ODN

Abstract content :

Objective: To assess the effect of immuno-chemotherapy on the extent of local tumour recurrence in an established rat model of malignant pleural mesothelioma (MPM).
Methods: Six days after subpleural inoculation of a syngeneic MPM cell line (IL-45), tumour nodule was resected after left-sided pneumonectomy. Animals were randomized into 4 treatments groups for intrapleural therapy: control (n=6), 500 ;g CpG-ODN (Cytosine-phosphate-guanosine-oligodeoxynucleotide) (n=6), cisplatin-fibrin (n=6), cisplatin-fibrin+500 ;g CpG (n=6). 6 days later the volume of tumour recurrence was assessed, which was the primary endpoint. Secondary endpoints were the SRY-gene (sex-determining-region Y) expression for quantification of the ratio host/tumour cells in the local recurrence and cytokine expression profile in the tumour tissue by qPCR. T lymphocyte subpopulations in the tumour recurrence tissue were evaluated by immunohistochemistry. Treatment-related toxicity was assessed by repeated blood sampling.
Results: The volume of tumour recurrence was significantly reduced from 610 mm3 in the control group to 11.7 mm3 in the cisplatin-fibrin group (p=0.004) and to 21.8 mm3 in the cisplatin-fibrin+CpG group (p=0.004). Pro-inflammatory cytokines (IFN-, IL-6, IL-12) were increased after treatment with cisplatin-fibrin+CpG in comparison to cisplatin-fibrin alone but differences were not statistically significant. The determination of SRY gene by qPCR-technique showed a higher ratio of host/tumour cells in the cisplatin-fibrin+CpG group (45/55%) compared to the cisplatin-fibrin group (27/73%). In comparison to the control group, animals treated with cisplatin-fibrin+CpG showed a statistically significant higher number of CD8+ cells in the tumour tissue ($p<0.05$). No significant treatment-related toxicity was observed.
Conclusions: Adjuvant treatment with chemo- or chemo-immunotherapy leads to significant reduction of mesothelioma recurrence after surgery in this rat MPM model. Chemo-immunotherapy resulted in an increased recruitment of inflammatory cells to the site of tumourigenesis and elicited higher level of tumour growth inhibiting cytokines.

Number: 70

Abstract title:
The effect of chemotherapy on the immune system in patients with malignant mesothelioma

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Abstract content:

Chemotherapy and immunotherapy have historically been considered antagonistic treatment modalities due to the variable lymphopaenia experienced as a side effect of many cytotoxic drugs. Recently however, research using animal models has demonstrated that certain chemotherapy drugs, despite causing decreases in lymphocyte numbers, can actually enhance the anti-cancer immune response, possibly via the induction of 'immunogenic' tumour cell death. We are currently undertaking a study to determine the effect of different chemotherapy regimes on the anti-tumour immune response in patients with mesothelioma. The generation of an effective immune response against a tumour involves the presentation of antigen to CD8+ effector T cells, which are able to kill tumour cells directly. T regulatory cells (Tregs), on the other hand, have been shown to exert a suppressive effect. The effect of chemotherapy on these two cell types is therefore being specifically assessed. Once known, this will have major implications for the development of combined chemo-immunotherapy treatment protocols. Patients with histologically or cytologically confirmed mesothelioma who are to begin chemotherapy as part of usual care are being invited to take part in the study. Blood samples are taken from patients prior to commencement of chemotherapy and then at 3 time points across the course of treatment. Our work confirms the feasibility of using 8-parameter flow cytometry to perform longitudinal analyses of changes in the number, activation status and proliferation of CD8+ T cells and Tregs.

Number: 71

Abstract title:
Modulation of translesion synthesis: Impact on chemotherapy resistance in malignant pleural mesothelioma

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Keywords:
translesion synthesis, rev3, malignant pleural mesothelioma, siRNA, shRNA, cisplatin

Abstract content (maximal 350 words, no graphs)**:**

Background: Malignant pleural mesothelioma (MPM) is most commonly treated with a multimodality therapy including treatment with cisplatin or cisplatin-analogues, which lead to the formation of inter- or intrastrand DNA adducts. Cisplatin adducts can be repaired or, if not repaired, induce replication fork stalling which can by overcome by specific translesion polymerases.
Translesion polymerase ζ consists of two subunits, Rev3 is the catalytic- and Rev7 the structural subunit. The translesion polymerase ζ is responsible for the translesion synthesis (TLS) of cisplatin based adducts and the repair of DNA interstrand crosslinks. Rev3 deficient vertebrate cell lines show the highest sensitivity to cisplatin compared to other repair-deficient cell lines. Rev3 inhibition by antisense treatment confers higher cisplatin sensitivity and lower mutagenicity in immortal human fibroblasts.
Working hypothesis: Down-regulation of Rev 3 sensitizes MPM cells to cisplatin treatment and reduces the formation of cisplatin resistance.
Results: We showed that the expression of Rev3 in human MPM cells is dependent on cell culture confluency and is also affected by cisplatin treatment in a time-dependent manner. Functional inhibition of REV3 by siRNA increased replication fork breakdown as indicated by enhanced H2AX phosphorylation. REV3 expression in rat and human MPM cells was successfully inhibited by transient transfection with plasmids containing short hairpin constructs targeting REV3.
We generated stable HEK293 and human lung fibroblast (Wi38-SV40) cell lines with decreased REV3 expression. Functional inhibition of REV3 in the HEK293 and Wi38-SV40 cell lines resulted in increased genotoxic stress as indicated by increased p53 expression, a slower growth rate and increased cisplatin sensitivity.
Conclusions: We showed that functional inhibition of translesion polymerase ζ by shRNA against REV3 increased replicative stress in MPM cell lines and increased cisplatin sensitivity in human cells.

Number: 72

Abstract title:
NONSPECIFIC ACTIVE IMMUNOTHERAPY INCREASED SURVIVAL IN MALIGNANT MESOTHELIOMA

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Keywords:

Nonspecific active immunotherapy - macrophages - immunity - therapy

Abstract content:

Introduction:

Immunization with an inactivated-bacteria vaccine is a way to create immunity against certain diseases. The injection of *"Pneumovax23"prior to the surgical treatment of malignant mesothelioma (MM) is a tool to taget tumor cells (Tc) by mounting an immune response. The success of this approach depends upon the ability to stimulate effectively both the cell-mediated and the antibody-mediated immunity, which must work in concert to overcome Tc growth. In this report, we examined the possibility to activate the immune system in order to slow down Tc proliferation or to maintain the cells in a dormant state allowing the development of an appropriate treatment. * [Pneumococcal polysaccharide vaccine (PPV)]

Methods and Results
Three patients accepted to donate 50 ml of peripheral blood cells to evaluate their cell-mediated immune reactivity after pneumopleurectomy. Peripheral blood cells were separated by gradient centrifugation and cultivated on collagen in the presence of a gram+ bacteria vaccine (PPV) and Tc supernatant.
Results demonstrated the proliferation of large granular lymphocytes, B cells and macrophages (Mø). These indicate a stimulating effect and differentiation of monocytic cells. A Cytotoxic assay demonstrated that activated macrophages (AM) were able to kill Tc.
Two patients died some months later without any vaccination. The Third one, who received a gram+ vaccine 3 months before the surgical therapy, continued the chemotherapy and was clinically fit and able to return to work at 40%. He did not receive any other therapy for 4 years before experiencing a recurrence, proven by pathological analysis. Monocytic cell proliferation was not observed in vitro. The patient was immediately reboosted with "Prevenar7"**. This injection was associated with peripheral blood cell proliferation. Two years later, this response disappeared again.

This observation suggested that successive revaccination should be provided whenever a decrease in the immune response occurs, which may last as long as 2 years. He received a new injection of PCV in June 2008. **[Pneumococcal conjugate vaccine (PCV)]

Perspective and Conclusion :

In a future assay, treatment based on the transfert of autologous AM by adoptive immunotherapy will be used as another arm against Tc.

This study reports for the first time marked prolongation of survival with a good quality of life for the patient treated with associated therapies, including nonspecific active immunotherapy.

This is a single informative and undergoing case report with an unusually long survival of almost 7 years after the onset of MM. Future studies of the correlation between the vaccination response and clinical evolution are warranted.

Number: 73

Abstract title:
International mortality trends

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Keywords:
UK, Australia, mesothelioma, amosite, case-control

Abstract content:

By 1970 the UK had stopped using crocidolite and led the world in asbestos regulation, yet it now has over 2,000 mesothelioma deaths per year, the highest rate in the world and five times that in the US in men born between 1940 and 1955.
We conducted the first UK population-based study of mesothelioma and the largest worldwide, interviewing 612 mesothelioma patients and 1420 controls. We also compared death-rates, asbestos imports and male:female mortality ratios of mesothelioma in other countries to assess the contribution of different asbestos types on mesothelioma rates and to estimate the background rate in the absence of asbestos use.
Our main conclusion is that end-user exposure to amosite was a major cause of the extraordinary mesothelioma rate in British men born in the 1940s. The UK was the main importer of amosite, which carried the same control limit as chrysotile until 1983. Current mesothelioma mortality and historical patterns of amosite use in Australia are similar to those in the UK.
Other findings include: (1) about 1 in 17 of British carpenters and 1 in 50 of plumbers, electricians and painters born between 1940 and 1950 will die of mesothelioma; (2) only about 1% of mesotheliomas were caused by work in asbestos factories; (3) there appears to be a worldwide background rate unrelated to asbestos producing a lifetime risk of approximately 1 per 5,000 in both sexes; (4) the excess rate above this background in women throughout the world is approximately one tenth of the male rate; and (5) the lifetime risk in British men and women who report no potential asbestos exposure is four times this background (almost 1 per 1,000), suggesting that mesotheliomas were caused by unsuspected asbestos exposure in a wide range of occupational and non-occupational settings.

Number: 74

Abstract title:
The Latrobe Valley Power Industry Cohort Study: A multi-disciplinary approach to studying asbestos related diseases

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Keywords:
cohort study

Abstract content:

The Latrobe Valley has been the site of electricity generation for the State of Victoria, Australia, since the 1920's. Large amounts of asbestos were used in the construction and maintenance of power stations, and significant asbestos exposures have been documented. The mortality due to mesothelioma in the Latrobe Valley is the highest in Victoria, at 4.6 times the state average. This concentration of cases, plus the fact that the former State Electricity Commission (SEC), a government body responsible for construction and operation of the power stations, was the dominant employer of a highly unionised workforce makes the Latrobe Valley an ideal place to recruit and study a cohort of highly asbestos exposed individuals. An estimated 55,000 current or former SEC workers were still alive in 2003.
We have used a combination of a local Community Group and relevant Trade Unions to assist with the recruitment of approximately 900 (out of an anticipated total of 1,000) current or former power industry workers into the study. All participants are asked to donate a blood sample each year for three years and to date, more than 300 blood samples have been collected. Each participant is also asked to complete a detailed questionnaire from which we will calculate likely asbestos exposure, and collect other demographic and health related information. We have also commenced determination of mesothelin levels in the blood samples to quantitate the natural variation in this protein's levels in an otherwise healthy asbestos exposed population. We are also offering a tailored smoking cessation program to any smokers in the cohort. Where a participant has consented, all samples collected are available to other researchers conducting ethically-approved research into asbestos.
We will present our considerations around the design of the study, some analysis of the cohort to date, and preliminary results of mesothelin testing. We will also discuss how researchers may use this resource in their research.

Number: 75

Abstract title:
The French national program for post-occupational surveillance of subjects exposed to asbestos

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Keywords:
occupational asbestos exposure, retired workers, medical surveillance, epidemiological surveillance, cancers

Abstract content:

Background and aims: The French national Institutes for Public Health Surveillance (InVS) and for Medical Research (Inserm) have established a surveillance program for retired subjects exposed to asbestos during their working life. Its objectives are to identify exposed workers and to propose them a medical surveillance, to describe past exposures and their long-term health effects, and to assess the program in terms of benefits for health and compensation.

Methods: Since 2005, two prospective cohorts of retired workers have been set up among former male salaried workers (“Spirale” cohort) and self-employed craftsmen (“Espri” cohort). In 2008, both cohorts cover 31 French “départements” (covering one third of the population). Each year, a questionnaire is mailed to new retired workers (50 000 salaried workers and 4 500 craftsmen) to detect past occupational asbestos exposure. The exposure assessment is made by medical and industrial hygiene experts. The medical surveillance is proposed to subjects according to specific exposure criteria. The French national medical databases are used for the cohort follow-up.

Results: During the pilot stage (2005-2007), the participation rate was 24% for salaried workers (without reminder) and 67% for craftsmen (with one reminder). Heavy exposures were found for occupations in construction, ship-building and fabrication of metal products, and also for motor vehicle mechanics. First estimates of the lifelong prevalence of occupational asbestos exposure indicated than about one half of retired craftsmen have been exposed during their working life, versus one quarter of the salaried workers. Among craftsmen who had a chest CT scan, about one quarter showed asbestos-related abnormalities or pathologies, essentially pleural plaques.

Discussion and conclusions: The first results from the French national program for post-occupational surveillance highlighted the expectation of retired workers for surveillance of past occupational exposures. Its expansion to the whole territory is planned and will include around 250 000 male salaried workers retiring each year and 17 000 self-employed craftsmen. The assessment of the impact of the program on benefits for health and compensation during the cohort follow-up will provide guidance for public policy about surveillance of workers exposed to carcinogenic agents.

Number: 76

Abstract title:
A public health critique of South African mesothelioma compensation

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Keywords:
Compensation, Public health, Health promotion

Abstract content:

Introduction
There have been five broad avenues in South Africa for mesothelioma victims to achieve compensation. These are:
1. The statutory compensation law for miners, the Occupational Diseases in Mines and Works Act of 1973, which offers compensation for all dust diseases suffered by miners in South Africa. This is funded by ongoing statutory mine levies, and miners are paid €7200 for mesothelioma.
2. The Cape PLC case of 2002, where litigation eventuated in a judgement for compensation, which was appealed and a reduced fund worth €7 Million was set up.
3. The Asbestos Relief Trust of 2003, which was established in a out-of-court settlement between asbestos sufferers and the mining companies Msauli, Gefco and their parent company Gencor, which was in the process of dissolving. These three companies agreed to set aside €42 Million to compensate ex-workers who had worked in South African mines for all asbestos related conditions.
4. The Kgalagadi Relief Trust of 2006, which was set up in a voluntary settlement with the successors of previously Eternit-owned mines, where compensation was guaranteed for all incident cases. This settlement is estimated to be worth €9 Million, and
5. Private individual litigation settlements in our courts, which occur occasionally. These are estimated to be worth €90 000 each.
Method
The activities of these compensation avenues were measured against an idealized public health approach – the prevention of disease, promotion of health and prolongation of life through the organized efforts of society.
Results
Avenues 1, 2 and 5 have remained compensation schemes. The Trusts (avenues 3 and 4) have by contrast distinguished themselves by adopting a more holistic approach to mesothelioma, and have performed at the primary, secondary and tertiary levels of prevention, as well as in health promotion. The Trusts have engaged government in different sectors to improve public policies; improved the diagnosis, management and palliation of mesothelioma in prevalent areas; funded community organizations that create awareness of mesothelioma and support victims.
Discussion
Compensation schemes make a public health impact if they also work developmentally, with affected communities in mind.

Number: 77

Abstract title:
"Dutch Asbestos Victims Institute": a social responsable solution for a complex historical problem
Abstract

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Abstract content :

The "Dutch Asbestos Victims Institute" is an example of the famous "poldermodel". Government, employers, insurance companies, trade unions and victims organisations found an, for all parties, acceptable solution regarding the compensation of mesothelioma victims. Currently, financial compensation is restricted to cases with proven mesothelioma and occupational asbestos exposure. The corner stones of a succesful claim are sufficient medical evidence and "reasonable" exposure rates. Therefore, medical science and expertise are indispensable in order to excecute any compensation scheme. Professor De Mol will give an insight into the background of the institute and the procedure it works with. In the second part he will pay attention to the medical research programme the institute is going to fulfil in the coming years.

Number: 78

Abstract title:
Deadly Dust: Mitigating the Impact of Asbestos Through Education and Prevention, Early Detection, and Increased Funding for Research

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Abstract content:

Although she is neither doctor nor scientist, Mrs Linda Reinstein co-founded the Asbestos Disease Awareness Organization which is dedicated to providing resources, support, and advocacy for asbestos victims and their loved ones, world-wide.
Mrs Linda Reinstein will focus on mitigating the impact of asbestos requiring a three prong approach: prevention in both occupational and non-occupational settings, improvement in early detection and diagnosis, and increased research funding.
Occupational dust-related disease is on the decline (e.b., silicosis, bysinosis, CWP) in the United States, except for asbestos exposure which remains on the rise. Non-occupational asbestos exposure continues, and is becoming more prevalent, resulting in exposure in more unusual settings and to a less typical population that is younger and female. The ADAO (Asbestos Disease Awareness Organization) has been working for increased product testing, recognition and justice for victims of asbestos exposure, The World Health Organization (WHO) and International Labor Organization (ILO) both have adopted policies to eliminate all asbestos-related disease. Yet, work place exposures continue while the asbestos industry argues that chrysotile is the safe form of asbestos. Earlier diagnosis is the first step to improving treatment for victims of asbestos-related diseases.
Recognition of early warning signs by clinicians and consumers, along with identification of high risk patients by occupational and exposure history is essential. The patient profile of those with asbestos-related disease is changing as unsuspected sources of exposure increase. Inaccuracy of reporting of asbestos-related disease and deaths is another barrier to improved care and treatment. Increased attention is needed to improve non-occupational reporting. Death certificate inaccuracies in reporting mesothelioma as an underlining cause of death and codes for reporting of pleural and peritoneal malignancies are necessary for more accurate data on which to develop policies.
Advocacy work to increase research funding through registries and valid statistics must occur if we are to move closer to eliminating asbestos-related disease.
An underlying theme of this presentation will be the urgent importance of communication and cooperation between scientists, doctors, governments, labor groups, and the worldwide community of victims.

Number: 79

Abstract title:
Mesothelioma in Japan after the enactment of Asbestos-Related Health Damage Relief Law

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Keywords:
mesothelioma, occupation, relief, compensation

Abstract content:

In Japan, the Asbestos-Related Health Damage Relief Law was entered into force on 27 March 2006, and a new relief system started for the patients of mesothelioma and asbestos-related lung cancer. This law covers victims of these two malignancies, who are not compensated by worker's insurance scheme such as neighbors around asbestos factories, asbestos workers' families, and self employed workers.
From April 2006 to March 2008, 1,925 sufferers proposed to get this relief, and 1,152 mesothelioma patients were recognized by this Law and 181 were refused because of incorrect diagnosis of mesothelioma. As for lung cancer, 789 sufferers proposed but only 289 patients were recognized. 202 were refused according to the criteria for asbestos-related lung cancer..
During the first year of the enactment of this law, 631 cases of pleural mesothelioma were relieved. 414 were males, and 158 were females. There were 45 peritoneal mesothelioma (males 28, females 17), and 14 cases were pericardium and others. Among these pleural mesotheliomas, most were construction workers, and engaged in manufacturing, but 11 cases were teachers. Residence history was obtained by self-questionnaire by patients or his/her families. There were 50 pleural mesotheliomas who had the history of residence in Amagasaki City, where a large scale of asbestos factory was located , that had been manufacturing asbestos cement pipe between 1954 and 1975 using crocidolite and chrysotile.
During the same period (from April 2006 to March 2007), 1,007 mesothelioma and 790 lung cancer were compensated as occupational cancer by worker's insurance scheme.
Japan has now encountering the epidemic of asbestos-related cancers.

Number: 83

Abstract title:
A case-control study of malignant mesothelioma in subjects with no known exposure to asbestos

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Keywords:
aetiology, non-asbestos related mesothelioma, occupation, environment

Abstract content:

Background
Malignant mesothelioma (MM) is a rare and usually fatal cancer, generally caused by asbestos. However, in many series, up to a third of cases appear to have had no asbestos exposure.
Aims
To identify sources whereby people have been unknowingly exposed to asbestos and to identify other materials which may be lead to MM.
Methods
A matched case-control study design was used. Cases were selected from the Western Australian Mesothelioma Register with occupational and environmental histories but with no known exposure to asbestos. Two sets of 2 controls per case were selected from patients hospitalised for conditions unrelated to asbestos: (a) specific cancers (mainly breast and lymphomas), and (b) general medical conditions (mainly accidents and orthopaedic), matched for age, sex, postcode, and year. Occupational and environmental histories were obtained by questionnaire and coded by an expert industrial hygienist as to nature, likelihood, quantity and duration of exposure to 57 substances. Data were analysed using conditional logistic regression.
Results
Eligible cases without asbestos exposure were far fewer than anticipated. After 9 years there were 39 MM cases, 71 cancer and 76 medical controls recruited. Risk of MM was elevated, but not significantly so, after any exposure (probable or definite) to asbestos, silica, pesticides, welding fumes, other fumes, toxic metals, and other substances. There were also increasing risks (again not significant) with increasing quantity and duration of exposure to asbestos, wood dust, silica, pesticides, other fumes, synthetic mineral fibres, and toxic metals.
Discussion and Conclusions
Very few people have never been exposed to asbestos and careful elucidation of occupational and environmental histories usually uncovers exposures sufficient to cause MM. It seems likely that most cases of MM in people with no known exposure to asbestos occur, at a very low rate, among the huge numbers of people who have had small amounts of asbestos exposure.

Number: 84

Abstract title:
Onconase inhibits mesothelioma cells invasion induced by TNF-alpha.

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Abstract content:

Background: Onconase is a member of the pancreatic RNase A superfamily of ribonucleases. It has antitumor activity and is currently in clinical trial for the treatment of unresectable malignant mesothelioma. Previously, we reported that TNF-alpha plays a critical role in asbestos-induced oncogenesis and mesothelioma development. We found that TNF-alpha inhibits asbestos-induced cytotoxicity and increases the pool of asbestos-damaged human mesothelial cells (HM) that are susceptible to malignant transformation. Here, by using malignant mesothelioma cell lines, we further studied the effect of TNF-alpha on the process of tumor progression and mesothelioma cells invasion. The inhibitive effect of onconase on cell invasion was also analyzed.
Methods: Cytotoxicity was measured by lactate dehydrogenase (LDH) and MTT assays. Western blot and Electrophoretic Mobility Shift Assay (EMSA) were used to check NF-kB pathway. Metalloprotease (MMP)-9 expression and activity were measured by Western blot and zymography assay. Cell invasion was measured by invasion assay using matrigel invasion chamber.
Results and Conclusions: We found that TNF-alpha activated NF-kB pathway in mesothelioma cells. The activation of NF-kB induced the expression and activity of MMP-9, which promoted tumor cell migration and invasion. We report that onconase inhibited NF-kB activity induced by TNF-alpha in mesothelioma cells, and it suppressed tumor cells invasion by inhibiting MMP-9 expression and activity.

Number: 85

Abstract title:
Pleural mesothelioma as a second primary cancer post therapeutic radiation for Hodgkin's and non Hodgkin's disease.

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Keywords:
therapeutic radiation, Hodgkin\'s and non Hodgkin's lymphoma, survival

Abstract content:

Asbestos exposure is the dominant etiology for mesothelioma. Therapeutic radiation improved survival especially in childhood malignancies, yet it may be carcinogenic to the pleura and peritoneum resulting in secondary neoplasms. We reviewed 1875 medical records of MPM patients identifying those with reported history of therapeutic radiation (TR) for Hodgkin\'s and non Hodgkin's lymphoma (HL, NHL). Survival was estimated using Kaplan Meier with logrank comparison. We report demographic, clinical, pathologic features and outcome of these patients.
RESULTS:
Twenty-four patients, 19 male and 5 female with a median age of 45 (27 – 79) years were identified. Twelve patients had left-sided disease, 11 had right sided, and site was undocumented in one patient. Cell type was epithelial in 19 (79%) patients, mixed in 4 (17%) patients, and sarcomatoid in 1 (4%) patient. Latency from TR to diagnosis was 21.4 (1.6 – 43) years. Twenty patients (83%) had radiation for HL, while 4 patients (17%) had for NHL. Surgerical resection was performed in 14 out of the 24 patients; extra pleural pneumonectomy (EPP) (7: 29%) and pleurectomy (7; 29%). Of the resected, 11 were epithelial and 3 were mixed type. The median age of resected patients was 44 years. Median preoperative lab values were: WBC 10.3 (K/uL), RBC 4.3 (M/uL), and PLT 340.5(K/uL). Surgical staging was available for the 7 patients who underwent EPP: 2 were stage II and 5 were stage III (AJCC 6th Edition). Median survival for all patients was 16 months. Median survival for 14 patients who underwent resection was 32.6 months versus 12.5 months for 10 patients that had no resection (p = 0.046). The median asbestos body count in 4 resected specimens was 35.5 (12 - 108) ppg.
CONCLUSIONS:
Patients with pleural mesothelioma secondary to radiation are younger and have a survival advantage compared to historical controls. These patients may benefit from surgical resection. The atypical demographic and histological distribution of this subgroup support radiation therapy as an additional etiology or a risk factor for MPM.

Number: 86

Abstract title:
A population-based study on Radiotherapy (RT) as a risk factor for Malignant Mesothelioma (MM)

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Keywords:
second cancer, radiation, epidemiology, mesothelioma registry

Abstract content:

Background:
An increased risk of MM was observed among subjects followed up after adsorbed doses of radiation (Thorotrast) (Andersson, 1995) or who underwent RT for testicular cancers (Travis, 2005), HD and NHL (Tward, 2006; Teta, 2007; Hodgson, 2007).
We estimated the occurrence of MM due to RT in a population followed by a Mesothelioma Registry.
Methods:
We investigated 1177 new cases of MM, diagnosed by means of a morphological examination, occurred among the population of the Veneto region (North-east of Italy, 4.5 millions of residents) between 1987 and 2005 (843 cases among males; 1063 pleural, 107 peritoneal). Disease classification and exposure assessment followed predefined criteria. A face-to-face interview with patients or relatives was the main strategy to collect information but previous diseases and treatments were also assessed through the examination of clinical records.
A standardized incidence (standard: European population) was computed for the period 1990-2003.
Results.
Different degree of probability of asbestos exposure could be attributed in 946 MM cases (83% of the total) and very high percentages of MM were considered to have been exposed to asbestos, because of work or familiar and domestic exposures.
8 MM cases, all pleural, underwent RT for the treatment of HD (6 cases), reticulo-sarcoma, or NHL (one case, respectively).
These MM arose always time after a RT with no less than 20 Gy, homo-laterally to the side of treatment, inside the irradiated area, even among subjects not treated with chemotherapy and without asbestos exposure. The mean age at disease onset for MM due to RT is younger than the age of all MM cases, and latency is shorter than the one for asbestos exposure.
The MM incidence among the general population was 20.5 (95% IC 18.9-22) and 6,4 (5.62-9.2); 17.4 (15.9-18.8) and 3.7 (3.-4.3) among MM due to asbestos; 0,084 (0-0.181) and 0.126 (0-0.251) x 10 6 among MM associated with RT, among males and females, respectively.
Conclusion. We confirm that long survivors of some primary cancers treated with RT, especially those treated with field Mantle, can develop a MM. The incidence of these MM in the general population is however definitively low.

Number: 87

Abstract title:
Mesothelioma diagnosis in Québec: Pathology, Epidemiology and Compensation.

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Abstract content:

A recent study showed 22% concordance of Quebec Tumour Registry (QTR) incident mesothelioma cases from 1982 to 1996 (N=832) to cases compensated (N=184) by the responsible Provincial Board (CSST). We assessed possible overdiagnosis by ascertaining 2001-2002 incident QTR cases. All 187 incident cases had summary medical chart review; 64% gave consent for pathology re-evaluation. Respectively 8.6%, 10%, and 18% refused consent, did not reply, or were untraceable. Pathology samples were obtained for 89% of 119 consenting. 118 had medical imaging for review. Charts indicated occupation was sought in most (87%) cases; questions about past asbestos exposure were asked in 64%. 40% of charts mentioned the possibility of referring patients for compensation. New review of pathology and clinical diagnoses of mesothelioma were rated along five categories: definite/probable, possible, unlikely, definitely not, or unclassifiable. Clinically, 51% had a preliminary rating of definite/probable and 24% possible, with 18% unlikely or definitely not mesothelioma. Rate per 100,000 for clinically definite/probable and possible cases was 1.61 for men and 0.35 for women; overdiagnosis of about 34% compared to "unvalidated" QTR rates. Pathologically, for the first 64 cases, 55% were considered definite/probable, 23% possible, and 17% unlikely or definitely not mesothelioma; 5% had inadequate tissue. More than half of "possible" cases had alternative diagnoses which clinical correlation may resolve, and immunostains unavailable in 2001/2002 may help. Overall pathological-clinical correlation has to date been very good (80% for adjacent probability categories), and pathology reduces apparent clinical overdiagnosis further. Overall, we estimate pending further study QTR overdiagnosis at approximately 20%. This overdiagnosis may however be modified by other under-ascertained mesothelioma incident cases (such as misclassified lung cancers). We cannot estimate the true proportion of compensable incident QTR cases, because other CSST criteria are also involved, but if 100% of probable or definite cases were compensable it would exceed 50% and including all possible cases would lead it to exceed 70%. Overdiagnosis exists, but is probably not the principal reason for failure of concordance of compensation cases with QTR diagnoses. Possible solutions which have worked elsewhere include direct reporting of cases from the cancer registries to those concerned.

Number: 88

Abstract title:
Wittenoom, Women and Mesothelioma

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Keywords:
women, mesothelioma, crocidolite

Abstract content:

Introduction: Most of what we know epidemiologically about mesothelioma has been determined through the examination of cohort studies of men exposed to asbestos in their workplace. However, most women have been exposed to asbestos non-occupationally. Therefore, we do not know if these studies of men characterise the risks adequately for women. The aim of this study is to describe mesothelioma patterns among the Wittenoom women and to predict future mesotheliomas to 2030.
Methods: 2968 women and girls lived and worked at the crocidolite mining township of Wittenoom, in Western Australia, between 1943 and 1966. 416 worked for the Australian Blue Asbestos Company (ABA), and 2,552 were there as the wives or daughters of ABA workers. Quantitative asbestos exposure measurements were calculated for each individual based on their place and duration of work or their period and duration of residence. Models incorporating parameters for time since first exposure, competing risks of mortality from other causes and an amount for the annual clearance of fibres from the lung were used to predict mesothelioma mortality to 2030.
Results: 47 incident mesotheliomas occurred between 1960 and 2005, 36 among the residents and 11 among the ABA workers. Standardised Incidence Ratios were: for All women 77 (95%CI 57-103); Workers 83 (95%CI 41-148); and Residents 77 (95%CI 54-106) compared with the female Western Australian population. Exposure-response relationships were confirmed separately for women exposed environmentally OR=2.7 f/ml year (95%CI 1.9-3.8) and occupationally OR=1.7 f/ml year (95%CI 1.1-2.8). Women who lived with OR=2.6 (95%CI 1.0-6.8) or washed the clothes of an ABA worker OR=1.7 (95%CI 0.9-4.3) had a non statistically significant increased risk of mesothelioma compared with women who did not live with or wash the clothes of an ABA worker. Between 66 and 87 further mesotheliomas, many more than have arisen already, were predicted to occur by the end of 2030.
Conclusion: The brief period of the Wittenoom crocidolite industry will continue to exert a detrimental impact well into the future.

Number: 89

Abstract title:
FRENCH NATIONAL MESOTHELIOMA REGISTRY [MESONAT]: THE CONTRIBUTION OF PATHOLOGY.

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Keywords:
Mesothelioma, Registry, pathology,

Abstract content:

Background: French National Mesothelioma Registry (MESONAT) has been created in 1998 to support the research activities of the French National Mesothelioma Surveillance Program (PNSM). MESONAT is based on an exhaustive registration of all incidental pleural mesothelioma cases in specified geographical zones. These districts were chosen to be representative of France (employement and economic activity caracteristics). The registry, which is today, by its population (30 % of the french population in 2007) and its quality, one of the most important international systems of mesothelioma registration. All cases are validated according to a standardised procedure of pathological diagnosis certification performed by the French group of pathologists expert in the fields of mesothelioma (Mesopath Group). The aims of this procedure is to improve the exhaustiveness of cases and ascertain a better knowledge of the disease.

Design: From the files of the MESONAT registry, 1680 cases of suspected pleural malignant mesothelioma, validated according to the french procedure of pathological diagnosis certification, were collected between 1998-2005. Three experts, blindly reviewed the slides (H&E, plus immunohistochemical analysis with a panel of antibodies; two positive and two negative markers for the diagnosis of mesothelioma) without the knowledge of asbestos exposure or clinical information. They had to classify each case according to the WHO 2004 classification, as certain, uncertain (unclassifiable tumors or because of inadequate materials) and definitively excluded from mesothelioma diagnosis. In case of disagreement between one of the experts, the case was reviewed collectively during a consensus meeting with a quorum of at least 11 Mesopath members and was classified as above.

Results: Among these 1680 cases, 1287 (76 %) were mesothelial tumors (1274 malignant mesothelioma, 12 well-differentiated superficial papillary mesothelioma and 1 adenomatoid tumors), 263 (16 %) were uncertain and 130 (8 %) were excluded from mesothelioma diagnosis (80 metastasis, 18 others primitive tumors, 6 pseudo-mesotheliomatous adenocarcinoma and 26 other diagnosis). Pleural mesotheliomas developed mainly in men (80 %) and the average age was 70 years, range [27- 96 years old]. Epithelioid subtype was predominant (77 %), followed by the biphasic subtype (13 %). Sarcomatoid and desmoplastic subtypes were rarely observed (respectively 8% and 2 %). Median survival time since first biopsy was 12 months for epithelioid subtype, 8 months for biphasic, 4 months for sarcomatoid and 5 months for desmoplastic. 165 cases of unusual mesothelioma variants were observed, notably 40 cases of pleomorphic mesothelioma and 20 cases of lymphohistiocytoid mesothelioma. Median survival time since first biopsy was 7 months for pleomorphic and 11 months for lymphohistiocytoid.

Conclusion: Our results show the important contribution of a standardised pathological procedure of certification in a specialized registry. Mesopath Group involvement allows to exclude cases (8 %) from mesothelioma diagnosis. Our results show that the procedure facilitates the classification of the histological subtypes, mandatory in survival analysis.

Number: 90

Abstract title:
The French National Mesothelioma Surveillance Program: Estimates of the national mesothelioma incidence – Period 1998-2005

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Keywords:
mesothelioma; Epidemiological surveillance; Occupational disease

Abstract content:

Objectives: Due to the lack of observed data, most previous estimates of mesothelioma incidence in France were based on theoretical models. The French National Mesothelioma Surveillance Program (PNSM) was established in 1998 by the National Institute for Health Surveillance (InVS) in order to provide an estimate of the trends in mesothelioma national incidence.
Methods: The PNSM records incident pleural tumours in 22 French districts (approximately 30% of the French population). A standardized procedure of pathologic and clinical diagnosis ascertainment is used. The data on mesothelioma incidence collected by the PNSM is compared to the malignant pleural cancer mortality. Incidence/Mortality ratios (I/M) ratios were computed in each disctrict, and; geographical disparities were analysed Different hypothesis regarding the national I/M ratio were considered in order to provide estimates of the national mesothelioma incidence.
Results: Among the 1,823 reported incident cases (years 1998-2005), pathology review confirmed the initial pathologist\'s diagnosis in 78% of cases, ruled it out in 8%, and left it uncertain for the others; for half of the latter, the clinical findings strongly supported a mesothelioma diagnosis. Mean age of the non-excluded cases was 71 for women and 70 for men (80% of all cases). Over the 1998-2005 period, taking into account the heterogeneity in the I/M ratio for pleural cancer, we estimated the mean annual incidence to vary from 525 to 630 cases among men (incidence rate: 1.8 to 2.2 per 100,000), and from 150 to 200 for women (incidence rate: 0.5 to 0.75 per 100,000).
Conclusions: The estimated number of incident cases of pleural mesothelioma are close to the others national estimates made by the INSERM expert advisory panel or based on modelling of the data of the FRANCIM network of cancer registers, the difference being mainly due to the fact that more than 10% of the cases regularly registered were excluded by the PNSM diagnosis ascertainment procedure. As reported in previous publications, mesothelioma epidemic should continue to develop in France for at least two or three more decades. The analysis of the PNSM data on the period 1998-2005 does not show any particular trend.

Number: 91

Abstract title:
Individual comparison of incident cases of pleural mesothelioma recorded by the French National Mesothelioma Surveillance Program and the recorded cause of death for estimating the national incidence

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Keywords:
Pleural mesothelioma; death certificate; International Classification of Diseases

Abstract content:

Objectives: In most countries, estimates of the national incidence of pleural mesothelioma rely of death certificates. The objective of this study is to estimate the proportion of death certificates coded C450-9 (ICD 10th revision) which are really pleural mesotheliomas, and the fraction of pleural mesothelioma which are correctly coded.

Methods: In a first step we individually matched the death certificates coded C450-9 in 2005 in the districts covered by the National Mesothelioma Surveillance Program (PNSM) with the incident cases of pleural mesothelioma to estimate the part of mesothelioma deaths unknown by the PNSM. In a second step: we individually matched the incident pleural mesothelioma cases registered by the PNSM in 2000 with the deaths coded C45-9 from 2000 to 2005 to estimate the part of true pleural mesothelioma not coded C45. In the third step, we computed an Incidence / Mortality (I/M) ratio, and applied it to the national mortality (C450-9) to estimate the national pleural mesothelioma incidence.

Results: First step: 65%of the C450-9 death certificates were known as pleural mesotheliomas by the PNSM; 5% were excluded by the certification procedure and should not have been coded C450-9; for the 30% coded C450-9 in 2005 which were unknown by the PNSM, we made two extreme hypothesis: i) the PNSM missses cases and all are true mesothelioma ii) none of these deaths should have been coded C450-9.

Second step: about 20% of the incident cases who died were not coded C450-9. Third step: according to the two hypotheses, the I/M ratio varied from 80% (73% among women) to 120%, and the annual national pleural mesothelioma incidence varies from 520 to 780 among men and from 150 to 240 among women.

Conclusions: Those comparisons showed that: i) a non negligible part of the deaths coded C450-9 are unknown by the PNSM and a part of them should not have been coded as mesotheliomas; we plan to review the medical records of these deaths in order to check the real diagnosis;; ii) about one fifth of the pleural mesothelioma cases are not coded C450-9 on death certificates as they should have be. The systematic comparison of incident ascertained cases and mortality data is of great importance for the estimation of national incidence rates.

Number: 92

Abstract title:
Mesothelioma Survival: Effects of Management and Histological Type

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Keywords:
survival, treatment, mesothelioma register, site, histology

Abstract content:

Background
Malignant mesothelioma of the pleura and peritoneum is a universally fatal disease attracting increasing medical interventions and escalating health care costs as novel treatments are tried. Since the first clinical trial of gemcitibine and cisplatinum showing partial response rates of 30-40% and similar stable disease rates and the demonstration of significantly prolonged survival with pemetrexed and cisplatinum more patients are submitting to active treatment regimes. Trimodality therapy with radical pleuro-pneumonectomy, radiotherapy and chemotherapy still attracts some people with \"early\" disease. Reports of gene therapy and immunotherapy trials abound in conference proceedings and reports. Cancer is a notifiable disease in Western Australia and all incident cases of mesothelioma in the state, since the first case in 1961, are formally reviewed by a committee to confirm the diagnosis and document dates and methods of diagnosis, site, and date of death, as well as asbestos exposure status.

Aims
To examine the changes in survival and the factors affecting survival of all patients ever diagnosed with malignant mesothelioma in Western Australia over the past five decades.

Methods
Patients were identified from the Cancer Registry. Date and method of diagnosis, site of disease and histological type were recorded. Survival analysis was examined separately for each 5 and 10 year periods using Cox regression. Cases with a confirmed diagnosis up to the end of 2004 were included. Follow-up for deaths was censored at the end of 2006.

Results
survival was inversely related to age, worse for males (hr 1.4 95% ci 1.2-1.6) and worse for peritoneal mesothelioma (hr 1.4 95% ci 1.1-1.7). survival improved after the 1970s and has made incremental improvements since then (median survival by decade in days with interquartile range were 64 (0-198), 177 (48-350), 221 (97-504), 238 (108-502), and 301 (134-611).

Discussion
despite increasing resources and treatment costs of malignant mesothelioma over the past 40 years there have been only modest improvements in survival and no complete remissions. earlier diagnosis with concomitant increased apparent survival may be one explanation and improvements in treatment another. prevention of exposure to asbestos still remains the urgent priority for mesothelioma prevention.

Number: 95

Abstract title:
Preoperative staging of mesothelioma by 18F-fluoro-2-deoxy-D-glucose Positron Emission Tomography-Computed Tomography fused imaging and mediastinoscopy compared to pathological findings after extrapleural pneumonectomy

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Keywords:
Staging, PET-CT Scan, mediastinoscopy, extrapleural pneumonectomy

Abstract content:

Objectives: Extrapleural pneumonectomy (EPP) in MPM may be confined with both morbidity and mortality and careful preoperative staging identifying resectable patients is important. Staging is difficult and the accuracy of preoperative CT-scan, 18F-FDG-PET/CT-scan (PET/CT), and mediastinoscopy is unclear. The objectives were to compare these staging techniques to each other and to surgical-pathological findings.
Methods: Patients had epithelial subtype MPM, age ≤ 70 years, and lung function test allowing pneumonectomy. Preoperative staging after 3-6 courses of induction chemotherapy included conventional CT-scan, PET/CT, and mediastinoscopy. Surgical-pathological findings were compared to preoperative findings.
Results: 42 consecutive patients were without T4 or M on CT-scan. PET/CT showed inoperability in 12 patients (29%) due to T4 (7 patients) and M1 (7 pts). Among 30 patients with subsequent mediastinoscopy, including 10 with N2/N3 on PET/CT, N2 were histologically verified in 6 (20%). Among 24 resected patients, T4 occurred in 2 patients (8%), and N2 in 4 (17%), all being PET/CT negative. PET/CT accuracy of T4 and N2/N3 compared to combined histological results of mediastinoscopy and EPP showed sensitivity, specificity, pos. predictive value, neg. predictive value, and pos. and neg. likelihood ratios of 78% and 50%, 100% and 75%, 100% and 50%, 94% and 75%, not applicable and 5.0, and 0.22 and 0.67, respectively.
Conclusions: Non-curative surgery is avoided in 29% out of 42 MPM patients by preoperative PET/CT and in further 14% by mediastinoscopy. Even though both procedures are valuable, there are false negative findings with both, urging for even more accurate staging procedures.

Number: 96

Abstract title:
Detection of N2 adenopathy by cervical mediastinoscopy in 175 consecutive pleural mesothelioma patients.

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Keywords:
Cervical Mediastinoscopy, N2 Adenopathy, Resectability, Survival, Progression Free Survival

Introduction: Extrapleural lymph node metastasis is well established as a strong predictor of poor prognosis in malignant pleural mesothelioma (MPM) patients.
Objective: To determine the effectiveness of cervical mediastinoscopy (cMED) in detecting N2 adenopathy in patients with MPM.
Methods: A retrospective review of 175 cMED performed between January 2004 and June 2006 in MPM patients.
Results: The median age of the 175 patients was 63 years (range 27-83), 142 patients were male (81%) and 33 were female (19%). Histology was epithelial for 114 (65%) and sarcomatoid/mixed for 61 (35%). Twenty seven patients had positive N2 nodes by mediastinoscopy (15.4%).
Of the 148 patients with no positive N2 nodes at cMED (84.6%), 98 underwent EPP and 84 patients were resectable (86%), allowing complete evaluation of N2 nodes. Resectability rate for epithelial patients was 82% and for the sarcomatoid/mixed was 92%. Positive N2 nodes were found in 26 patients at the time of EPP (31%). N2 node location was undefined for four patients.
The majority of positive nodes were in the lower stations that are not accessible during cMED (5,6,8,9, low 7, n= 22 patients).

	Resectability	Positive lymph nodes at EPP	Upper Nodes (2,4)	Lower Nodes (5,6,7,8,9,IM)	Upper and Lower
Epithelial	49/60(82%)	18/49 (37%)	0	12	2
Non-Epithelial	35/38(92%)	8/35 (23%)	0	8	0
Total	84/98(86%)	26/84 (31%)	0	20	2

Overall median survival for the 84 patients resectable by EPP and with negative cMED was 12.9 months. Median survival for patients with positive N2 nodes at EPP was 9.7 months versus 15 months for the 58 Patients without positive extrapleural nodes (*not significant*). Progression free survival (PFS) was 10.5 months. Median PFS for patients with positive N2 nodes at EPP was 6.7 months versus 11.6 months for the patients with negative nodes (p = 0.046).

Conclusions:

- cMED correctly identify negative N2 nodes in 69% of mesothelioma patients who underwent EPP.
- Non-epithelial mesothelioma is highly resectable (92%) when the preoperative cMED is negative.
- Other staging procedures such as Endoscopic and Endobronchial Ultrasounds should be nvestigated to enhance preoperatively identification of N2 disease in the lower mediastinal stations.

Number: 97

Abstract title:
Reduced lung volume measured by CT predicts unresectability in mesothelioma patients

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Keywords:
unresectability, extrapleural pneumonectomy, lung volume , volumetric analysis , predictor

Abstract content:

Introduction: Resectability approaches 85% in patients with malignant pleural mesothelioma (MPM) evaluated for extrapleural pneumonectomy (EPP). Preoperative identification of unresectable patients can avoid unnecessary operation and contribute to the patient's quality of life.
Objective: To identify preoperative variables contributing to unresectability in MPM patients.
Methods: A retrospective review of 64 mesothelioma patients who underwent explorative operation with intent to perform EPP in the year 2007. The review included demographic variables, clinical symptoms and volumetric analysis of the tumor and the lung. Categorical variables were tested for significance using Fisher's exact test while continuous variables were tested using Wilcoxon rank sum.
Results: Of the 64 patients, 52 were male and 12 were female. The median age was 62 years (31-81), 48 had epithelial histology and 52 were resectable (52/64, 81% resectability). Twelve were unresectable due to tumor involvement of chest wall (9), SVC or aorta (5) or the spine (2). Formatted CT images were available for 12 unresectable patients and for 42 resectable patients.
Non-epithelial tumors were more likely to be unresectable than epithelial tumors, 44% (7/16) versus 10% (5/48), respectively (p = 0.0068). Unresectable tumors had larger tumor volume (median=1090.2 cc; range=136.9-3001.8) compared to resectable patients (median=588.5 cc; range=44-2199.6) (p = 0.0375). Unresectable patients had smaller normalized lung volume (22.2%; 0-91.7) compared to patients with resectable tumors (42.3%; 0-81.1) (p = 0.0436).
There were no significant differences between sex, age, tumor site, weight loss, smoking history, pain or taking pain medications.
Conclusions:
- Reduced lung volume is a predictor of unresectability in mesothelioma patients.
- Non-epithelial type is also associated with low resectability.
- Preoperative volumetric analysis of the tumor and the lung may help assessing respectability and avoiding unnecessary operations in mesothelioma patients.
- A prospective study is required to validate these parameters.

Number: 98

Abstract title:
TRIMODALITY TREATMENT FOR MPM: THE HEIDELBERG EXPERIENCE

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Keywords:
Chemotherapy, Extrapleural Pneumonectomy, Intensity-modulated radiotherapy

Abstract content:

Purpose:
To investigate combined modality treatment with neoadjuvant chemotherapy followed by extrapleural pneumonectomy and intensity modulated radiotherapy in patients with stage I-III (IMIG) malignant pleural mesothelioma (MPM) in a prospective study.

Patients and Methods:
Between January 2003 and December 2006, 50 patients with MPM stage I-III (IMIG) considered to be completely resectable and ECOG performance status ≤ 1 were enrolled in the study. Neoadjuvant chemotherapy consisted of a combination of cisplatin and pemetrexed or cisplatin and gemcitabine. Extrapleural pneumonectomy (EPP) was performed as an en bloc resection of the pleura, the lung, ipsilateral hemidiaphragm, and pericardium. Postoperative inverse planned intensity modulated radiation therapy (IMRT) with a median target dose of 50 to 54 Gy was applied in 2 Gy fractions.

Results:
50 patients were enrolled in the study and underwent extrapleural pneumonectomy (EPP). Forty-seven patients received 2 or more cycles of neoadjuvant systemic chemotherapy and 31 of these patients received IMRT as intended. There were 2 postoperative deaths (4 %). With a median follow up of 30.3 months the median survival for the entire group of 50 patients was 22.9 months (95 % confidence interval, 15.5 – 30.3). For the 31 patients who completed the trimodality treatment protocol as intended, median survival was 27.3 months.

Conclusion:
The results of this trial suggest that combined modality treatment of patients with MPM is feasible and effective in achieving longer survival.

Number: 99

Abstract title:
Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in the treatment of diffuse malignant peritoneal mesothelioma

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Keywords:

peritoneal mesothelioma, local regional therapy

Abstract content:

Background: diffuse malignant peritoneal mesothelioma (DMPM) is a very rare disease with a poor prognosis. In the former times the condition was considered terminal and amenable only to palliative interventions. The median survival was approximately 1 year after systemic chemotherapy. The emergence of a combined modality of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS+HIPEC) seems to have changed positively the outcome of DMPM patients. In the present study we propose to report the experience of NCI of Milan in the treatment of DMPM with CRS+HIPEC focusing results in terms of survival and morbidity.
Methods: From a data base of 86 cases of peritoneal mesothelioma we selected 66 patients (30M/36F) with DMPM histology submitted to CRS+HIPEC with a curative intent. CRS was performed using peritonectomy procedures. HIPEC through the closed abdomen technique was conducted with cisplatin (25mg/m2/L of perfusate)+mitomycin C (3.3 mg/m2/L of perfusate) or cisplatin (43mg/L of perfusate)+doxorubicin (15.25 mg/L of perfusate), at 42.5°C. We tested the prognostic significance of the followings: age, sex, carcinomatosis extension, completeness of cytoreduction (CC) and HIPEC drug schedule. The survival was calculated from the date of operation until the date of death or of the last contact. The median follow-up was 30.5 months (range: 1-118). The adverse events were graded according to NCI CTCAE v3 criteria. The survival curve distribution was calculated by the Kaplan-Meier method. The Log-rank test was used to assess the significance of survival distributions.
RESULTS: Five-year OS and PFS were 45% and 21%, respectively. The completeness of cytoreduction impacted the OS and the age>52 impacted on the PFS. The postoperative surgical morbidity G3-5 and systemic toxicity G3-5 rates were 31% and 36%, respectively.
CONCLUSIONS: Unfortunately the rarity of the disease represents the major drawback for the conduction of a prospective randomized study, in acceptable timeframe, to confirm these promising results in terms of survival. Notwithstanding the peritoneal surface malignancy program of NCI of Milan is also exerting efforts in the molecular biology field, in order to obtain a better understanding of the underlining tumor kinetics, identify new prognostic markers and try to validate new targeted therapies.

Number: 100

Abstract title:
Clinical and Pharmacologic Information Controlling a Comprehensive Management of Diffuse Malignant Peritoneal Mesothelioma

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Keywords:
Peritoneal mesothelioma, cytoreductive surgery, peritonectomy, intraperitoneal chemotherapy

Abstract content:

Aims: In the past, diffuse malignant peritoneal mesothelioma (DMPM) has been regarded as a terminal condition. The length of the survival was dependent upon the aggressive versus indolent biology of the neoplasm, nevertheless cure was not considered as a reasonable expectation and the overall median survival was approximately one year.

Methods: Clinical information and pharmacologic data accumulated over two decades have been used to formulate the current treatment strategy for DMPM.

Results: To date 116 patients have been managed using cytoreductive surgery and perioperative intraperitoneal chemotherapy. Pharmacologic studies were used to design the hyperthermic intraoperative intraperitoneal chemotherapy treatments with cisplatin and doxorubicin. Also, early perioperative intraperitoneal paclitaxel is routinely used for the first 5 postoperative days. Long-term bidirectional chemotherapy with intraperitoneal pemetrexed and intravenous cisplatin has been initiated as an adjuvant treatment as a result of pharmacologic data. Morbidity of the comprehensive management plan is 14% and perioperative morbidity 3%. Survival analysis shows a median of 80 months.

Conclusions: The current standard of care at our institution has evolved from a series of pharmacologic protocols. Increased perioperative dose intensity and long-term adjuvant treatment has converted DMPM into a chronic disease for most patients.

Number: 101

Abstract title:
Evidence-based adjustments to pathologic staging of epithelial MPM

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Keywords:
pathologic staging, extrapleural pneumonectomy, surgery

Abstract content:

Cancer staging systems predict outcome for a given tumor biology based on a consistent therapeutic intervention. Several pathologic staging systems for malignant pleural mesothelioma (MPM) have been published, but none optimally stratifies survival among patients treated with surgery. Existing systems fail to identify many patients with either favorable and unfavorable outcome, categorizing most patients as Stage III. Tumor histology has been shown to profoundly affect outcome in MPM and may contribute to inconsistency of current staging systems. Similarly, interpretation of prior studies correlating pathologic factors with outcome has been confounded by inclusion of patients with differing surgical procedures and tumor histology.

We examined all published tumor staging (T) factors in relation to outcome among patients undergoing extrapleural pneumonectomy (EPP) for epithelial subtype MPM. Logrank comparisons of survival among patients with and without each T factor guided adjustments to AJCC T stage criteria according to objective rules. Kaplan Meier analysis of adjusted T stage stratified by lymph node (N) stage guided adjustments to stage groupings.

Of 473 patients with epithelial mesothelioma undergoing surgical exploration for planned EPP, 365 were resectable by that procedure with 5% operative mortality. Median age was 57 years; 72% were male. Overall median survival was 20 months. Two hundred forty-seven (68%) and 202 (55%) patients were stage III by AJCC and Brigham criteria, respectively. Combining criteria from both systems based on logrank statistic resulted in improved stage distribution and survival stratification (Table).

Data-driven adjustment of AJCC T staging and stage grouping criteria resulted in improved stratification of survival in this cohort of patients with epithelial tumor histology who received definitive surgical therapy by EPP. This revised TNM staging system may provide the basis for more accurate prognostication and allow for more appropriate selection criteria for adjuvant therapy.

Adjusted TNM Stage	N	Median	1-yr	2-yr	3-yr	5-yr
Stage I	19	53	95%	79%	63%	38%
Stage II	101	29	81%	56%	43%	22%
Stage III	186	18	68%	37%	22%	11%
Stage IV	48	10	45%	21%	10%	0%

Number: 102

Abstract title:
Recent experience with a modified Clagett' s procedure in patients with empyema and bronchopleural fistula following extrapleural pneumonectomy for malignant mesothelioma.

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Keywords:
Mesothelioma. Extrapleural pneumonectomy. Empyema. Open window thoracostomy. Clagett.

Abstract content:

Objectives: To study the outcome of patients with malignant mesothelioma treated by a modified Clagett's procedure for empyema and bronchopleural fistula (BPF) occuring after extrapleural pneumonectomy (EPP).Methods: Prospective study of all patients presenting with empyema and BPF following EPP and treated at our institution since 2003. The modified Clagett's procedure consisted of a large open window thoracostomy with staged removal of the diaphragmatic mesh in all patients. 18FDG-PET-CT was used routinely to guide therapeutic decision.
Results: Three patients had a modified Clagett's procedure done 80, 102, and 210 days, respectively, after right EPP. All patients had received induction chemotherapy and had BPF documented at bronchoscopy. Histopathology showed one epithelioid and two biphasic mesotheliomas stage pT3N2M0, pT3N0M0 and pT3N0M0, respectively. All patients had removal of the diaphragmatic mesh 3 weeks following the open window thoracostomy. Antibiotics were administered for a minimum of 2 weeks following this procedure and cavity dressings were changed daily and then every alternate day, depending on the granulation of the cavity. No patient received adjuvant radiotherapy or chemotherapy. In-hospital stay was 75+/-29 days. 18FDG-PET-CT done at 9, 11 and 13 months, respectively showed mesothelioma recurrence in the mediastinum, chest wall and contralateral lung of the first patient. Biopsies of the pleural cavities showed inflammatory cell infiltrates without malignancy in all 3 patients. BPF failed to close in the first patient, but did close in the last two patients who are awaiting chest wall reconstruction and closure. The first patient died at 13 months of disease progression and the other two patients are alive and disease-free at 15 and 16 months, respectively.
Conclusions: The modified Clagett's procedure is a safe option when patients present with empyema and BPF following EPP. In this situation, 18FDG-PET-CT is useful to exclude mesothelioma recurrence and help plan chest wall reconstruction.

Number: 104

Abstract title:
Novel management approach for malignant effusions: Targeting fluid formation

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Abstract content:

Malignant pleural effusion (MPE) occurs in the course of various malignancies, signaling incurability, shortened life expectancy, and severely compromised quality of life. Treatment of MPE mainly aims to the relieve dyspnea caused by the pleural fluid (PF). This is accomplished by removing and preventing the re-accumulation of the PF. Current treatment modalities are of suboptimal efficacy and associated with (even life-threatening) side effects. Thus, novel, effective and safe therapeutic measures are urgently needed in the management of patients with MPE. It has been believed that understanding the pathogenesis of MPE will lead to the development of therapeutic tools that specifically block PF accumulation when the pleural cavity is invaded by tumor cells. Several lines of evidence suggest that excess pleural fluid production is the result of increased pleural vascular permeability and resultant plasma extravassation induced by a variety of mediators which are released in the pleural cavity by tumor, inflammatory and mesothelial cells.

Recently, in vivo studies using animal models of MPE provided important insights into the pathogenesis of the disease and unveil the crucial role of certain mediators including Vascular Endothelial Growth Factor, Interleukin-6, Tumor-Necrosis-Facto-alpha, Monocyte Chemotactic Protein-1, osteopontin and angiopoieitins. These studies not only underscored the importance of vascular-hyperpermeability in MPE formation but also demonstrated that pleural vascular leakage is closely associated with angiogenesis and pleural space infiltration by inflammatory cells. The above findings suggest that targeting certain hyper-permeability/angiogenetic factors involved in MPE progression may prove to be beneficial in patients with MPE.

However, it is likely that a specific antagonist against a single mediator will not be similarly effective in every patient with MPE caused by tumor of any histological type, meaning that surrogate markers of sensitivity to specific agents will be required to direct treatment. In addition, drugs that inhibit several steps of MPE pathogenesis represent an attractive alternative strategy. In connection to this, zolendronic acid, an amino-biophosphonate, suppresses murine MPE progression through inhibition of tumor angiogenesis, vascular hyper-permeability and pleural space macrophage accumulation, the above effects being associated with prevention of ras and Rho protein prenylation.

Number: 105

Abstract title:
Understanding the psychological issues; the neglected aspect of mesothelioma care

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Abstract content:

The diagnosis of mesothelioma is associated with specific and often particularly difficult psychological issues. These are additional to the acknowledged problems for patients facing death from malignant disease and those also known to affect their families.

A qualitative interview study of patients in Northern England suffering from mesothelioma revealed that their particular problems could be described under the following headings: anticipatory anxiety (the Damocles' syndrome), reactions to the diagnosis, attribution, coping with severe symptoms and rapid physical deterioration, and the stress related to pursuing a civil claim for negligent exposure to asbestos by previous employers. Patients tended to develop a 'narrative of coping' as a means of minimising emotional distress and maintaining some control. However, this strategy prevented some patients from accessing the support that they, and their close family, required. A review of the medical notes of 80 patients who died from mesothelioma revealed a record of psycho-emotional symptoms in 46%.

A focus group study demonstrated that, during the illness, family members followed the lead set by patients in most cases but many suffered severe and enduring distress in bereavement. Retrospective accounts from relatives contrasted dramatically with the mainly stoical accounts from patients. Additional suffering experienced by family members related to the medico-legal procedures after death and also to the civil compensation claims procedures that were often not completed before the death of the patient, both of these led to a sense of 'no closure'. Bereaved family members often experienced persisting anger and outrage; some regarded the deaths due to mesothelioma as 'mass murder'.

The role of support groups for patients with mesothelioma and their families has not been previously reported. This paper will include a brief description of a unique support group that was developed after consulting the public in a town with a high incidence of mesothelioma.

Number: 106

Abstract title:
TARGETING SURVIVAL AND CHEMORESISTANCE IN MALIGNANT MESOTHELIOMA

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Keywords:
malignant mesothelioma, Akt, chemoresistance, microRNA, microarray

Abstract content:

Malignant pleural mesothelioma (MMe) is an asbestos-related, highly aggressive malignancy. The increase in MMe incidence is recognized worldwide and is predicted to persist until the next two decades. Cell survival rescues Human Mesothelial Cells (HMC) cells from asbestos damages as part of the multistep process leading to neoplastic transformation and tumor chemoresistance, which is a major drawback in MMe therapy. Recently, we showed that the combined treatment of the PDGFR inhibitor Imatinib with gemcitabine synergizes in inducing MMe cell death in vitro and in vivo.
Tumor specific miRNA (small RNA molecules controlling the translation of target mRNAs) are dysregulated in several cancers their genes may function as potential oncogenes or tumor suppressor genes, contributing to cell transformation and tumorigenesis. During a preliminary survey by microarray analysis of microRNA expression, confirmed by Real Time quantitative Reverse Transcription PCR (qRT-PCR), we found that specific miRNAs were differentially expressed in MMe cells compared to HMC. Moreover, by combining miRNA expression analysis with gene expression profiles, followed by a computational analysis, we attained an accurate prediction of genes potentially targeted by dysregulated miRNAs. Among the predicted genes several are involved in the development and progression of malignant mesothelioma (BTG1, CDKN1B, HGF, MECP2), suggesting that miRNAs may be key players in mesothelioma oncogenesis.
Furthermore, we investigated miRNA expression by qRT-PCR on a panel of 24 mesothelioma specimens, representative of the three histotypes (epithelioid, biphasic and sarcomatoid) and noteworthy the upregulation of seven miRNAs was significantly associated with a better patient survival.
Our data remarkably highlight miRNAs as diagnostic and prognostic markers of mesothelioma and useful tools for development of novel therapeutic approaches for this malignancy.

Number: 107

Abstract title:
Targeting of Human Mesothelioma Cells after Bifunctionalization of the Surface of Amorphous Silica Spheres with Tetraethylene Glycol (TEG) and an Antibody to Mesothelin

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Keywords:
Mesothelioma, Amorphous Silica Spheres, Mesothelin

Abstract content:

There are no effective treatment regimens for malignant mesothelioma (MM), a tumor associated with exposure to asbestos in which patients exhibit an average 10 month survival period after diagnosis. Intravenous administration of chemotherapeutic drugs is problematic due to the drug resistance of MMs and consequent systemic toxicity. Here we describe a unique strategy for modifying the external surface of highly porous amorphous silica spheres (APMS) (originally described by Blumen et al., Am J Respir Cell Mol Biol, 33:333-342, 2007) that can be loaded with chemotherapeutic drugs, small interfering RNAs or molecular constructs. APMS modified with the surface functionalities, tetraethylene glycol (TEG) and a monoclonal antibody to mesothelin (Affinity Bioreagents), a protein overexpressed in human MMs, are taken up preferentially by human MM cells in contrast to particles modified with the generic protein, bovine serum albumin (BSA). Using confocal scanning laser microscopy and flow cytometry, we verified that maximal cell uptake was achieved using APMS-TEG. In contrast, APMS-mesothelin was not taken up by human MM. The combination of APMS-TEG-mesothelin allowed targeted and maximal association of particles with MM cells whereas a lung cancer cell line (A549) did not show a preference for either type of modified particle. APMS-TEG modified with MM-specific antibodies allowing targeted delivery of their loaded "cargo" drugs will be invaluable in therapeutic approaches to MM. Supported by a grant from MARF and a STTR grant from the National Cancer Institute.

Number: 108

Abstract title:
Chemoprevention of asbestos induced genetic instability

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Keywords:
chemoprevention; asbestos; clinical trial

Abstract content:

Chemoprevention of asbestos induced genetic instability
Exposure to asbestos fibers can lead to neoplastic diseases such as malignant pleural mesothelioma (MM), lung cancer (LC) and to severe non-cancer conditions such as asbestosis. Asbestos has been used extensively in manufactures and building due to its resistance to heat; in the last decades it has been banned in a number of countries. Because of the long latency of these tumors, especially MM, subjects occupationally or environmentally exposed to asbestos are still at increased risk even where the presence of asbestos in the environment is progressively decreasing. The incidence of MM is particularly high in areas characterized by the presence of asbestos-associated industrial and shipping activities. In these areas workers with an occupational history of asbestos exposure are invited to enter programs of medical surveillance. However, these programs are substantially inefficient in reducing cancer risk or mortality rates. Smoking cessation reduces LC risk but is ineffective in decreasing MM risk. An appropriate approach may be chemoprevention, i.e., the use of specific agents to prevent, arrest or reverse either the initiation phase of carcinogenesis or the progression of neoplastic cells to cancer. Few chemoprevention trials have been conducted to date in asbestos exposed subjects. Given the relatively low incidence of LC and especially of MM, very large and expensive trials would be required to properly test the effect of chemopreventive treatment. On the other hand, the use of biomarkers as surrogate endpoints is increasingly reported in the literature as a suitable approach to test treatment activity in short and cheap studies. A mechanism known to mediate asbestos toxicity and carcinogenicity is the generation of reactive oxygen or nitrogen species, whose consequences include genomic instability. A phase IIb randomized clinical trial is proposed, aimed at evaluating the activity of antioxidant drugs in subjects with documented occupational exposure to asbestos. The extent of genomic instability will be evaluated using biomarkers of nuclear and mitochondrial DNA damage.

Number: 109

Abstract title:
malignant mesothelioma in Canada

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Keywords:
Future Trends: Canada

Abstract content:

The incidence of malignant mesothelioma in Canada has increased dramatically since the 1960s, although it is expected to plateau following the introduction of safety guidelines in the workplace and a decline in the domestic use of asbestos. The latest data available from the Canadian Cancer Registry is that there were 406 new cases of mesothelioma diagnosed in 2004. Aggressive surgical management of the disease is restricted to a few specialized thoracic surgery programs across the country. Treatment with chemotherapy is now a routine consideration, although reimbursement of drug costs is an issue in some provinces. A national clinical research strategy is focusing on new drug development and establishment of a mesothelioma registry and tumour bank. Efforts to improve access to compensation for patients have included automatic reminders to primary health care providers to file reports with workers' compensation boards.

Number: 111

Abstract title:
Response to induction chemotherapy is the strongest predictor of survival in a multicenter U.S. trial of trimodality therapy for resectable malignant pleural mesothelioma

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Keywords:
Multimodality therapy, extrapleural pneumonectomy

Abstract content:

Background: An aggressive surgical approach is frequently offered to fit patients with early stage mesothelioma, but the variable natural history makes it difficult to determine which patients are most likely to benefit. The current analysis explores patterns of survival within patient subgroups in a multicenter feasibility study of trimodality therapy. Methods: Eligibility criteria included stage T1-3 N0-2, post-op predicted FEV1>35%, PS 0-1. Patients received pemetrexed 500 mg/m2 plus cisplatin 75 mg/m2 with vitamin supplementation for 4 cycles. Patients without disease progression underwent extrapleural pneumonectomy followed by hemithoracic radiation (54 Gy). The primary endpoint was pathologic complete response rate. Univariate comparisons of survival were made within patient subgroups. Enrollment was completed in March, 2006.
Results: 77 patients were enrolled. 83% received all 4 cycles of induction chemotherapy. Median age = 63.0 (range 34-78), M:F = 56:21, Clinical stage I:II:III:IV = 6:33:35:1, epithelial:other = 62:15, ECOG PS 0:1:2 = 28:47:2. Response to chemotherapy was 1.3% CR, 31.2% PR, 46.8% SD. 3 patients had a pathologic CR. Median survival for the ITT population was 16.8 m (95% CI = 13.6, 23.2), 1-year survival 65.2%, 2-year survival 37.2%. For patients undergoing EPP (N=57), median survival was 21.9 m (95% CI=16.8, 29.1), and for patients completing all therapy (through RT, N=40), median survival was 29.1 m (19.3, NE) and 2-year survival was 61.2%. Within the ITT population, median survival was 17.4 m for epithelial histology vs 13.8 m for other; 17.1 m for N0 vs 16.1 m for N1 or N2; 26.0 m for CR or PR vs 13.9 m for SD or PD (P for comparison ≤ .05); 16.8 m for males vs. 17.3 m for females; and 17.3 for clinical stage I or II vs. 16.8 m for stage III or IV. Survival differences within patient subgroups were not significant for the EPP or RT completed populations.
Conclusions: Within the ITT population, differences in survival were significant by response to chemotherapy but not by histology, nodal status, gender, or stage. Patients who were able to complete all therapy had an excellent 2-year survival rate. Sponsored by Eli Lilly & Company.

Number: 112

Abstract title:
RISK FACTORS FOR ACUTE KIDNEY INJURY (AKI) IN PATIENTS UNDERGOING EXTRAPLEURAL PNEUMONECTOMY

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Keywords:
acute kidney injury, Cisplatin, extrapleaural pneumonectomy, mesothelioma

Abstract content:

Background: The survival of patients undergoing therapy for mesothelioma has improved with extrapleural pneumonectomy (EPP) in combination with intraoperative, intracavitary heated cisplatin chemotherapy (IOHC). However, EPP is associated with 2.7% incidence of renal failure, a risk further increased with the addition of cisplatin chemotherapy. In order to minimize the risk of acute kidney injury (AKI) our objective was to identify modifiable perioperative risk factors of AKI, and to develop strategies for the early recognition of AKI to prevent renal failure.
Methods: Analysis of perioperative risk factors of AKI using a database of a cohort of 227 patients who underwent EPP, pleurectomy, or exploratory thoracotomy with (n=114) or without (n=113) IOHC. We hypothesized that preoperative factors (decreased estimated glomerular filtration rate, low hematocrit, prior use of NSAIDs) or intra- and post-operative variables (amount of red blood cells received, need for vasopressors) may contribute to AKI (defined as a 0.3 mg/dl increase of serum creatinine from baseline). A prediction model was created using multiple stepwise logistic regression.
Results: The overall incidence of AKI (with the strictest definition of a 0.3mg/dl rise in serum creatinine from baseline) in the entire population was 50.22%, 64.9% for patients who received IOHC and 35.4% for those who did not (RR: 1.84 [CI95%:1.39 - 2.45]). A multivariate stepwise logistic regression model, built on the findings of the univariate analysis, indicated that IOHC was the strongest predictor of AKI (OR:3.81 [CI95%:2.12-6.87]) The following additional factors showed statistically significant correlation with the development of AKI: need for the use of vasopressors (OR: 2.49 [CI95%:1.34-4.63]); reoperation (OR:1.99 [CI95%:0.99-4.12]). A trend of correlation was observed for age over 60 (OR:1.45 [CI95%:0.77-2.74]); and age over 70 (OR:1.75 [CI95%:0.73-4.24]). Our analysis also suggested that female gender maybe protective (OR: 0.53 [CI95%:0/24-1.15]).
Conclusions: Our preliminary analysis indicates that IOHC and postoperative use of vasopressors are the strongest predictors of postoperative AKI in patients undergoing EPP and IOHC. Reoperation and age over 60 may also contribute to AKI. Further analysis, encompassing all our mesothelioma patients, is planned to confirm these findings and to identify additional modifiable risk factors.

Number: 113

Abstract title:
Urinary kidney injury molecule-1 for the early detection of kidney injury with following cytoreductive surgery and intracavitary cisplatin lavage for mesothelioma

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Keywords:
Acute renal failure, biomarkers, cisplatin nephrotoxicity

Abstract content:

Body: Acute kidney injury (AKI) is a common and devastating postoperative complication in patients undergoing cytoreductive surgery and intracavitary cisplatin lavage for pleural mesothelioma. Serum creatinine (SCr) is the gold standard for the diagnosis of AKI but takes more than 24h to rise significantly even after severe injury, leading to delayed diagnosis. Kidney injury molecule-1 (KIM-1) is a type 1 transmembrane protein that is not detectable in normal kidney tissue but expressed at high levels in dedifferentiated proximal tubule epithelial cells in human and rodent kidneys after ischemic or toxic injury. The KIM-1 ectodomain is shed into the urine and can be detected in humans with AKI as an early and sensitive biomarker of AKI.
We measured preoperative and postoperative urinary KIM-1 in 30 patients undergoing treatment for pleural malignant mesothelioma. The surgical approach involves extrapleural pneumonectomy or pleurectomy, as well as 1h of intraoperative intracavitary hyperthermic cisplatin lavage (225 mg/m2) in most patients. Mean age was 64y (range, 50 to 78y) and mean preoperative SCr was 0.9 mg/dL (range, 0.5 to 1.6 mg/dL).
12 patients (40%) developed AKI as defined by a 0.5 mg/dL increase in SCr. There was no difference in pre-operative KIM-1 levels between those who did and did not develop AKI (0.5 ng/mg creat in both). At 24, 48, and 72h postoperatively, mean KIM-1 levels rose to 3.6, 6.5 and 4.7 ng/mg in those who went on to develop AKI and 1.7, 2.0, and 1.8 ng/mg in those who did not develop AKI (P = 0.02, 0.02, and 0.15, respectively). The areas under the receiver operating characteristics curve (AUC-ROC) were 0.80, 0.82, and 0.71 at 24, 48, and 72h. The diagnosis of AKI was made by SCr at 24h in 4 of 12 patients and not until 72h in 8 of 12 patients.
We conclude that urinary KIM-1 levels 24h postoperatively can provide early and accurate identification of AKI, enabling the prompt institution of renal protective strategies that would otherwise be significantly delayed using serum creatinine for diagnosis.

Number: 114

Abstract title:
New Chemotherapeutic Drugs in the Treatment of Advanced Malignant Pleural Mesothelioma in Egypt

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Keywords:
mesothelioma, chemotherapy, new drugs

Abstract content:

Purpose:
Patients with malignant pleural mesothelioma, a rapidly progressive malignancy with a median survival of 6 to 9 months, are well known to have poor response to chemotherapy. The aim of this work was to evaluate the efficacy and safety of new chemotherapeutic agents for the treatment of Egyptian MPM patients.

Patients and methods
The first study was a nonrandomized, open-label trial (part of an International Compassionate trial). It included 34 eligible patients that were assigned to receive either cisplatin/pemetrexed or pemetrexed alone if cisplatin was contraindicated. The regimen consisted of pemetrexed 500 mg/m2 IV followed by cisplatin 75 mg/m2 IV or pemetrexed 500mg/m2 IV on day 1 of each 21-day cycles for a maximum of 8 cycles. In the second trial 21 chemonaive patients with histologically proven advanced MPM were included. Eligibility included WHO performance status (PS) 0 to 2, adequate hematological, renal, and hepatic function .They received cisplatin and raltitrexed as part of EORTC 08983 protocol. The regimen consisted of raltitrexed 3 mg/m2 IV followed by Cisplatin at a dose of 80 mg/m2 IV on day 1 of each 21 day cycles for a maximum of 6 cycles.

Results:
In the first trial, the median age was 43.5 years (range 25–69), the response rate was (37.5%), and the clinical benefit (response plus stable disease) was evident in 28 patients (87.5%). The median time to progression and overall survival from the start of therapy was 7 and 14 months respectively. Survival at 1 year was 64.7%.
No toxicity was observed in 17.6% of patients, grade 3-4 toxicity was evident in 11.8% (neutropenia), 8.8% (anemia), and 2.9% (vomiting and diarrhea).
In the second trial, the median age was 46 years (range 19- 71), the overall response rate was 28.6%, including one complete remission. Stable disease was noticed in 13 patients (61.9%).

The median time to progression and overall survival from the start of therapy was 6 and 12 months respectively. Survival at 1 year was 51.6%.

Conclusion:
Both cisplatin/ pemetrexed and cisplatin/ raltitrexed are effective and safe regimens for the treatment of MPM.

Number: 115

Abstract title:
Cisplatin and Vinorelbine first line chemotherapy in non-resectable Malignant Pleural Mesothelioma (MPM).

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Keywords:
chemotherapy, vinorelbine, first line

Abstract content:

Aim:The aim was to evaluate the activity of cisplatin and vinorelbine in previously untreated, inoperable patients having histologically verified MPM, normal organ function and performance status 0-2.
Methods: Treatment was vinorelbine 25 mg/m2 i.v. weekly and cisplatin 100 mg/m2 i.v. every four weeks with hydration and standard prophylactic antiemetic treatment. Patients gave written informed consent.
Results: Characteristics of 54 consecutive patients were: Males 85%, epithelial subtype 74%, IMIG stages III and IV 35% and 46%, performance status 0, 1, and 2 26%, 69%, and 6%, and median age 63 years (31-78 years). CTC grade 3 or 4 toxicity occurred with respect to leucocytopenia (48% of pts, grade 4 in 13%), nausea (13%), neurotoxicity (11%), nephrotoxicity (4%), and other toxicities (9%). There were no toxic deaths. Median no. of cycles was 4. The fraction of patients alive at 1-, 2-, and 3-yrs were 61%, 31%, and 4%, respectively, and median survival and median time to progression were 16.8 months (0.5-46.4+months) and 7.2 months (1.6-40.6+ months). There were two CRs and 14 PRs (response rate 29.6%).
Conclusions: Cisplatin and intraveneous vinorelbine is a highly active regimen in MPM with a response rate and survival comparable to the most active regimens so far reported.

Number: 116

Abstract title:
Phase II study of sunitinib as second-line therapy in malignant pleural mesothelioma (MPM)

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Abstract content:

Background:
There is no standard second-line therapy for progressive MPM following first line chemotherapy. Sunitinib is a multi-targeted tyrosine kinase inhibitor of VEGFR, PDGFR, c-Kit and Flt-3. VEGFR and PDGFR are potential targets in MPM. We examined the safety and efficacy of sunitinib as second line treatment in MPM.
Methods:
Eligible patients had progressive MPM during or after first-line chemotherapy with platinum and an antimetabolite, ECOG PS 0-1, adequate organ function, measurable disease, and gave informed consent. Treatment: sunitinib 50 mg/day x28d q6 weeks. Primary endpoint was objective response defined by either a). Modified RECIST Criteria (MRC) on CT scan or b) metabolic response on FDG-PET in patients without prior talc pleuradesis (Francis et al, J Nuc Med (48) 1449-58; 2007). Imaging was performed at baseline and after cycles 1, 2, and every 2 cycles thereafter. Simon's 2 stage design required 2 responses in 23 patients (stage I) to give α = 0.05, β = 0.1 assuming a true RR of 20% to be of interest. Stage I is reported here.
Results:
From May 2006 to October 2007 23 patients were accrued: 22 were radiologically assessable for response. Demographics: M/F (18:5); median age 65 (range 49-81); histology epithelial/sarcomatoid/mixed/unknown (16:0:2:5). ECOG PS 0/1 (4:19). Prior platinum/pemetrexed 57%, prior platinum gemcitabine 43%. Best MRC response: CR 0; PR 4 (18%); SD 11 (55%); PD 7 (32%). Metabolic response on PET: 3 of 11 assessable (27%), 1 also with MRC response. Total protocol-defined response 6/22 (27%, 95% CI 5%- 40%). Median follow up is 15 months (range 7-24 months). Median OS was 8.2 months (95% CI 3.1- 13.2). Median TTP was 3.7 months (95% CI 2.9-4.5). Total cycles given is 64. Adverse events (% of all cycles): Grade 4, thrombocytopenia 1%; Grade 3, fatigue 17%, anorexia 3%, diarrhea 3%. 7/23 required dose reduction. There was one possible treatment-related death from pulmonary infiltrates and respiratory failure. Four patients developed increasing pleural effusions or ascites without other radiological evidence of PD. Treatment was otherwise well tolerated.

Conclusions:
Sunitinib has activity in previously treated MPM. Stage II continues to accrue to a planned 51 patients.

Number: 118

Abstract title:
Discovery of Differentially expressed alternative splicing transcript variants in Malignant Pleural Mesothelioma (MPM) using next generation transcriptome sequencing

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Abstract content:

Background:
Alternative splicing of pre-mRNA is tightly regulated during development. Different tissue types as well as disease processes including tumors can effect changes in pre-mRNA splicing patterns. Recently, we adopted whole-transcriptome shotgun 454 pyrosequencing to characterize the transcriptomes of 4 pleural mesothelioma tumors, 1 lung adenocarcinoma and 1 normal lung. We hypothesized that alternative splicing profiles should be preserved in these sequencing data for the expressed genes.
Methods:
We developed a software pipeline to map all transcriptome read sequences of each tumor onto known exon junction sequences in AceView and count how many reads map to each junction. The exon junction expression index (EJEI) was calculated for each exon junction per sample to represent the pure alternative splicing regulation effect on exon junction expression. Ten exon junctions with the biggest EJEI difference between the 4 mesothelioma and 1 normal lung samples were then examined for differential expression using a Q-RT-PCR platform in the five sequenced samples. Two of the exon junctions (ACTG2.aAug05.547 and CDK4.aAug05.1246) were further validated with Q-RT-PCR platform in additional 18 mesothelioma and 18 normal lung specimens.
Result:
Among the 10 identified differentially expressed exon junctions, 6 were confirmed by Q-RT-PCR to have the same EJEI trend as initially discovered by the 454 sequencing platform in at least 4 of the 5 specimens. EJEI of ACTG2.aAug05.547 and CDK4.aAug05.1246 by Q-RT-PCR platform can successfully classify mesothelioma and normal lung specimens with high sensitivity (89% or 16/18 and 100% or 18/18 respectively) and Specificity (89% or 16/18 and 78% or 14/18 respectively).
Conclusion:
Whole-transcriptome shotgun sequencing and downstream bioinformatics pipeline are powerful tools for the identification of differentially expressed exon junctions resulting from alternative splicing variants. Unlike exon arrays which are limited to known splice variants, new generation sequencing can be used to provide an unbiased analysis of differentially expressed alternative splicing variants which may be involved in cancer pathobiology.

Number: 119

Abstract title:
MicroRNA Alterations in Malignant Pleural Mesothelioma as Biomarkers of Disease

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Keywords:
miRNA, differential diagnosis, adenocarcinoma, biomarker

Abstract content:

The involvement of microRNAs (miRNAs) in carcinogenesis is becoming increasingly appreciated, as these small non-coding RNA species have the ability to alter the translation of mature mRNA and have been shown to act functionally as both oncogenes and tumor suppressors. In many solid tumors, alterations of these miRNA have been demonstrated to possess great potential as biomarkers of disease presence, pathologic diagnosis, treatment efficacy, and survival. Alterations of miRNA in malignant pleural mesothelioma have been less well characterized. Thus, we sought to identify miRNAs altered in MPM and to examine whether this profile can act as disease biomarkers or aid in differential diagnosis. MPM samples were obtained from patients treated through the International Mesothelioma Program at Brigham and Women's Hospital in Boston, while lung adenocarcinoma tumors were obtained from patients involved in a retrospective case-control study of non-small cell lung cancer at Massachusetts General Hospital. Total RNA was isolated from 15 fresh frozen MPMs representing all histologies, 4 fresh frozen lung adenocarcinomas, and 2 non-tumorigenic mesothelial cell lines. miRNA profiling was carried out by Asuragen Services using the mirVANA miRNA Bioarrays v2 platform (Ambion, Inc.) after manufacturer indicated miRNA fractionation, labeling, and hybridization procedures. The resulting data was analyzed using Significance Analysis of Microarrays (SAM) and Prediction Analysis of Microarrays (PAM) approaches and a false-discovery rate cut-off of 5%. A striking difference in miRNA expression was observed between MPM tumors and non-tumorigenic cell lines, with 116 miRNAs significantly upregulated in tumors compared to cell lines, and 4 miRNAs significantly downregulated. We also identified 7 miRNAs differentially expressed between epithelioid and sarcomatoid MPM histologies, but surprisingly, only 1 miRNA differentially expressed between MPM and lung adenocarcinoma. A number of these miRNAs have previously been identified as oncogenic or tumor suppressive, and thus it is suggested that these miRNAs play a critical role in the genesis of this disease. These results, consistent with the literature, suggest that although cell lines may have significant use in understanding the mechanistic aspects of miRNA function, they may not be appropriate in the identification of clinically relevant miRNA biomarkers.

Continuing work in the laboratory is focused on confirming these results and examining their clinical utility and relationship to etiologic contributors in a larger series of MPM and normal pleura samples. This work aims to define novel and clinically useful biomarkers and to identify new pathways and targets for advanced, potentially patient-specific therapies.

Number: 120

Abstract title:
Cell Surface Proteomics reveals new protein markers for the discrimination of malignant pleural mesothelioma from lung adenocarcinoma

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Keywords:
malignant pleural mesothelioma ; lung adenocarcinoma ; cell surface capturin ; cell surface glycoproteins ; classification marker

Abstract content:

Introduction
The correct diagnosis of malignant pleural mesothelioma (MPM) is still a major problem for clinicians as well as for the pathologists. The histopathological approach is complicated by a broad differential diagnosis and currently, a panel of histopathological marker are needed to discriminate MPM from anatomically related malignancies like lung adenocarcinoma. Therefore, we set out to identify cell surface protein patterns via mass-spectrometry (MS) which would allow for the discrimination of MPM from lung adenocarcinoma at tissue level .

Methods
We investigated the cell surface subproteome of one epithelial MPM cell line (ZL55) in comparison to one adenocarcinoma cell line (Ca-Lu3) via the Cell Surface Capturing (CSC) technology. Relative quantification of the identified cell surface proteins was achieved by SILAC (Stable Isotope Labeling by Amino Acids in Cell Culture) labeling. Differentially expressed cell surface proteins were further investigated on the mRNA level by Low Density Microarray RT-PCR on a collection of MPM and adenocarcinoma cell lines. Confirmed classification marker candidates were further validated by IHC stainings on cell lines and frozen-tissue samples from patients affected by late-stage MPM or lung adenocarcinoma.

Results
Over 130 bona fide cell surface glycoproteins were identified and quantified via CSC technology, among them 37 CD annotated proteins. 62 cell surface glycoproteins were found to be differentially expressed between the two cell lines at least two-fold. RT-PCR analysis of 29 differentially expressed protein candidates on 15 epithelial MPM and 6 adenocarcinoma cell lines revealed two glycoproteins as potentially good discrimination markers between MPM and adenocarcinoma.

These two classification marker candidates were further investigated in antibody-based IHC experiments on patient samples. A commercially available antibody against one out of the two target cell surface glycoproteins discriminated MPM from adenocarcinoma in clinical relevant IHC stainings on biopsies from selected patients.

Conclusion
By using cell surface capturing technology in a quantitative proteomics approach we were able to identify cell surface glycoproteins which are differentially expressed between mesothelioma and adenocarcinoma cells. Initial validation of two selected proteins on patient samples indicate their potential for aiding in the correct classification of MPM in contrast to adenocarcinoma.

Number: 121

Abstract title:
Genome-wide profile of mesothelioma versus parietal pleura may explain its chemo- and radio-resistance and indicate new targets.

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Keywords:
Chemo-resistance, DNA repair, Drug target, Fanconi anemia, Homologous recombination, Radiation resistance

Abstract content:

Background: Malignant mesothelioma is a tumour highly resistant to most chemotherapeutic and irradiation regimens. Little is known about its molecular basis. Methods: Needle biopsies from five patients with mesothelioma were obtained and snap-frozen. Normal visceral and parietal pleura samples, were obtained by Video Assisted Thoracoscopy from six cancer-free patients with spontaneous pneumothorax, anatomically dissected and snap-frozen. Adjacent tissue was formalin-fixed and Hematoxylin-Eosin- Safran (HES) stained for analysis of cell types. RNA was extracted and analyzed with the Affymetrix Human Genome U133 Plus 2.0 Chip oligoarray of 38 500 genes. Differentially expressed genes were detected using a Bayesian linear model and genes with corrected P-values smaller than 0.05 were taken as significant. The lists of significant genes were tested for overrepresented KEGG PATHWAYS, and gene ontology terms using Fishers exact test. Cell specific expression of proteins encoded by some of the overexpressed genes were detected by immunohistochemistry. Results and conclusion: Parietal, visceral pleura and mesothelioma had distinct expression profiles. When parietal pleura and tumor were compared, target genes of chemo- (e.g. TOP2A, BIRC5/Survivin and proteasome) and radiotherapy (e.g. BRCA2, FANCA, FANCD2, CCNB1 and RAD50) were overexpressed. We discovered a close relation between gene profile and resistance towards topoisomerase poisons, antitubulines, antifolates, platinum compounds and radiation therapy. Leukocyte transendothelial down-regulation could be a part of the tumour defence. The Fanconi anemia/BRCA2 pathway responsible for homologous recombinational DNA repair may be a key pathway in mesothelioma chemo- and radio-resistance. Common expression features with other resistant cancers related to DNA repair and replication could indicate that these findings may serve as a general model of tumour resistance.

Targeted suppression of some of these key genes/ pathways combined with chemotherapy or radiation could improve outcome of mesothelioma. We propose CHEK1, RAD21, FANCD2 and RAN as new co-targets for mesothelioma treatment. Both AGGF1 mRNA and protein were highly over-expressed in all tumours and may serve as a target for anti-angiogenic treatment. Over-expression of NQO1 may render mesothelioma sensitive to the novel compound beta-Lapachone.

Number: 122

Abstract title:
Redox Regulation of FoxM1 in Mesothelioma

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Keywords:
Mesothelioma, Redox Regulation, NAPDH Oxidase

Abstract content:

Targeted microarrays were used to assess the expression levels of 96 genes involved redox metabolism is four malignant mesothelioma (MM) cell lines. The LP-9 mesothelial cell line immortalized with hTERT was used as control. Cytoglobin (a stress response factor), Duox1 (dual oxidase), Duox 2 (dual oxidase), DUSP1 (MAPK phosphatase 1), peroxiredoxin 4 (secreted 2-cys peroxidase), PTGS1 and 2 (prostoglandin-endoperoxidases), SOD2 (mitochondrial Mn superoxide dismutase) were all down-regulated, whereas CCL5 (C-C motif chemokine 5), FoxM1 (G2/M transcription factor) GPX5 (glutathione peroxidase 5), GPX6 (glutathione peroxidase 6), GPX7 (glutathione peroxidase 7), LPO (lactoperoxidase), MSRA (methionine sulfoxide reductase), NCF2 (p67phox), NME5 (nucleoside diphosphate kinase), Nox4 (NADPH oxidase 4), Nox5 (NADPH oxidase 5), NUDT1 (8-oxoguanine DNA glycosylase), PRDX5 (peroxiredoxin 5), STK25 (STE20 homolog, yeast), and TXNRD2 (mitochondrial thioredoxin reductase) were all up-regulated in all 4 MM cell lines. These changes in gene expression are indicative enhanced production of reactive oxygen species (ROS), a common property of tumor cells with constitutively active mitogenic signaling. All 4 MM cell lines expressed isoforms of the FoxM1 transcription factor that activate transcription of genes required for the G2/M transition of the cell cycle, and 3 of 4 MM cell lines continued to express FoxM1 in the absence of growth factors. Inhibitors of NADPH oxidase activity markedly reduced expression of FoxM1, which correlated with dose-dependent decreases in MM cell proliferation and viability. Thiostrepton, an inhibitor of FoxM1, showed similar dose-dependent effects on MM cell viability. These studies indicate that altered oxidant metabolism that supports expression of FoxM1 may represent a useful therapeutic target in the treatment of MM.

Number: 123

Abstract title:
Identification of DNA Methylation Markers for Mesothelioma

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Keywords:

Epigenetics, Early diagnosis, DNA methylation, MethyLight, Illumina

Abstract content:

Studies of the DNA methylation patterns found in cancer cells are important for two reasons. On the one hand, identification of CpG islands that are specifically methylated in a given type of cancer can lead to the identification of tumor suppressor genes that are silenced in these cancers. Identifying the tumors suppressor genes inactivated in mesothelioma is critical to understanding the multi-step pathway that underlies the development and progression of this disease. Secondly, methylation patterns can be used as powerful signatures to identify particular kinds of cancers. As such, mesothelioma-specific DNA methylation signatures could be invaluable tools for the accurate diagnosis of mesothelioma, especially in cases where the distinction between mesothelioma and other malignant or benign conditions is difficult. Our objective has been to identify DNA methylation markers for early detection of mesothelioma. To this end, we have used a multitude of approaches, including application of the quantitative MethyLight technology in a candidate gene approach, CpG island microarrays and the Illumina GoldenGate assay. For comparison, we have analyzed lung adenocarcinoma, non-tumor adjacent lung from lung adenocarcinoma patients (since this forms a very stringent comparison due to expected high methylation background), and non-tumor pleura. We have also compared mesothelioma methylation profiles to those from a variety of other cancer types. We note that DNA methylation appears to be less frequent in mesothelioma compared to many types of cancer. However, with the examination of sufficient loci, we have been able to identify a number of genes that show highly significant hypermethylation compared to lung adenocarcinoma, non-tumor lung and non-tumor pleura. Here we report on our top marker genes.

Number: 124

Abstract title:
Argininosuccinate synthetase expression and survival outcome in patients with malignant mesothelioma: molecular analysis and therapeutic implications

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Keywords:
argininosuccinate synthetase,malignant pleural mesothelioma, survival, arginine depletion

Abstract content:

Malignant pleural mesothelioma (MPM) is an increasing health burden in many parts of the world, and remains therapeutically challenging with a median survival of less than 12 months. Novel approaches are needed to go beyond the current standard of antifolate and platinum-based chemotherapy. Tumoral expression of the rate-limiting enzyme for arginine biosynthesis, argininosuccinate synthetase (ASS) is absent in half of patients with MPM. We have previously shown that arginine deprivation triggers apoptosis of ASS negative MPM and this strategy is being tested in a clinical trial of the arginine lowering agent, pegylated arginine deminase in patients with MPM in the UK (Clin Cancer Res 2006). Here, we have assessed whether expression of ASS is linked to clinical outcome in MPM, applying immunohistochemistry to mesothelioma archival tissue with survival follow-up data. Analysis of a MPM tissue microarray with forty-one tumour samples each in triplicate with appropriate controls (32 epithelioid; 3 biphasic; 3 sarcomatoid; 2 desmoplastic; 1 uncertain) revealed a worse prognosis in the ASS 'low expressor' group with a median survival of 5 months compared to 12 months in the ASS 'high expressor' group (p=0.001). Validation of ASS as a prognostic marker is currently being performed using a second independent cohort of eighty patients with MPM. We are employing ASS overexpression and siRNA with gene expression profiling to elucidate the role of ASS in MPM biology. A molecularly-targeted approach based on ASS expression may become an option in the management of patients with MPM in the future.

Number: 125

Abstract title:
Chromosome Xq27 harbors a mesothelioma susceptibility locus associated with patient survival

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Keywords:
genetic susceptibility, polymorphism

Abstract content:

Epidemiologic data from regions of endemic asbestos exposure have provided evidence of genetic susceptibility to mesothelioma. To date, candidate gene approaches have resulted in fairly weak associations between genetic polymorphisms and disease risk. We used a modified whole genome association study to identify new gene regions associated with mesothelioma susceptibility. Cases of malignant pleural mesothelioma were identified through the International Mesothelioma Program at Brigham and Womens Hospital, Boston, MA (USA). Controls were cancer-free residents derived from the Boston, MA region, including both asbestos-exposed and unexposed individuals. Fifty cases and 25 controls were genotyped using the Affymetrix 500K genotyping array. Candidate loci from this screening effort that were associated with the disease after control for false discovery were subsequently genotyped in the entire study population (143 cases and 502 controls). Two SNPs mapping to chromosome Xq27.3 were associated with a 2.5-fold increased risk of mesothelioma in men ($p<0.0001$). We further investigated these X chromosome SNPs in relation to patient survival. In this context, these same polymorphisms were associated with a 50% improvement in patient survival (HR 0.5, 95% CI 0.3 – 0.9). These data highlight a novel susceptibility locus that is also predictive of patient outcome and provide new insight into the genetic and biologic basis of mesothelioma.

Number: 126

Abstract title:
Association study of the XRCC1 gene with asbestos-related malignant mesothelioma (MM)

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Keywords:
DNA repair gene; Single Nucleotide Polymorphism; Haplotype

Abstract content:

Background. Polymorphisms in DNA repair genes may be associated with differences in DNA repair capacity, thereby influencing the individual susceptibility to cancer. In a previous study we investigated the association of DNA repair genes with MM of the pleura in 81 patients and 110 controls living in a small Piedmontese town exposed to asbestos pollution (Dianzani et al. 2006). Our data showed an association of MM with XRCC1 399Q in asbestos-exposed individuals.
Methods & Results. Using unconditional multivariate logistic regression adjusted for age and gender to estimate odd ratios (OR) and 95% confidence intervals (CIs), we confirmed the association between XRCC1-399Q and MM risk in a different panel of 52 patients and 72 controls (OR=1.50 95% CI 0.8-2.8 in asbestos exposed individuals). Analysis of the entire panel of 151 patients and 252 age- and sex-matched controls showed a significant association in asbestos-exposed individuals (adjusted OR=2.08; 95% CI=1.00-4.40). To evaluate whether 399Q was directly responsible of the association or whether a different change could have a role, we decide to genotype further 9 SNPs reported in the HAPMAP database as the XRCC1 tag-SNPs (i.e. SNPs that allow to detect all the haplotypic combinations at the locus). To date the haplotype frequency was estimated from the genotype data of five of the selected SNPs (rs 3213245 T>C exon 1, rs3213247 G>T IVS2, rs2023614 C>G IVS3, rs3213356 A>G IVS4, rs3213371 C>G IVS10) using the maximum likelihood estimation (Haploview software 4.1). None of these SNPs was associated to MM, but the haplotype TGGAAG was found more frequently in patients as compared to controls (crude frequencies 0.342 vs 0.264, 2 =4.546, p-value=0.033) among the subjects exposed to asbestos (131 cases, 194 controls). The haplotype association was slightly higher than that shown by 399Q alone, thus suggesting the presence of a different responsible variation on this haplotypic combination. To evaluate this hypothesis the XRCC1 gene was sequenced in 30 patients homozygous for the associated haplotype. Several changes were identified, but their role needs to be evaluated.
Conclusion. Our data support the hypothesis that XRCC1 polymorphism is a risk factor for MM in subjects exposed to asbestos.

Number: 127

Abstract title:
Pooled analysis of NAT2 genotypes as risk factors for asbestos-related malignant mesothelioma

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Keywords:
N-Acetyltransferase; Oxidative Stress; Single Nucleotide Polymorphism

Abstract content:

Background. The most important causal factor for the development of malignant mesothelioma (MM) is occupational exposure to asbestos. Different lines of evidence suggest a role of genetic background in MM development, as for other cancers. Two published studies observed an association between MM and N-acetyl-transferase 2 (NAT2) polymorphisms. First, a Finnish study observed that the NAT2 slow acetylator phenotype was associated with an increased risk of MM. Conversely, MM risk was higher in Italian subjects carrying the NAT2 fast acetylator phenotypes. The conflicting results obtained in Finland and Italy could be ascribed to random chance, considering the small panel of patients and controls in the two studies, but also ethnic or other differences may have been important.
Method. To ascertain the role of NAT2 genotype we performed a study on 252 MM patients and 262 controls recruited in two Northern Italy areas that were characterized by high asbestos exposure, due to intense industrial activities (an asbestos cement factory in Casale Monferrato, mainly shipyards and refineries in Liguria). Unconditional multivariate logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs).
Results. NAT2 fast acetylator phenotypes showed an increased OR, although not statistically significant, both in asbestos-exposed subjects (OR=1.47; 95% CI=0.96–2.26) and in the entire population (OR=1.38; 95% CI= 0.93–2.04).
Conclusion. These results suggest that NAT2 polymorphisms do not exert a strong effect on individual susceptibility to MM.

Number: 128

Abstract title:
Detection of circulating tumor cells (CTCs) in malignant pleural mesothelioma (MPM)

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Keywords:
Circulating tumor cell, CTC, Diagnosis, Mesothelioma

Abstract content:

"CellSearchTM" is an automated quantitative evaluation system of circulating tumor cell (CTC) captured with an anti-EpCAM antibody, and the CTC-test has been established and approved as a clinical marker for breast cancer in USA. As expression of EpCAM, a marker of epithelium, was positive in 55% of malignant pleural mesothelioma (MPM) tissues in our preliminary experiment, we examined the diagnostic value of CTC in the present study; 7.5mL of peripheral blood was taken from a total of 77 consecutive patients presented at our institute with suspicion or diagnosis of MPM (final diagnosis, MPM in 55 and non-malignant diseases in 22 patients), and CTCs was evaluated with "CellSearchTM" without knowledge of final diagnosis. There was no difference in patient characteristics between MPM and non-malignant groups (mean age, 64.6 vs 64.3years; female percentage, 31.0% vs 13.6%). For MPM-group, CTC-count(/7.5mL) was 0 in 36 patients (62.1%), 1 in 12 (20.7%), 2 in 5 (8.6%), 3 in 2 (3.4%), and 5, 6 and 27 in one each patient (1.7%), and there was no significant difference between CTC-count and tumor progression. For non-malignant group, CTC-count was 0 in most patients (19/22, 86.4%), but 1 in two (9.1%) and 2 in one patient (4.5%). When "1" (cell/7.5mL) was used as a cut-off value of the CTC-test for the diagnosis of MPM, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were 37.9%, 86.4%, 88.0%, 34.5%, and 53.2%, respectively. When "3" (cells/7.5mL) was used as the cut-off, the specificity and PPV were 100% but the sensitivity was only 9.1% (PPV and accuracy, 29.3%, and 34.5%, respectively). In conclusion, CTCs can be detected in peripheral blood of MPM patients, and can be a useful tool for the diagnosis with high specificity and PPV. However, the current CTC-test using anti-EpCAM antibody provides low sensitivity and NPV for the diagnosis of MPM, which suggest a need for more effective CTC-detection system.

Number: 129

Abstract title:
Circulating endothelial cells (CECs) in the diagnosis of malignant pleural mesothelioma (MPM)

Fumihiro Tanaka, Kazue Yoneda, Masaki Hashimoto, Teruhisa Takuwa, Nobuyuki Kondo, Yoshitomo Okumura, Seiki Hasegawa, Kozo Kuribayashi, Kazuya Fukuoka, Takashi Nakano
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Keywords:
Circulating endothelial cell, angiogenesis, malignant pleural mesothelioma
Abstract content:

Malignant pleural mesothelioma (MPM) is a malignant tumor with aggressive angiogenic behavior, and angiogenesis can be a diagnostic and therapeutic target of MPM. Circulating endothelial cell (CEC) is potential surrogate of angiogenesis, which can be quantitatively evaluated by the "CellSearchTM" system where CECs were captured with an anti-CD105 antibody. In the present study, therefore, we assessed the diagnostic value of CEC in MPM. A total of 67 consecutive patients with suspicion or diagnosis of MPM (final diagnosis, MPM in 50 and non-malignant diseases in 17 patients) were included, and CEC-count in 4.0mL of peripheral blood was evaluated with "CellSearchTM" without knowledge of final diagnosis. There was no difference in patient characteristics between MPM and non-malignant groups. The mean CEC-count for MPM-group was 90.9 (range, 13-302), which was marginally higher than that for non-malignant group (mean, 53.0 [range, 9-194]; p=0.071). For MPM-group, the mean CEC-counts in stage I, II, III, and IV diseases were 42.0, 74.9, 67.9, and 117.2, respectively (p=0.068 for all stage and p=0.049 for stage I-III vs stage IV). When "35" (cells/4.0mL) was used as a cut-off value for distinguishing MPM from non-malignant diaseses, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were 76.0%, 52.9%, 82.6%, 42.9%, and 68.7%, respectively (p=0.036). When "50" (cells/4.0mL) was used as the cut-off, the specificity and PPV were as high as 70.6% and 85.3%, but the sensitivity and NPV were as low as 58.0% and 36.4%. In conclusion, CEC-count is an useful clinical marker in the diagnosis of MPM, and patients with higher CEC-count (35 or more) may be candidates for further examination including surgical procedures for the diagnosis of MPM. In addition, CEC-count may be surrogate of tumor progression, and also can be a marker of therapeutic effect.

Number: 130

Abstract title:
Prognostic marker for Malignant Pleural Mesothelioma

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Keywords:
Malignant Pleural Mesothelioma – Tissue Microarray –prognostic marker– immunohistochemistry – Survival

Abstract content:

Objective: To assess the impact of marker expression such as the tumour suppressor PTEN, the oncogene EGFR, p27 (cell cycle inhibtor) and the excision repair cross-complementation group 1 (ERCC1) protein – also relevant for survival and response to platinol chemotherapy in NSCLC-patients – on overall survival of mesothelioma patients as well as the correlation to established prognostic marker as histological subtype in a tissue microarray-based (TMA-) based study. Patients and Methods: Quadriple punches of 341 MPM were studied for the expression of PTEN, EGFR, p27 and ERCC1 by immunohistochemistry using different antibodies. Staining intensity was semi quantitatively scored (0-3) and for ERCC1 percentage of positive stained cells (0-100%) was additionally measured. A final H-score was calculated by summing up intensities or by multiplication of intensity with percentage (ERCC1). This H-score was correlated to overall survival.
Results: More than 50% of the biopsies showed a biphasic growth pattern of mesothelioma, 34 % were an epitheloid subtype and 13% a sarcomatoid subtype. PTEN expression was lost in 62% of the cases; ERCC1 was expressed in 80%, EGFR in 90% and p27 in 53% of these cases. Stepwise cox-regression analysis revealed that EGFR expression only correlates to epitheloid subtype. Survival time was correlated to marker expression in 126 cases with complete follow-up data. Univariate analysis revealed age (p=0.02), histological subtype (p=0.01), treatment (none with trimodality therapy) (p= 0.0015) and PTEN H-Score (p=0.00001), H-Score ERCC1 (p=0.0004) and p27 as prognostic marker. Stepwise cox-regression analysis revealed PTEN and ERCC1 H-score as the only independent marker for overall survival (p= 0.001 and p= 0.02, respectively).
Conclusion: EGFR expression correlates with epitheloid growth pattern in mesothelioma patients. Overall survival is independently predicted by protein expression of ERCC1 and PTEN, which will be further analysied in a prospectively documented database of MPM patients undergoing cisplatin chemotherapy.

Number: 131

Abstract title:
The role of pleural effusion cytology in the diagnosis of malignant mesothelioma in 2008.

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Keywords:

mesothelioma, atypical mesothelial hyperplasia, cytology, FISH , homozygous deletion CDKN2A

Abstract content:

Background: It is well known that a definitive diagnosis of mesothelioma based on conventional effusion cytology is controversial. This is due to the fact that benign reactive mesothelial cells may have cytologic features that mimic malignancies and malignant mesothelioma is a great mimicker of benign or malignant disease. The literature, 10 years ago showed that the diagnostic accuracy of effusion cytology was unsatisfactory with a low sensitivity of 30% in favor of the diagnosis of malignant mesothelioma. Moreover, the diagnosis provided by effusion cytology had to be confirmed by thoracoscopy or surgical biopsy and until now, generally no therapy was instituted based on cytology diagnosis alone. The aim of this study was to evaluate the diagnostic accuracy of conventional pleural effusion cytology in the diagnosis of malignant mesothelioma and to assess the usefulness of p16/CDKN2A deletion by FISH as a diagnostic marker for the distinction between benign reactive and malignant mesothelial cells.
Design: A series of 16 710 patients were retrieved from the department of pathology in CHU Caen from january1998-to may 2008 period of time. Among them 3483 exfoliative pleural cytology specimens were collected. 4 slides either smears or cytospins were systematically analyzed and compared with clinical and or/histological follow up. Additionnally, a series of 143 patients with a diagnosis of mesothelioma made either by cytology and/or by a biopsy were retrieved according to the French system of codification ADICAP code: M7P*, M4P0,M0P*, 0C82, C082. The diagnosis of malignant methelioma were systematically validated according to the standardized procedure of certification of the Mesopath group. A dual color FISH for p 16/CDKN2A and chromosome 9 centromere was performed either on frozen or paraffin embedded cell blocks from 11 reactive mesothelial hyperplasia and 9 cytologically positive effusions (all histologically certified mesothelioma by the Mesopath group).
Results: From the 3483 pleural effusion specimens, a diagnosis of malignancy was performed in 12% (n= 411), and of non malignant disease in 88% (n=3072). Among the 411 patients with a positive cytology for cancer a diagnosis of mesothelioma was observed in 9% of cases, of other cancers (carcinomas) in 84% and of lymphoma in 7%. From the series of 143 patients with a diagnosis of mesothelioma made either by cytology and /or biopsy, the diagnosis of mesothelioma was made by thoracoscopy or surgical biopsy in 50% of cases (n=71), by cytology alone in 3% (n=5) and by thoracoscopy with cytology in 47% (n=67). The sensitivity of our cytological diagnosis on pleural effusions was 30% with a positive predictive value [PPV] of 86%. Among the 45 negative cytology specimens with a positive biopsy for mesothelioma, the cytological diagnoses were; definitively malignant in 29% (n=13), suspicious for malignancy in 11%(n=5), definitively reactive in 33%(n=13) and inadequate in 27%(n=12). False negative results were observed in 33% of the cases.

Due to the overlap features, when the cells were truly malignant in 9/13, the pathologist was not able to decide if the malignant cells were from a malignant mesothelioma of from an adenocarcinoma origin.When we compare the period of time from january 1998 to dec 2003 and the period of time from dec 2003 to may 2008, the sensitivitity and PPV were respectively 15 %(n=65) with a PPV of 80% and 39% (n=78) with a PPV of 88%. Homozygous deletion CDKN2A was detected by FISH in 2/9 mesothelioma cases and in none of the atypical reactive mesothelial hyperplasia (0/11).
Conclusion: Our results show that the diagnostic accuracy of pleural effusion cytology is still unsatisfactory (low sensitivity 39%) but is improving with a better definition of criteria for the diagnosis of malignant mesothelial cells and the recognition of pitfalls. Moreover the detection of homozygous CDKN2A deletion by FISH could be extremely useful for the diagnosis of mesothelioma over atypical reactive mesothelial hyperplasia. Genetic molecular could be a good driver for screening and research for innovative therapies.

Number: 132

Abstract title:
Role of the mesothelin-CA125 interaction in mesothelioma

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Keywords:
Mesothelioma, mesothelin, CA125, MUC16, antibody, ovarian cancer

Abstract content:

Mesothelin is a GPI–anchored glycoprotein present on the cell surface. Mesothelin is overexpressed in a variety of cancers including malignant mesothelioma and ovarian cancer, making mesothelin an ideal target for anti-cancer agents. We have shown that mesothelin is shed from tumor cells. Shed serum mesothelin has been approved by FDA as a new diagnostic biomarker in mesothelioma. We have found that antibodies specific for mesothelin are elevated in the sera of patients with mesothelioma and ovarian cancer, and that this elevation is associated with high expression of mesothelin in tumors.
Several groups including ours have showed that mesothelin binds CA125 (also known as MUC16), and that the interaction of mesothelin and CA125 may mediate tumor cell adhesion. It has been suggested that this may contribute to the metastasis of tumors to the peritoneum. CA125, which was originally found as a biomarker in ovarian cancer, is expressed by 88% of malignant mesothelioma. Mesothelioma has the second highest co-expression of CA125 and mesothelin after ovarian cancer. It has been shown that CA125-asscociated N-glycans are required for binding to mesothelin. The mesothelin-CA125 interaction may represent a novel biological mechanism in cell adhesion.
To identify the CA125-binding domain of mesothelin, we have generated truncated mutants of mesothelin and assessed their binding capability to CA125. Although full-length mesothelin contains 622 amino acids, a fragment consisting of only 65 amino acids maintains 100% binding to CA125. Smaller fragments from within this region show no binding to CA125. Furthermore, our studies have indicated critical amino acids involved in the mesothelin-CA125 interaction. Characterizing the mesothelin-CA125 interaction will allow a better understanding of the progression of mesothelioma in peritoneal cavity and may also lead to therapeutics that can prevent or reverse tumor metastasis.
This work is supported by NCI Intramural Research Program. M. Ho is the recipient of 2007 Mesothelioma Applied Research Foundation Grant in Honor of Craig Kozicki.

Number: 133

Abstract title:
A novel mechanism of late gene silencing drives SV40 transformation of human mesothelial cells.

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Keywords:
carcinogenesis, SV40, DNA tumor viruses, antisense control of gene expression, oncogenes, tumor antigens,viral tranformation and carcinogenesis

Abstract content:

Suppression of the late gene expression, usually by integration of the viral DNA into the host genome, is a critical step in DNA tumor viruses carcinogenesis. Simian virus 40 (SV40) induces high rates of transformation in infected primary human mesothelial cells (S-HM) in tissue culture, leading to the formation of immortal cell lines (S-HML). The studies described here were designed to elucidate the unusual susceptibility of primary human mesothelial cells (HM) to SV40 carcinogenesis. We found that S-HML contained wild-type, mostly episomal SV40 DNA. In these cells the early genes that code for the viral oncogenes are expressed, at he same time, the synthesis of the late genes capsid proteins is suppressed and S-HML are not lysed. Late genes suppression is achieved through the production of antisense RNA molecules. These antisense RNA molecules originate in the early region of the SV40 circular chromosome and proceed in antisense orientation into the late gene region, leading to the formation of highly unstable double strand RNA that is rapidly degraded. Our results reveal a novel biological mechanism responsible for the suppression of late viral gene products, an important step in viral carcinogenesis in humans.

Number: 134

Abstract title:
Identification of cells with stem cell/self renewal properties in malignant pleural mesothelioma

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Keywords:
chronic injury, tissue repair, Hedgehog pathway, side population

Abstract content:

Mesothelioma tumorigenesis is felt to be based on chronic tissue repair caused by the accumulations of fibers in the pleural space. The expression of stem cell renewal genes such as Bmi-1 has been shown to be inversely correlated with survival in mesothelioma patients (Glinsky et al, JCI 115: 1503, 2005). Bmi-1 is a downstream target of the stem cell signaling Hedgehog pathway. We made the hypothesis that in mesothelioma a fraction of cells with self-renewal/stem cell signaling properties is present. Therefore we tested whether Hedgehog signaling is active in mesothelioma and whether a subpopulation of cells with self renewal properties could be detected. Epithelial mesothelioma had a significantly higher expression of Gli-1 compared to normal pleura, indicating the Hedgehog pathway to be indeed active in tumors. To investigate whether this pathway is involved in cell growth, twenty four primary mesothelioma cell cultures, established from surgical specimen, were investigated. Cyclopamine, an inhibitor of the Hedgehog signaling pathway, significantly inhibited cell growth in 50% of the primary cultures. Tomatidine, which was used as control, had no effect. Furthermore, GANT61, an inhibitor of Hedgehog pathway acting downstream of Smo, inhibited cell growth in 66% of the cultures. These effects were accompanied by inhibition of the expression of genes downstream Hedghog signaling. In order to further characterize the stem cell component of tumors we used a functional approach based on the ability of stem cells to efflux Hoechst33342. These cells can be identified by FACS as not stained cells and are called “side population”. Using this functional approach we were able to isolate a side population from ZL55 cells which represented 3.8±1.7% of cells (mean±SD, n=12). We could show that the sorted ZL55 side population again gave rise to a small side population fraction and a non-side population fraction, suggesting that the side population indeed includes cells with self-renewal properties. On the other hand the ZL55 non-side population only gave rise to the non-side population fraction. Similar results were obtained, for two out of three primary mesothelioma cultures. Taken together these results indicate that cells with stem cell renewal properties are present in mesothelioma.

Number: 135

Abstract title:
The SV40 large T antigen-p53 complexes bind and activate the IGF-1 promoter stimulating cell growth

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Keywords:
SV40 Large T antigen, DNA tumor viruses, p53, IGF-1, cell transformation, cancer, mesothelioma

Abstract content:

Inactivation of cellular p53 is a crucial step in carcinogenesis. Accordingly, p53 is inactivated in most human cancers by different mechanisms. In cells infected with DNA tumor viruses, p53 is bound to the viral Tumor antigens (Tags). The current “dogma” views the Tag-p53 complexes as a way of sequestering and inactivating p53. Using primary human cells and SV40-transformed human cells, we show that in addition of inactivating p53 tumor suppressor activities, the Tag-p53 complex has growth stimulatory activities that are required for malignant cell growth. We found that in human cells, Tag/p53 complexes regulate transcription of the IGF-1 gene by binding to the IGF-1 promoter together with pRb and p300. Depletion of p53 leads to structural rearrangements of this multi-protein complex, resulting in IGF-1 promoter transcriptional repression and growth arrest. Our data provide a novel mechanistic and biological interpretation of the p53/Tags complexes and of DNA tumor virus transformation in general. In the model we propose, p53 is not a passive inactive partner of Tag. Instead the p53/Tag complex promotes malignant cell growth through its ability to activate the IGF-1 signaling pathway.

Number: 136

Abstract title:
Increased uPAR Expression and Virulence of REN Human Malignant Pleural Mesothelioma Cells.

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Keywords:
Malignant mesothelioma, Urokinase Receptor, Urokinase

Abstract content:

Malignant pleural mesothelioma (MPM) is a lethal neoplasm for which current therapy is largely ineffective. To assess differences in the growth of MPM cells in vivo, we developed an orthotopic model of MPM in which MS-1, M9K or REN cells were administered by intrapleural injection in nude mice. As was previously reported in MPM in humans, prominent extravascular fibrin deposition characterized all of the neoplasms and encapsulated the tumors. REN-derived tumors were larger at 2, 3 and 4 weeks after intrapleural injection and exhibited more rapid growth and lethality in vivo. The urokinase plasminogen activator receptor; uPAR, has been implicated in the pathogenesis of a number of solid neoplasms including malignant mesothelioma. We therefore sought evidence of a link between the level of uPAR expression and virulence of the REN, MS-1 and M9K cell lines in the orthoptopic model. REN tumors and the cells cultured in vitro were found to overexpress uPAR at both the mRNA and protein levels. As opposed to the other cell lines, REN had no detectable LRP at the cell surface, suggesting that impaired internalization could contribute to the overexpression of cell surface uPAR. Excised REN tumors and immunohistochemical analyses demonstrated uPA antigen while no uPA protein or message was detectable in cultured cells. Murine uPA was found to bind human suPAR or REN cells in vitro. REN cells exhibited increased migration in three-dimensional fibrin gel analyses and the effect was blocked by antibodies that prevented the binding of uPA to uPAR. Traces of uPA antigen and activity were detectable in the fetal calf serum component of the media and an antibody to uPA also blocked REN cell migration in the fibrin gel system. uPAR or uPA blocking antibodies also decreased REN cell migration and invasiveness in Boyden chamber analyses. uPAR silencing significantly reduced REN cell migration and invasiveness. These studies suggest that uPAR expression and association with host uPA may contribute to the malignant potential of MPM and suggest a potentially promising target for future therapeutic intervention. Supported by NIH PO-1HL076406 (SI, TT, CD, KK, AK), The Gina Sabatasse Research Grant Award, The Texas Lung Injury Institute and Attenuon, LLC.The University of Texas Health Science Center at Tyler.

Number: 137

Abstract title:
Mechanism of anoikis resistance in mesothelioma cells

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Keywords:
mesothelioma; anoikis; apoptosis; micropapillary; signaling pathways

Abstract content:

Pleural fluid (PF) accumulation is a frequent clinical observation in diffuse malignant pleural mesothelioma. The cytological analysis of PF often revealed the presence of spheroidal clusters of malignant cells (micropapillaries), addressing the question of the ability of non-adherent tumor cells to survive and to develop new tumor foci in the pleural cavity. As anoikis is the mechanism whereby cells die following loss of matricial anchorage, the aim of the present work was to determine whether mesothelioma cells are resistant to anoikis.
To study anoikis resistance of malignant mesothelioma (MM) cells, three mesothelioma cell lines and the non-tumoral mesothelial cell line MeT-5A were cultured on poly-2-hydroxyethyl methacrylate (polyHEMA)-coated plates. Cell cycle was evaluated by studying Ki-67 antigen expression coupled to PI staining, and cell death was determined by assessing DNA fragmentation, by flow cytometry. Contribution of the SAPK/JNK pathway and of the pro-apoptotic proteins Bim and caspase-9 to anoikis was evaluated using chemical effectors and RNA interference strategy. Expression of phospho-SAPK/JNK, Bim and of the cleaved forms of the caspase-9 and caspase-3 were estimated by western-immunoblot.
In non-adherent (NA) condition, MM cells form micropapillary-like structures composed of viable cells. While the PI3K/Akt, ERK and SAPK/JNK signaling pathways are activated in adherent MM cells, loss of anchorage results in an inactivation of these pathways. Accordingly, MM cells in micropapillaries enter in G0 phase earlier than adherent cells. In comparison, MeT-5A cells enter anoikis in a SAPK/JNK, Bim and caspase-9 dependent pathway. Resistance to anoikis in MM cells can be reversed by activating SAPK/JNK with anisomycin, according to a Bim and caspase-9 dependent pathway. Finally, we found that blocking micropapillary assembly by culturing cells under spinning activated SAPK/JNK and Bim, and made MM cells to enter anoikis. These results point out the importance of cell clustering in the anoikis resistance of MM cells.

Number: 138

Abstract title:
Genomic and functional profiling of malignant mesothelioma

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Keywords:
microarray, gene profiling

Abstract content:

Before normal mesothelial cells of pleura transform to neoplastic and malignant cells, numerous genetic changes are needed. In malignant mesothelioma a distinct chromosomal instability is a characteristic feature visualized by karyotypic (chromosome and array CGH included) analyses. What are the causes of the instability? Do inherited congenital genetic changes in addition to the asbestos fiber burden have any role in the malignant transformation? What is the role of the inflammation? Furthermore, do the changes serve as diagnostic, prognostic, predictive or therapeutic markers in malignant mesothelioma? So far very little is known about all the issues related to the questions. The novel genome-wide profiling has, however, opened a new era for the understanding of mesothelioma to the extent that we can find clinically and therapeutically relevant markers for this fatal disease.
My presentation reviews the results of studies related to the genomic and functional profiling of malignant mesothelioma. Our recent publications (1,2) and the soon appearing book chapter (3) give additional information for the subject.
1. Musti M, Kettunen E, Dragonieri S, Lindholm P, Cavone D, Serio G & Knuutila S: Cytogenetic and molecular genetic changes in malignant mesothelioma. A review. Cancer Genet Cytogenet 170:9-15, 2006.
2. Lindholm PM, Salmenkivi K, Vauhkonen H, Nicholson AG, Anttila S, Kinnula V & Knuutila S: Gene copy number analysis in malignant pleural mesothelioma using oligonucleotide array CGH. Cytogenet Genome Res 119:46-52, 2007. (Epub Dec 14, 2007).
3. Nymark P, Kettunen E & Knuutila S: Tumors of the respiratory tract. In Cancer Cytogenetics. Chromosomal and Molecular Genetic Aberrations in Tumor Cells. 3rd edition, Heim S & Mitelman F (eds.). In press.

Number: 139

Abstract title:
NOVEL SYNTHETIC INHIBITORS OF THE mTOR PATHWAY IN MALIGNANT MESOTHELIOMA

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Keywords:
malignant mesothelioma, mTOR, kinase activity, p70s6k, 4ebp1

Abstract content:

Malignant Mesothelioma is an aggressive cancer with poor prognosis and low median survival, refractory to current therapies. Mammalian target of rapamycin (mTOR) promotes uncontrolled proliferation, through cell cycle progression, regulation of protein synthesis and protein degradation, playing a critical role in tumor cell survival and resistance to chemotherapy. The mTOR pathway becomes activated in most human tumors, including malignant mesothelioma. Rapamycin and its derivatives are known as mTOR inhibitors, however we aimed at testing novel small molecules, synthetized by the split-Ugi multi-component reaction, as selective inhibitors of this enzyme activity, to develop effective strategies for the treatment of this neoplasm. We evaluated cytotoxicity of the synthesized compounds on three mesothelioma cell lines: MPP-89, MSTO-211H and REN. After preliminary screenings we observed a marked decrease of cell viability in all three cell lines for two out of ten compounds, which displayed IC50 values about of 15 μM. Moreover, they inhibited the autophosphorylation of mTOR on Ser2481 as well as the phosphorylation of two mTOR downstream effectors 70-kDa ribosomal protein S6 kinase 1 (p70S6K) and the eukaryotic translation initiation factor 4E (eIF4E)-binding protein 1 (4EBP1). Conversely, no inhibition on Akt (Ser473) and mTOR (Ser2448) phosphorylation was observed.
Interestingly, the inhibition of mTOR kinase activity of both p70S6K and 4EBP1 was observed in MPP-89 cells, while in MSTO-211H cells was inhibited only the phosphorylation of p70S6K, which was slightly affected in REN cells. These preliminary data highlight these compounds as new inhibitors of the mTOR pathway, exerting cytotoxic effects on all mesothelioma cells examined and suggest selective effects, dependent on the different cell phenotypes.

Number: 140

Abstract title:
EORTC 08031

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Abstract content:

Malignant pleural mesothelioma (MPM) is a highly lethal disease and optimal treatment has not been determined yet. The use of radical surgery in the treatment of potentially resectable MPM remains controversial. The median survival for patients undergoing extrapleural pneumonectomy (EPP) is approximately 12 months. Surgery is seldom radical due to diffuse thoracic involvement. In experienced centres operative mortality is < 10 % but postoperative morbidity remains high [1]. Neoadjuvant chemotherapy is a new therapeutic option in MPM and promising results of a multicenter phase II trial were recently reported [2]. In total, 58 patients completed induction chemotherapy consisting of 3 cycles of cisplatin and gemcitabine. For the 45 patients undergoing EPP median survival was 23 months. Pemetrexed is also an active agent for the treatment of MPM. In 2005 the EORTC initiated a phase II feasibility trial consisting of induction chemotherapy with cisplatin and pemetrexed followed by EPP and postoperative radiotherapy (EORTC 08031). The general outline is depicted in figure 1. The primary endpoint is “success of treatment” which is defined as a patient who received the full protocol treatment, is still alive 90 days after the end of protocol treatment without progression and without evidence of grade 3-4 toxicity at 90 days after the end of protocol treatment. The secondary endpoints include toxicity of this trimodality treatment, overall survival and progression-free survival. In patients with preoperative PET scan, the value of PET scan for staging is also considered as a secondary endpoint. Translational research will also be performed. Total number of patients required was 52. The study was initiated in July 2005 and closed in August 2007 when 59 patients were registered. Demographic data are available on 55 patients and 44 of them were men. Age range was from 26 to 67 years with the median of 57 years. Thirty one percent of patients had associated chronic disease. All patients underwent mediastinoscopy, cT1/T2/T3 64%/27%/9%, cN0/N1 98%/2%, performance status 0/1 36%/64% and 2 had focal chest wall infiltration. Final results will be available early 2009. If the trimodality treatment in this EORTC 08031 study proves to be feasible, it will be used as experimental arm in a future randomized clinical trial.

References

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2. Weder W, Stahel RA, Bernhard J et al. Multicenter trial of neoadjuvant chemotherapy followed by extrapleural pneumonectomy in malignant pleural mesothelioma. Ann Oncol 2007; 18:1196-1202.

Number: 142

Abstract title:
MesoVATS study

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Abstract content:

The MesoVATS study is a randomised controlled study to compare the effectiveness of talc pleurodesis against VATS cytoreductive pleurectomy in suspected or confirmed malignant mesothelioma. The primary outcome measure is survival at one year. Secondary outcomes are control of pleural effusion, symptoms and quality of life at 3, 6 and 12 months, assessment of procedure related complications in each arm and cost to the health service in terms of resources used for procedures, hospital bed usage and cost to primary and secondary care for 12 months from time of randomisation. For inclusion, patients must have confirmed or suspected mesothelioma, a pleural effusion and be clinically fit and suitable for a VATS pleurectomy or talc pleurodesis via an intercostal chest drain. Based on data available at the time of set up, the study is powered to detect a 22% difference in survival at one year between the two arms. The n number is 196 patients. To date 70 patients have been randomised although 151 have been screened. The main reasons for exclusion are either not meeting inclusion criteria (69 cases) or the patient declined to participate (12 cases). In addition 7 patients, who would otherwise have been suitable, were entered into the Mesothelioma and Radical Surgery (MARS) study. Slow recruitment has led to expansion from a single centre study to a multi-centre study. Five surgical centres within the UK are now open. Similarly, recent changes in the preferred management of malignant pleural effusion have led to the study being modified to include medical thoracoscopy both as a means of obtaining biopsies and for instillation of talc. It is hoped that these changes will increase recruitment over the coming months.

Number: 149

Abstract title:
An Advocate's Perspective: A Call for a Data-based Approach

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Abstract content:

Meso clients suffer from a lack of information about treatment. Thanks to the Internet, patients are beginning to ask frank questions. The questions provoke conflicting answers reflected by confusion within the medical community about mesothelioma. As an advocate, it is important to be able to provide thumbnail answers in order to refer clients to the best treaters. A lack of consensus on research priorities and other issues are exacerbated by a crippling lack of accessible data. From an advocate's perspective, without this data clients cannot make informed decisions about treatment, which affects the viability of their lawsuit and ultimate financial compensation. A questionnaire sent out to the most well known surgeons in the U.S. who treat meso patients received a disappointing response. One way to address this problem is a global meso database that would take advantage of the extraordinary medical data generated by litigation. Uploading medical records, films, charts, prescriptions, exposure information, and patient surveys into a confidential, web-based, multi-lingual database would help provide critically needed data. The problem of data accessibility occurs in tandem with meso remaining grossly underfunded despite billions of dollars changing hands in asbestos litigation. Recent litigation changes have provided industry with an estimated $60 billion windfall that has not, and will not, find its way into research coffers. The U.S. Congress could use money held in asbestos settlement trust funds for research. The value of these trusts is between $40 and $60 billion USD, and a small percentage of those funds dedicated to meso research would go a long way to finally jumpstarting research into prevention and treatment for an asbestos related cancer known since the late 1940's.

Number: 150

Abstract title:
Who owes what to whom in clinical and surgical research?(Humanistic perspective – future research in cardio-thoracic surgery)

H.M. Evans

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Abstract content:

What obligations arise in clinical research, and to whom – and by whom – are they owed?
The elaboration of clinical research ethics has focused on protecting vulnerable research subjects from exploitation, most visibly by ensuring voluntary participation through mechanisms of consent. Significantly, consent is itself preceded by consideration of whether research would be ethical in terms of permissible levels of harm, even if those harms were undergone voluntarily. These obligations are owed by researchers to research subject participants, to patients generally, and to society as whole.
These important protections arose when the research subject's vulnerability was recognised and taken seriously – things were not always thus. However, has the pendulum swung too far the other way? In general terms, probably not; but there are two important aspects of ethical obligation that are usually overlooked, but that need themselves to be taken seriously.
First, patients accessing treatments provided by publicly-funded healthcare have a general obligation to contribute to developing better treatments for future patients– as they themselves benefit from research carried out on patients in the past. Not all moral obligations are owed by society to individuals; some obligations are owed in the other direction, something that we recognise clearly enough in terms of law-abiding conduct and the payment of taxes. Why should healthcare be any different?
Second, researchers and clinicians have an obligation to reduce the uncertainty within which they provide treatment to patients, especially in terms of safety and efficacy. This means a commitment to undertaking research to improve future treatment, especially where we are less than certain about the benefits and harms of what we currently do – an obligation owed to both present and future patients.
Together these two obligations constitute a compelling moral argument in favour of including far more existing treatment episodes within the rubric of clinical trials protocols, with all that that entails, especially – and most contentiously for individual clinicians – the subjection of treatment allocation choices to randomisation where this is scientifically appropriate.
This paper will consider this challenging suggestion on its merits and in the light of obvious objections to it.

Number 151

Abstract title:
IASLC/IMIG Mesothelioma Staging Project

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Abstract content:
The International Association for the Study of Lung Cancer / International Mesothelioma Interest Group Mesothelioma Staging Project aims to collect data retrospectively and prospectively to explore and validate clinical and pathological staging criteria. The project was launched at the Society of Thoracic Surgeons annual meeting in January 2008. Data are being collected by Cancer Research and Biostatistics (Seattle, USA) by the team who analysed the IASLC Lung Cancer Staging Project data. Dr Valerie Rusch (New York, USA) and Mr John Edwards (Sheffield, UK) are the project co-chairs, with support from Prof Peter Goldstraw (London, UK), Dr John Crowley (CRAB) and numerous leading surgeons and physicians.

The Project will have three phases:

Phase Ia: Review of retrospectively collected data from currently identified major surgical units

Phase Ib: Review of retrospectively collected data from oncology trial datasets.

Phase II: Retrospective data review from the wider surgical and oncological community

Phase III: Prospective Data Collection

Work is underway to identify and approach units willing to share data for the project for phases I and II. The prospective dataset is under development. It is hoped that data collection will start on 1 January 2009 and continue until 31 December 2014, allowing up to two years for data to mature and to be analysed in advance of submission of the 8th Edition of the AJCC Manual.

Funding for retrospective data collection and analysis has been received from the Mesothelioma Applied Research Foundation. Further funding will be sought from charitable organisations and industry.

Number: 154

Abstract title:
Does Radiotherapy Add Anything To Extrapleural Pneumonectomy?

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Abstract content:

Malignant pleural mesothelioma (MPM) remains a challenging disease from the surgical perspective. Its diffuse nature with involvement of the lung, pericardium and diaphragm, the inability to reliably obtain negative margins, the significant morbidity and mortality associated with radical resection, and most importantly, the high recurrence rate after surgery, all contribute to the nihilistic attitude with which most clinicians view this disease. Despite major improvements in operative mortality over the last two decades, which is now between 2% and 8% at most centers, surgery alone is associated with high rates of local failure. For this reason, adjuvant and neoadjuvant modalities have been integrated into the surgical management of MPM. In most centers today aggressive therapeutic approaches involve a trimodality regimen including extrapleural pneumonectomy (EPP), radiation therapy and chemotherapy.

There is a rationale for using of radiation therapy after EPP. First, despite traditional beliefs, mesothelioma cells are radiation-sensitive, at least to doses greater than 40Gy. The problem has been in delivering therapeutic radiation doses to the involved hemithorax while avoiding radiation-sensitive organs such as the lung, liver, heart and spinal cord. For this reason radiation therapy as a primary modality has failed. However, after EPP the ipsilateral lung no longer is a limiting factor, and with modern radiation techniques the complex target area of the post-pneumonectomy space can usually be safely covered. Second, at EPP microscopically negative margins are notoriously difficult to achieve. Thus, local recurrence rates are as high as 50% after EPP alone. Furthermore intrapleural adjuvant therapies such as photodynamic therapy, heated chemotherapy and immunotherapy have not had any major impact on local recurrence.

What data exist to support the use of radiation therapy after EPP? DaValle was first to describe the use of adjuvant radiation after EPP in a small series of patients with MPM (Davalle, 1986). Throughout the late 80's and 90's the Brigham group employed a trimodality regimen which included adjuvant chemotherapy and radiation of 30.6 Gy to the hemithorax (40 Gy to the mediastinum) and a booster dose of 50 Gy to areas thought to be at high risk for recurrence. In 1999, Sugarbaker reported outcomes of 183 patients treated in this fashion, and demonstrated feasibility of the multimodality approach and an enviable 5-year survival of 46% for epithelioid, node-negative, patients who were completely resected (Sugarbaker, 1999). Details of the radiation treatment of a subset of these patients who received their treatment at the Brigham were reported by Baldini and colleagues (Baldini, 1997). 11 of 35 patients (31%) who received trimodality therapy developed tumor recurrence within the ipsilateral chest. Despite the high rate of locoregional failure, the 3-year survival was 34%.

The Brigham group recently reported patterns of failure of a more recent group of patients who had undergone EPP and radiation. Some were treated with medium-dose hemithoracic radiation therapy (MDRT) to 30 Gy, while others received higher-dose radiation (HDRT) to 54 Gy (Allen, 2007). Local failure remained a significant problem and occurred in 50% (12 of 24) patients treated with MDRT but in only 27% (4 of 15) patients who received HDRT, suggesting that higher dose hemithoracic radiation may be more efficacious.

In 2001 the Memorial Sloan Kettering group reported encouraging results from a multi-institutional phase II trial (Rusch, 2001). Patients with MPM underwent EPP and then received adjuvant 'high-dose' radiation to the ipsilateral hemithorax. No chemotherapy was given. The technique employed photon radiation to a dose of 54 Gy in 30 fractions. Radiation sensitive organs such as the liver, heart and spinal cord were shielded using customized blocks after they had received their threshold dose limit. The chest wall and pleura in the shielded regions were then irradiated with matched electron fields, which have shallower penetrance than photons. Of 54 patients who underwent EPP and adjuvant radiation, only 7 (13%) had locoregional recurrence. Despite excellent local control, 30 patients (56%) recurred distally. A subsequent report by the same investigators detailed radiation administered to 35 patients who were treated at MSKCC (Yajnik, 2003). Local recurrence developed in 13 of 35 patients (37%), and in the majority of cases failure occurred at the inferior posterior and medial margins - regions notoriously difficult to treat with 3D-conformal radiation. It should be noted that radiation was generally well tolerated and no major pulmonary-related events occurred.

In 2004, Weder and colleagues reported 13 patients who underwent neoadjuvant chemotherapy, EPP and adjuvant radiation therapy to (Weder, 2004). Radiation therapy included either hemithoracic photon beam therapy to 30 Gy with boosts to 50 Gy in areas defined as being at high risk for recurrence (n=6), or 'involved field' local radiation to 48 Gy to 60 Gy (n=7). 8 (62%) patients developed recurrences within the field of radiation. The authors subsequently reported results of a phase II study using a similar regimen, in which 45 patients underwent neoadjuvant chemotherapy followed by EPP (Weder, 2007). 36 patients received adjuvant radiation. Median survival was 23 months and 38 patients (84%) developed recurrence, however the specific patterns of failure were not described.

Because of the difficulty in adequately targeting the entire post-pneumonectomy space with conventional radiation, several centers have evaluated the use of intensity modulated radiation therapy (IMRT) . IMRT is an advanced method of delivering 3-dimensional treatment using multiple fluctuating radiation beam intensities to maximize the intended dose to the tumoral target while minimizing unwanted radiation dose to normal tissues. It has been shown to improve planning target volume coverage after EPP compared to 3D-conformal radiation (Krayenbuehl, 2007). Using this technique, the group at M.D. Anderson recently published outcomes in 63 patients (median dose 45 Gy) (Rice, 2007). The majority of patients (87%) were stage III/IV. Like the MSKCC series, locoregional recurrences occurred in 13% of patients, however only 3 of these had 'in-field' failure. Unfortunately distant recurrences were frequent (54%) and limited survival in this group of advanced stage patients (median survival 14 months). More recently, the Duke University group published results of IMRT in 13 patients after EPP (70% Stage III/IV) and reported a higher incidence of local recurrences (46%) (Miles, 2008).

There has been recent debate regarding the safety of IMRT after EPP. The Brigham group

reported fatal radiation pneumonitis in 6 of 13 patients (46%) treated with IMRT to a median dose of 54 Gy (Allen, 2006). We reviewed pulmonary related deaths in 63 patients who underwent IMRT after EPP at M.D. Anderson Cancer Center (Rice, 2007). 6 patients (10%) died of pulmonary causes within 6 months of initiation of IMRT, and of these, 2 clearly had radiation pneumonitis. Analysis of multiple dosimetric parameters revealed that patients who died from pulmonary related events received significantly more radiation to the remaining lung than survivors did. However, in comparison to the Brigham series, overall radiation doses to the contralateral lung were much lower. In addition, neither the Duke (n=13) nor the Heidelberg (n=11) groups reported significant pulmonary toxicity with IMRT (Miles, 2008; Münter, 2005).

In contrast to standard hemithoracic radiation using AP/PA beam geometry, where very little of the contralateral lung receives any radiation, IMRT results in a relatively large proportion of the contralateral hemithorax receiving a small dose of radiation. In our series, the median percentage of lung that received at least 5 Gy was 75%. It is therefore not unexpected that there might be more pulmonary-related events associated with IMRT compared with standard hemithoracic radiation. However using strict dosimetric constraints for normal tissue and careful treatment planning, IMRT can usually be administered safely after EPP. The trade off for this increased risk appears to be better coverage of the at-risk target volume and possibly improved local control.

In summary, hemithoracic radiation to 45 Gy or higher appears to be effective in reducing locoregional recurrence of mesothelioma after EPP. Both 3D-conformal and IMRT appear to be acceptable techniques. If IMRT is used, strict adherence to normal tissue constraints must be employed, and care should be given to limit the radiation dose to the contralateral lung. Despite improved local control, distant recurrences remain a significant problem and until better systemic therapy becomes available, adjuvant radiation may not add much in terms of overall survival.

Number: 155

Abstract title:
Estimating the survival benefit associated with radical surgery

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Keywords:
Surgery

Abstract content:

The role of radical surgery in the treatment of mesothelioma is contentious. In the absence of data from randomised controlled studies, we have explored the possibility of using data from published observational and follow-up studies to estimate the magnitude of any survival benefit associated with this practice, whether in conjunction with adjuvant treatment or alone. Selection bias is inevitable when making comparisons between treatment groups in contexts where allocation to treatment is influenced by clinical considerations as to the fitness and suitability of the patient. For this reason, we have limited ourselves to estimating the upper bound of any survival benefit. Given the burdensome nature of the surgery, it could be argued that even the most optimistic estimate of any survival benefit is meagre.

Number: 156

Abstract title:
MARS 2

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Abstract content:

MARS (Mesothelioma And Radical Surgery) is a study of the feasibility of a comparison of chemotherapy versus chemotherapy and extrapleural pneumonectomy with adjuvant radical hemithorax irradiation.
The inclusion criteria have included non-sarcomatoid histology and negative mediastinoscopy.
The initial criticism of the protocol included the suggestion that patients with early epithelioid disease would not want to forego the chance of cure by not receiving EPP.
In reality the trial has not recruited as fast as predicted for the following reasons :
1. many patients do not have sufficient cardiorespiratory reserve to tolerate EPP
2. age at presentation is increasing and performance status is decreasing
Chapman ,Thorax 2008;63:435
3. many patients present late with mediastinal node metastases
4. patients are reluctant to suffer the loss in lung function and therefore quality of life after EPP with no promise of long-term survival
5. patients may be more inclined to undergo lung- sparing surgery if an acceptable symptom-free interval can be offered
The role of surgery in prolonging survival in mesothelioma still needs to be confirmed in the eyes of many clinicians therefore a randomised trial is needed.
In MARS 2 the objective of surgery in the experimental arm should be :
"to obtain macroscopic tumour clearance with the least anatomical resection required"
This would permit radical pleurectomy/decortication and thus widen the potential study population to those with poorer lung function leading to increased recruitment It would also encourage patients who are reluctant to significantly risk their quality of life.
Selection criteria could probably be relaxed to omit mediastinoscopy but any radical surgery in sarcomatoid mesothelioma seems difficult to justify.
The control arm of the study should continue to offer maximum active symptom control including VATS pleurodesis but thoracoscopic debulking should not be performed. The choice of chemotherapy regime should be left to the discretion of the respective oncologist.

Number: 160

Abstract title:
Valproate synergizes with cisplatin and pemetrexed to induce apoptosis in malignant pleural mesothelioma cells

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Keywords:
HDAC inhibitors, apoptosis

Abstract:

The first line treatment for malignant pleural mesothelioma (MPM) includes a regimen of pemetrexed and cisplatin. The major issues of this chemotherapy are acute toxicity, low overall response rate and frequent relapse. We hypothesized that therapeutic efficacy is limited by inadequate gene expression in tumor cells. Therefore, we evaluated the activity of valproate (VPA), a histone deacetylase (HDAC) inhibitor known to activate gene transcription.

We show that VPA synergizes with pemetrexed and cisplatin to induce apoptosis in mesothelioma cell lines (M14K, M38K and ZL34) and in biopsies from MPM patients. Onset of apoptosis involves both extrinsic and intrinsic pathways requiring enzymatic activities of caspase 8 and caspase 9, respectively. In contrast to SAHA, VPA efficiently stimulates production of reactive oxygen species (ROS) and, interestingly, the free radical scavenger N-acetylcystein (NAC) inhibits apoptosis, indicating that ROS are major mediators of VPA activity. As expected, VPA alone or combined with pemetrexed and cisplatin triggers hyperacetylation of histone H3. VPA stimulates release of cytochrome c from mitochondria, cleavage of Bid and overexpression of p21 and Fas. Finally, VPA combined with pemetrexed and cisplatin prevents tumor growth in SCID mice engrafted with M14K cells.

These observations support a potential new regimen of VPA combined with pemetrexed and cisplatin for first line treatment of MPM.

Number: 161

Abstract title:
Inhibition of translesion synthesis sensitizes malignant pleural mesothelioma cells to cisplatin treatment

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Keywords:
translesion synthesis, rev3, malignant pleural mesothelioma, siRNA, shRNA, cisplatin

Abstract:

Background:
Malignant pleural mesothelioma (MPM) is most commonly treated with a multimodality therapy including treatment with cisplatin or cisplatin-analogues, which lead to the formation of inter- or intrastrand DNA adducts. Cisplatin adducts can be repaired or, if not repaired, induce replication fork stalling which can by overcome by specific translesion polymerases.
Translesion polymerase ζ consists of two subunits, Rev3 is the catalytic- and Rev7 the structural subunit. The translesion polymerase ζ is responsible for the translesion synthesis (TLS) of cisplatin based adducts and the repair of DNA interstrand crosslinks. Rev3 deficient vertebrate cell lines show the highest sensitivity to cisplatin compared to other repair-deficient cell lines. Rev3 inhibition by antisense treatment confers higher cisplatin sensitivity and lower mutagenicity in immortal human fibroblasts.
Working hypothesis:
Down-regulation of Rev 3 sensitizes MPM cells to cisplatin treatment and reduces the formation of cisplatin resistance.
Results:
We showed that the expression of Rev3 in human MPM cells is dependent on cell culture confluency and is also affected by cisplatin treatment in a time-dependent manner. Functional inhibition of REV3 by siRNA increased replication fork breakdown as indicated by enhanced H2AX phosphorylation. REV3 expression in rat and human MPM cells was successfully inhibited by transient transfection with plasmids containing short hairpin constructs targeting REV3.
We generated stable HEK293 and human lung fibroblast (Wi38-SV40) cell lines with decreased REV3 expression. Functional inhibition of REV3 in the HEK293 and Wi38-SV40 cell lines resulted in increased genotoxic stress as indicated by increased p53 expression, a slower growth rate and increased cisplatin sensitivity.
Conclusions:
We showed that functional inhibition of translesion polymerase ζ by shRNA against REV3 increased replicative stress in MPM cell lines and increased cisplatin sensitivity in human cells.

Number: 162

Abstract title:
MULTIMODALITY TREATMENT VERSUS CHEMOTHERAPY IN MALIGNANT PLEURAL MESOTHELIOMA

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Keywords:

mesothelioma; chemotherapy; multimodality therapy

Abstract:

Objectives:
For malignant pleural mesothelioma (MPM) treatment, multimodality therapy is declared to be the best treatment. However, this multimodality therapy can only be applied to the chosen group of patients. The criteria used for choosing the patients for this treatment are also good prognostic factors. In this study, we aimed to compare the survival of multimodality therapy applied MPM patients and chemotherapy applied patients with similar characteristics.
Methods:
Extrapleural pneumonectomy was performed to 21 of our patients. Four of them (19%) died because of procedure related to complications. Therefore 4 patients were excluded. For this study, based on age, gender, stage of multimodality therapy applied 17 patients a randomly chosen control group was formed among chemotherapy applied patients. The patients of control group refused surgical therapy. The median survival of these two groups was compared.
Results:
Twenty of the patients (58.8%) were male and 14 of them (41.2%) were female. The mean age was 52,4±9,1 (33–69) years. There was no any difference between two groups about age, gender, asbestos exposure, duration of asbestos exposure, smoking history, Karnofsky Performance Status, duration of symptoms, symptoms, histologic subtype, and stage. However, in the multimodality therapy group left side tumor was more frequent than the chemotherapy group. The median survival for multimodality therapy group was 21,0±4,1 months, for chemotherapy group was 15,0±1,9 months (Log-Rank= 2,883; p=0,090). The multimodality therapy group had a longer survival than chemotherapy group, when compared excluding patients with extrapleural lymph node metastasis (22,0 months vs. 15,0 months; p= 0,037).
Conclusion:
We concluded that multimodality therapy provides a better survival for suitable patients, when performed by experienced centers.

Number: 163

Abstract title:
RE-TREATMENT WITH PEMETREXED-BASED CHEMOTHERAPY IN PATIENTS WITH MALIGNANT PLEURAL MESOTHELIOMA (MPM): AN OBSERVATIONAL STUDY

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Keywords:
second line, chemotherapy, pemetrexed

Abstract:

Background: Second-line chemotherapy in patients (pts) with MPM is being increasingly used in clinical practice, but its role is currently undefined. Recent case series have suggested a possible role of re-treatment with pemetrexed-based chemotherapy (PBC) in this setting (Razak, Lung Cancer 2008). Aim of this observational study was to evaluate this therapeutic option in a consecutive series of pts previously treated with first-line PBC.
Methods: Pts who had partial response (PR) or stable disease (SD) for at least 3 months after first-line PBC were eligible for the study. Pts receiving re-treatment with PBC either as second-line (2L) or further-line (>2L) therapy were considered for analysis.
Results: Eighteen pts were evaluated (9 treated in 2L, 9 in >2L setting). There were 13 males and 5 females. Median age was 66 (range 47-80). Histology was epithelial in 15, mixed in 3. EORTC prognostic score was poor in 13, good in 5. Four SD and 2 PR were observed, all in 2L setting, for an overall disease control rate of 33%. Twelve pts had disease progression (9/9 pts treated in >2L). Grade 3/4 haematological toxicity was observed in 2 pts (11%), with 1 case of febrile neutropenia. Non-hematological toxicity was generally mild, with only 1 case of grade 3 constipation. Median time to progression (mTTP) was 3.5 mos (range 1.2-24.4 mos). Pts receiving PBC as 2L therapy had a longer mTTP in comparison to those treated with >2L therapy (5.6 vs 2.8 mos). Outcome after re-treatment with PBC was correlated to TTP achieved with first-line PBC (5.2 vs 2.4 mos in pts with first-line TTP ; or < 12 mos, respectively).
Conclusion: Re-treatment with PBC seems to be a possible option in the second-line setting in pts with MPM achieving a durable disease control with first-line treatment. Further evaluation in a prospective trial is warranted.

Number: 164

Abstract title:
Imaging Findings of Malignant Pleural Mesothelioma in Japan

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Keywords:
malignant pleural mesothelioma, CT, Diagnostic imaging, pleural plaque

Abstract:

Purpose: Our purpose is to find the radiological findings which can be the key to improve MPM diagnosis by reviewing the images of MPM cases in Japan.

Methods and Materials: Among 2742 mesothelioma death cases extracted by "Vital Statistics of Japan 2003 to 2005", We reviewed 211 MPM cases (182 men, 29 women; mean age, 69 years) in which the chest CT and XP were obtained. The accuracy of diagnosis of MPM was determined in all cases by discussion with the clinical and radiological materials.

1. We reviewed having pleural plaque or not on each CT and XP. The presence of a pleural effusion and asbestosis were also evaluated.
2. Abnormal findings in the pleura on CT images were evaluated, with categorization as follows, Category 1 (no thickening), Category 2 (smooth thickening), Category 3 (irregular thickening) and Category 4 (mass formation). The categories of each case was compared with T-stage according to IMIG.
3. We reviewed localization of the pleural irregularity. We focused on three places as follows, mediastinal, fissural and basal pleura.

Results

1. In all 211 cases, pleural plaque were present in 37% cases on CT and in 12% cases on XP. Each pleural effusion and asbestosis was present in 93% and 3% cases.
2. The ratio of each category of pleura was as follows, Cat-1; 5% cases, Cat-2; 17% cases, Cat-3; 35% cases, Cat-4; 43% cases. As for correlation with T-stage, the majority of patients og Cat-1 and Cat-2 were T1-2(91%), Cat-3 and Cat-4 were T3-4(85%)
3. Location of pleural thickening was mediastinal in 78% cases, fissural 47% cases, and basal in 73% cases.

Conclusion

These results show that degree of the pleural irregularity was mild in 22% cases of MPM, and T-stage was low in these cases. Most of MPM cases were accompanied with pleural effusion. Therefore, when the diagnose unidentified pleural effusion, MPM should be suspected in the case of pleural plaque and mediasitinal, fissural and basal pleural irregularity.

For early diagnosis of the MPM, it is necessary to pay attention to mediastinal, fissural and basal pleural irregularity and pleural plaque in unidentified pleural effusion case.

Number: 165

Abstract title:
Localized Malignant Mesothelioma. 2 new cases

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Keywords:
Localized Malignant Mesothelioma Diagnosis

Abstract content:

We present 2 new cases of localized malignant mesothelioma (LMM) and discuss the most important aspects of the diagnosis of this very uncommon variety of malignant mesothelioma.
Case 1:
A 49-year-old woman without a history of asbestos exposure presented with a history of severe chest pain for 3 months. The chest-CT revealed a left paravertebral pleural tumor.
The diagnosis of a neurinoma was considered. At surgery a sessile 3x2,5x2 cm tumor without infiltration of the neighbouring structures was found at the dorsal chest wall and resected.
Microscopically there were tubular structures with focal adenoid character and the typical immunohistochemical findings of mesothelioma.
Case 2:
A 65-year-old electrician presented with a history of chest pain for some months.
The chest-CT showed a tumor in the right anterior chest wall with destruction of the 5th rib without any evidence of diffuse growth.
The tumor was completely resected together with the adjacent chest wall and a wedge of the upper lung lobe. The pathological examination revealed a mesothelioma of predominant epitheloid type.
The immunohistochemical findings confirmed the mesothelial nature of the neoplasm.
In both cases the diagnosis of a LMM was established.The clinical course after surgery was uneventful. The patients underwent a local radiotherapy 6 weeks after the operation.

Discussion:
LMM are very rare. Less than 50 cases have been reported.
LMMs is defined by
a) the microscopic appearance of a malignant mesothelioma
b) the lack of diffuse or multicentric spread
Thus a very thorough radiologic and macroscopic examination is crucial for the diagnosis.
Diffuse malignant mesothelioma with a dominant mass can be confused with LMM and is the most important differential diagnosis.The analysis of the literature on LMM is difficult, mainly due to earlier denominations such as “benigne” or “localised” mesothelioma for solitary fibrous tumor.

The published cases of LMM demonstrate that also localised neoplasms with grossly benign appearance should be histologically examined without delay.
The role of asbestos exposure in the aetiology or LMM is not well established.
The separation of LMM from DMM is crucial because LMM seems to be associated with a better prognosis after complete resection.

Number: 166

Abstract title:
18FDG PET: a new predictive and prognostic tool in patients with malignant pleural mesothelioma

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Abstract content:

Introduction: FDG-PET seems to be a promising tool in malignant pleural mesothelioma (MPM) but its interest in the staging and in the monitoring of the patients is not really proved. We wanted to evaluate the usefulness of FDG-PET for diagnosis of MPM and assessment of the response to treatment.
Material and method: 46 MPM patients (sex ratio M/F= 35/11; mean age= 61 years (39-79)) were retrospectively studied. Preliminary results included 32 of these 46 patients. For diagnosis and staging, FDG-PET findings were compared with computed tomography (CT) and pathology data. International Mesothelioma Interest Group Staging classification distinguished the patients: stage I: n=3, II: n=13, III: n=11, IV: n=5). Thirteen patients were treated by chemotherapy then surgery (EPP) and radiotherapy, 17 patients had chemotherapy and palliative chest radiotherapy, and 2 patients received only best supportive care.
Results: all patients had abnormal pleural uptake (SUVmax: range= 3.8 -28.4 g/ mL, mean= 9.5 g/mL, median= 7.75 g/mL). Nodal involvement was potentially underestimated by FDG-PET in 10 (31%) patients compared to CT. Pathological findings on surgery samples confirmed that PET and CT underestimated nodal involvement in 6/13 patients. PET diagnosed distant metastasis in four patients, missed on CT.
Metabolic response assessment after chemotherapy (6 cycles of cisplatin-pemetrexed) was possible for 13 patients. FDG-PET predicted therapeutic response about 3 months earlier than CT in 4 of 13 patients. Presence of a metabolic response after chemotherapy visualized on FDG-PET seemed to be associated with a longer time to progression (19 months against 11 months when progression). There was no significant statistical correlation between SUV measurements and nodal involvement. However, SUVmax value was correlated with the survival of the patients (p=0.016).
Conclusion: FDG-PET seemed to be a useful tool for detection of distant metastasis of MPM, but its evaluation of local tumor extension and nodal involvement was rather disappointing. FDG-PET could be interesting to assess the patients' prognosis and to monitor the metabolic response to chemotherapy. Further study of our other patients is ongoing to validate these preliminary results.

Number: 167

Abstract title:
Thoracoscopy using narrow band imaging (NBI) and autofluorescence imaging (AFI) systems is a novel modality for the detection of early mesothelioma

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Keywords:
Thoracoscopy, Diagnosis,

Abstract:

INTRODUCTION:
Narrow band imaging (NBI) is a new endoscopic technique, which improves visualization of vascular architecture using specially designed optical filters. And, the use of autofluorescence imaging (AFI) in conjunction with conventional white light (WL) endoscopy has significantly improved the endoscopic diagnosis of preneoplastic lesion and early cancer. We evaluated the NBI and AFI systems in the detection of preinvasive and small lesions of the pleura in patients with early stage of mesothelioma.
MATERIALS and METHODS:
19 pts with atypical or suspicious cells in pleural fluids or radiological suspicion of mesothelioma were evaluated by thoracoscopy under local anesthesia. Pleura was first screened with conventional WL, and then was examined by NBI(Olympus LTF-240) and AFI (Olympus BF-260) for detection of additional lesions. The device of NBI and AFI systems has a function of two modalities, which easily switches between WL observation and NBI, WL and AFI, respectively. All suspicious areas detected by NBI, AFI or both were biopsied and compared with pathological diagnosis.
RESULTS:
NBI enabled clear visualization of vascular architecture in the pleura comparing with conventional WL, which could distinguish superficial blood vessels from deeper ones, i.e., blood vessels near the pleural surface were displayed in brownish tones, and thick vessels in the deeper layer were shown in cyan tones. Tortuous and irregular dilated vessels and short branch vessels could be visualized clearly in the involved pleura. AFI disclosed that normal mesothelium of the pleura appeared green a little, and that neoplastic areas appeared magenta. Small nodule of T1a mesothelioma appeared brown on NBI and magenta on AFI, with high vascularization on and surrounding the nodule, where a pathological diagnosis was made by biopsy.
CONCLUSIONS:
Advanced imaging modalities of NBI and AFI may allow the detection of early lesions of malignant pleural mesothelioma. And, magnified NBI is feasible for detecting submesothelial vascularization in the early stage of mesothelioma.

Number: 168

Abstract title:
A prognostic index for preoperative evaluation of patients with resectable epithelial mesothelioma

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Keywords:
Extrapleural pneumonectomy, Surgery, Epithelial, Prognosis

Abstract:

The use of prognostic factors independent of TNM stage may aid in the appropriate selection of patients for aggressive treatment strategies. Published studies examining prognostic factors in mesothelioma have lacked consensus on which are significant. Most have lacked statistical power to stratify for important factors such as treatment and histologic subtype. Our objective was to identify preoperative factors related to poor outcome following surgery-based multimodal therapy. To minimize variability, only patients with epithelial tumors who underwent extrapleural pneumonectomy (EPP) were analyzed. Epithelial mesothelioma is more amenable to treatment with multimodality regimens than mixed or sarcomatoid histologies.
Of 473 patients with epithelial mesothelioma who underwent surgical exploration for planned EPP, 365 were resectable by EPP. Among these, 72% were male, the median age was 57 years and the 30-day or in-hospital mortality was 5%.Factors that were measurable preoperatively, were significantly related to prognosis in at least 2 prior reports and could be documented for a majority of this patient cohort were considered. Continuous variables were dichotomized, and factors with univariate logrank p values less than 0.01 were analyzed in a step-up proportional hazards model.
Platelet count > 350K/uL (RR 1.97), white cell count > 10K/dL (RR1.63), hemoglobin < 11 g/dL (RR 1.71), male gender (RR 1.56) and age > 57 (RR 1.52) remained highly significant at each iteration of the model, indicating their independent prognostic value. The overall similarity of relative risk among the factors permitted their additive combination as a prognostic index for each patient, which significantly stratified outcome (see Table). As a component of preoperative assessment, this prognostic index may identify a subgroup of patients (index 3: 4 or 5 factors positive) who would benefit minimally from EPP and for whom alternative management should be considered.

Index	Factors	N	Median	1-yr	2-yr	3-yr	5-yr
1	0-1	140	37 mo	85%	66%	50%	31%
2	2-3	204	17 mo	64%	31%	18%	5%
3	4-5	21	9 mo	26%	5%	0%	0%

Number: 169

Abstract title:
Effect of aurora kinase inhibition in mesothelioma cell lines

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Keywords:

Aurora Kinase

Abstract:

Background: Aurora kinases regulate chromosome-microtubule attachments during cell division and provide mitotic checkpoint control. Amplification or overexpression of Aurora kinases is associated with aneuploidy, aggressive phenotype, and poor prognosis in several cancers. Our previous gene expression profiling study showed that more aggressive mesotheliomas express higher levels of Aurora kinases A (AURKA) and B (AURKB). Therefore, we examined the sensitivity of mesothelioma cell lines to the pan-Aurora kinase inhibitor, VE-465 (gift of Merck).
Methods: We studied the sensitivity of 14 mesothelioma cell lines to VE-465 by MTT assays at 96 hours. AURKA and AURKB transcript levels were examined by Q-RT-PCR and in Affymetrix U133Plus 2.0 microarray hybridization data. Western blotting for p53, p21, total Rb, phospho-Rb, phospho-histone H3, and actin was performed.
Results: The H-Meso cell line was very sensitive to VE-465 (IC50: 2nM). Other mesothelioma cell lines were relatively less sensitive, with IC50 values ranging from 2uM to 20uM. There was a significant correlation between IC50 values and phospho-histone H3 (p=0.045); phospho-histone H3 was highly expressed in H-Meso (the most sensitive line). VE-465 decreased the expression of phospho-histone H3 in sensitive lines. There was no significant correlation between IC50 values and mRNA levels of AURKA or AURKB or protein expression of AURKA, AURKB, p53, p21, or phospho-Rb.
Conclusions: In this study, 1/14 mesothelioma cell lines showed exquisite sensitivity to aurora kinase inhibition by VE-465 and moderate sensitivity was seen in several other lines. Phospho-histone H3 expression may be useful as a predictive and a pharmacodynamic marker in this setting. The therapeutic potential of Aurora kinase inhibition in a subset of mesothelioma patients warrants further investigation.

Number: 170

Abstract title:
Enzastaurin, a Protein kinase C beta (PKCβ) inhibitor in malignant pleural mesothelioma

Keywords:

Abstract:

Number: 171

Abstract title:
Extrapleural pneumonectomy with adjuvant Chemo-Radiotherapy for Treatment of Malignant Pleural Mesothelioma

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Keywords:
Extra pleural pneumonectomy, chemo-radiotherapy, mesothelioma

Abstract:

Background
Surgical resection has been considered the mainstay of treatment for malignant pleural mesothelioma by some. However, it is impossible to achieve microscopically complete resection with surgery alone.
Methods
Between 2001- 2004, 33 patients were operated upon as a part of multimodal therapy for MPM. Pre operative workup included: computed tomography, pulmonary function tests, pleural biopsy, full laboratory investigations, echocardiography in patients over 50 years. Other investigations as MRI chest, bone scan brain CT and ventilation perfusion scan were done when indicated.
IMIG staging system was used to stage our patients. Extrapleural pneumonectomy with mediastinal nodal dissection or sampling was done for all patients. Six cycles of carboplatin-,holoxan were added postoperatively to all patients except 3 with chest radiation in a dose of 4500 to 6000 cGy.

Results
There were 14 males and 19 female, age range was 23- 65y. All patients had asbestos exposure with a duration of exposure that ranged between 12-46y. Three patients had positive family history of the disease. Twenty patients had right sided disease and 13 had left sided disease.
By CT scan, twenty patients had unilateral pleural effusion and 13 had diffuse pleural thikening. Preoperative staging revealed 9 patients with stage I and 24 with stage II. Post operative staging showed 5 patients with stage I, 12 with stage II and 16 with stage III disease. Major morbidity developed in one patient, minor complications occurred in 7 patients. Two patients died after surgery. Epithelial histology was found in 24 patients, 8 with mixed histology and one with sarcomatiod type. There were 5 patients with N2 disease, one with both N1 and N2 disease and 2 with N1 disease only.Recurrent disease developed in 21 patients, 11 with local recurrence, 5 with peritoneal , contralateral hemithorax in 3, contralateral axilla in 1 and bone metastases in one. The Overall one year survival was 84.8%, overall 2 years survival was 51.5% ,overall 3 years survival was 18.2% and overall 4 years survival was 12.12%.

Conclusion
Multimodality treatment appears to benefit a subgroup of highly-selected patients with MPM.

Number: 172

Abstract title:
Trimodal Initial Videothoracoscopy, Intrapleural Chemotherapy and P-32 Radiation for Lung-Sparing Treatment of Pleural Mesothelioma: The Columbia Protocol

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Keywords:
intrapleural chemotherapy, P32, lung sparing

Abstract:

Background: We have developed a trimodal regimen for intracavitary treatment of patients with Stage I (IMIG T1-T2) malignant pleural mesothelioma, incorporating repeated outpatient courses of intrapleural (IP) chemotherapy plus IP radiation with P32 to selected patients with malignant pleural mesothelioma who were unwilling or unable to undergo extirpative surgery.
Methods: Pts underwent initial exploratory videothoracoscopy (VATS) to confirm the presence of disease, and the accessibility of the pleural space to intracavitary treatment. Two IP catheters were placed, anteriorly along the pericardial border up to the ipsilateral lung apex, and posteriorly along and into the diaphragmatic sulcus. Each catheter was attached proximally to a subcutaneous mediport chamber placed over the ipsilateral lower ribs. Over the next 6-12 weeks at 1-2 weekly intervals, cisplatin 20-40 mg, doxorubicin 20 mg, or gamma interferon (1,000 micrograms) in fluid volumes up to 200ml was injected into both ports to perfuse the entire pleural space. The distribution of injectate was verified by intracavitary iohexol CT imaging. The fluid was not removed but allowed to remain and be absorbed. Additional intravenous pemetrexed plus ciplatin chemotherapy was given to selected patients. At week 8-12 in suitable patients, the pleural cavity was imaged with radioactive Technetium-labelled sulfur colloid; if uniformly distributed, 15 mCi of radioactive p32 chromic phosphate sulfur colloid was injected, thereby delivering 4,000-6,000 cGy to accessible pleural surfaces. A second-look exploratory VATS was performed, the catheters and mediports were removed, and the pleural surfaces were inspected and biopsied.
Results: 8 males and 5 female pts aged 46-79 were treated, six with both peritoneal and pleural involvement, others with unresectable disease or who refused surgery. 8 pts received IP P32, one to both left and right pleural cavities. The above procedures were well tolerated without early or late complications. After up to two years of follow-up (as of Jan 2008) 2 patients show no overt disease at 21 and 26 months. 5 patients are alive
with disease; one has undergone pleurectomy / decortication (P/D) and
one has undergone extrapleural pneumonectomy (EPP); Surgical P/D or EPP
remain possible options in 3 others. 6 patients have died, 5 of progressive pleural disease.
Conclusions: This retrospective analysis allows the hypothesis that lung-sparing repeated intrapleural chemotherapy combined with intrapleural P32 radiotherapy may be safely used in patients with malignant pleural mesothelioma. This regimen deserves ongoing prospective study as to overall efficacy and potential incorporation into present day treatment paradigms.

Number: 173

Abstract title:
Improved safety with Extrapleural Pneumonectomy in Malignant Pleural Mesothelioma performed at high-volume hospital with high-volume surgeons.

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Keywords:
extrapleural pneumonectomy, learning curve, high-volume surgery

Abstract:

Background: Few patients with malignant pleural mesothelioma (MPM) are candidates for intended curative surgery by extrapleural pneumonectomy (EPP) which is thus a rare procedure to perform in most departments of thoracic surgery. Selection and correct staging is of outmost importance but still the surgical procedure of EPP for early stages of MPM is confined with considerable morbidity and also a 30-day peri-operative mortality rate around 3% to 5% in recent series. One way of reducing the morbidity and mortality of EPP in MPM may be to confine this high risk surgical procedure to few experienced centres.
Methods: The Nordic Mesothelioma Group decided in 2003 to centralize the high-risk EPP operation and preoperative staging for potentially resectable MPM in one Mesothelioma Research Unit at the National University hospital in Copenhagen, Denmark, covering the three Scandinavian countries (18 mill. Inhabitants). This study aims to examine the learning curve for the clinicians and the improved safety experienced in the first 4 cohorts of 10 patients each (totally 40 patients) undergoing EPP during this centralized programme. Endpoints are duration of operative procedures, surgical complications, and peri-operative 30-days and 90-days mortality.
Results: Four cohorts of 10 patients each had EPP after 3-6 courses of platinum-based induction chemotherapy from Oct-2003 to Sept-2007. There were 33 males, 27 had right hemithorax malignancy, and median age was overall 62 years (range 45-69 years) without any differences between cohorts. Ten % of patients had patch problems and 10 % had fistulations among the first 2 cohorts compared to 0% and 0% among the subsequent 2 cohorts, respectively. The duration of the surgical procedure declined from median 355 minutes in the first cohort to 220 minutes in the fourth cohort. The 30-days and 90-days peri-operative mortality was 0% in all cohorts.
Conclusions: Centralization of EPP lead to a sharp learning curve with diminished complications and shortened time spend on the surgical procedure without any peri-operative mortality. Potential explanations for this favorable outcomes may be that high-volume surgeons and high-volume hospitals may optimize patient selection, minimize technical errors, and improve expertise in critical care medicine and sophisticated diagnostic and treatment services

Number: 174

Abstract title:

PROGNOSTIC FACTORS ACCORDING TO TREATMENT SCHEDULE IN MALIGNANT PLEURAL MESOTHELIOMA

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Keywords:
mesothelioma; prognosis; survival

Abstract:

Objectives:
In this study we aimed to investigate according to treatment schedule the factors effected the survival of patients with malignant pleural mesothelioma (MPM).
Methods:
235 MPM patients who had diagnosed in our clinic between January 1991 and June 2008 were evaluated. The patients were classified into three groups according to their treatment schedule: the best supportive care group (71 patients), the chemotherapy group (147 patients) and, the multimodality therapy group (17 patients). Prognostic factors were detected for all patients, the best supportive care group, the chemotherapy group and the multimodality therapy group by univariate / multivariate analyses.
Results:
After the corrections were made according to therapy, non – epithelial subtype, Karnofsky Performance Status (KPS) 70, stage 3 – 4 disease, right side tumor, serum LDH 500 IU-1 were found as worse prognostic factors for all patients. The non – epithelial subtype, stage 3 – 4 disease, KPS 70 were found as worse prognostic factors for the best supportive care group. The worse prognostic factor for the chemotherapy group was only KPS 70. Histologic subtype and stage were not related to prognosis. The non – epithelial subtype and right side tumor were found as worse prognostic factors for the multimodality therapy group.
Conclusions:
That is just like expected, the patients, who had epithelial subtype, good KPS, and early stage tumor, had better prognosis, even if they do not have any treatment. Chemotherapy should be given to patients with the best performance status, regardless their histologic subtype and stage. For the patients who had mixed or sarcomatous subtype multimodality therapy can not be go under multi-modal therapy.

Number: 175

Abstract title:
Induction Chemotherapy Consisting of Pemetrexed plus Cisplatin Followed by Extrapleural Pneumonectomy for Malignant Pleural Mesothelioma

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Keywords:
Induction chemotherapy, pemetrexed, apoptosis

Abstract:

Background: Malignant pleural mesothelioma (MPM) is an unfavorable intractable tumor caused by asbestos-exposure. As local treatment, such as surgical resection or radiotherapy, is of limited efficacy, establishment of multimodality treatment including systemic chemotherapy, plays an important role in improvement of treatment outcome. In this study, we retrospectively evaluate the efficacy and safety of induction chemotherapy consisting of pemetrexed (Pem) plus cisplatin (Cis) followed by extrapleural pneumonectomy (EPP).
Results: Between 01/2005 and 12/2007, induction chemotherapy was administered to 13 patients, all of them underwent EPP. Of the 13 patients, 8 patients received the combination chemotherapy with Pem plus Cis. Characteristics of these 8 patients are as follows; patients (7 males and 1 female) were aged 49 to 71 (mean 63) years. Seven patients had a PS of 0/1, and one patient a PS of 2. All patients had epithelioid histology. Four patients had stage I disease, one patient stage II, one patient stage III, and 2 patients stage IV (T4). Three cycles of induction chemotherapy were administered in all patients. Overall response rate was 37%, with 3 partial responses. A stable disease was observed in 5 patients, with an overall disease control rate of 100%. Toxicity was mild with grade3/4 neutropenia in one patient, and no grade3/4 non-hematological toxicity was observed. Histological examinations of resected specimens revealed that apoptosis was induced in some tumor tissues, although pathological complete response was not achieved.
Conclusion: Induction chemotherapy consisting of Pem plus Cis was well tolerated against the patients with MPM, underwent EPP. A prospective multi-institutional study is now ongoing in Japan to evaluate the feasibility of induction chemotherapy consisting of Pem plus Cis, followed by EPP and postoperative hemithoracic radiation in patients with potentially respectable MPM.

Number: 176

Abstract title:
MALIGNANT MESOTHELIOMA OF THE PLEURA IN THE PROVINCE OF TRIESTE, ITALY, 2001-2007

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Keywords:
pleura, asbestos exposure, Trieste Province, shipbuilding, port activity, maritime trades, domestic exposure, latency period

Abstract:

Background. The Province of Trieste is a small coastal district, located in North-Eastern Italy, with a population of about 240,000 inhabitants. Studies conducted since 1971 showed a very high incidence of asbestos-related mesothelioma of the pleura in this area. Objectives. The present study was carried out to obtain data on the trend of mesothelioma epidemic in the Province of Trieste, during the last seven years, as well as to characterize the cases in terms of asbestos exposure. Methods. Pleural mesotheliomas diagnosed at the Thoracic Surgery Unit of the Trieste University, in the period Jan 2001-Dec 2007, were reviewed. The histological diagnosis was generally based on material obtained at thoracoscopy and at surgery. In three cases the pathological diagnosis was made by biopsy of the thoracic wall, and in one case by cytological examination of pleural fluid. Necropsy was carried out in 54 cases. Detailed occupational histories were obtained from the patients themselves at the time of their first admission. Results. The group included 124 men and 12 women, aged between 43 and 89 years (mean 69.2 years, median 69.0). A majority of patients had been employed in marine work, including shipbuilding (67 cases), port activity (17 cases), and maritime trades (10 cases). Sixteen people had worked in other industries (iron industry, petrochemical, etc.). A further 16 patients had been employed in a variety of occupations (cinema projectionist, fire-fighter, lift mechanic, pastry worker, telephone technician, etc.). Three men had worked as insulators. Seven women had histories of exposure to asbestos at home, having cleaned work clothes polluted by asbestos. A majority of patients had their first exposure to asbestos before 1960. Latency periods (time intervals elapsed between first exposure to asbestos and diagnosis of mesothelioma) ranged from 25 to 71 years (mean 48.7, median 48.0). One patient had a history of prior thoracic irradiation for Hodgkin's disease. Conclusions. In the Province of Trieste the mesothelioma epidemic does not show signs of abatement. Marine work, and in particular shipbuilding, remain the principal cause of pleural mesothelioma in this area. However, a variety of other occupations are also associated with the tumor.

Number: 177

Abstract title:
Geography of mesothelioma. Reliable data?

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Keywords:
mesothelioma, geography, asbestos exposure, incidence, mortality, diagnosis, registration, necropy

Abstract content:

Background. A dramatic increase in mesothelioma incidence has been observed in many industrialized countries during the last decades [Bianchi C, Bianchi T. Ind Health 2007; 45: 379-387] . A relationship between mesothelioma incidence at a national level and previous consumption of asbestos has been detected in several studies. Since in a large part of the world exposure to asbestos continues, it would be opportune that reliable epidemiological data on mesothelioma were available.
Methods. In the present study we reviewed the data reported on mesothelioma epidemiology in 2007-08, as well as those obtained at our Center, by interviewing researchers of numerous countries.
Results. Data are available for about 15% only of the world population. Three groups of countries may be identified. The first group with estimated annual crude incidence rates of 30 cases per million or more includes Australia, Belgium, and Great Britain. The second group with rates comprised between 11 and 23 per million includes a large part of Europe (France, Germany, Italy, Scandinavian countries, The Netherlands), New Zealand, and US. Rates lower than 11 per million have been reported for other countries, including Japan (7 per million). Very marked variations in the incidence/mortality from one area to another are observed in various countries (e.g. Croatia, Italy, Sweden, The Netherlands, Great Britain).
Comments. 1) The lack of data for enormous countries such as China, India, and Russia represents a serious obstacle in the knowledge on mesothelioma geography. 2) The marked differences in incidence between some highly industrialized countries such as Australia and Great Britain, and other countries such Japan and US, are in some way unexpected. 3) The very low incidence of mesothelioma in some European countries such as Greece and in large port areas such as Hong-Kong and Singapore is surprising. 4) Doubts on the reliability of the available data are suggested by various elements: a) major difficulties are often encountered in the diagnosis as well as in the registration of mesothelioma; b) in practice the percentage of necropsies is very low; c) in many countries mesothelioma epidemiology is largely or exclusively based on mortality data.

Number: 178

Abstract title:
Clinical investigation of malignant pleural mesothelioma: a nationwide survey of 502 death cases in Japan

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Keywords:
asbestos, EPP, systemic chemotherapy

Abstract:

Background: Clinical features of malignant mesothelioma (MM) have not been fully investigated in Japan. This study is a nationwide survey of MM cases selected on Vital Statistics of Japan. Methods: There were 2742 death cases of MM between 2003 and 2005, on the Vital Statistics. We examined clinical features including diagnostic procedure, treatment outcome, or occupational asbestos exposure in malignant pleural mesothelioma (MPM) cases, based on informed consents from their family members. Results: We selected 502 MPM cases with confirmed pathological diagnosis (M/F: 418/84, mean age at diagnosis: 67 year-old), in which the medical information was available. Histological subtypes were epithelioid in 190, sarcomatoid in 95, biphasic in 65, and others in 4 cases. As a diagnostic procedure, thoracoscopy, percutaneous needle biopsy, and thoracotomy were performed in 155, 152, and 98 cases, respectively. Sixty-three cases were diagnosed with cytological examination of pleural fluid and 14 were at autopsy. TNM staging (IMIG) was stage I or II in 104, III in 152, and IV in 114 cases. Curative resection was performed in 94 cases and 179 cases undergone systemic chemotherapy. Median survival time from diagnosis was 7.8 months. Log-rank test revealed that patients less than 70 year-old, with no symptoms at diagnosis, stage I or II disease, or who undergone extra pleural pneumonectomy (EPP) or platinum-based systemic chemotherapy (PBSC), had a preferable outcome. Cox-regression multivariate analysis indicated that no symptoms at diagnosis, stage I or II disease, or being undergone EPP or PBSC as a preferable prognostic factors. Conclusion: The usefulness of EPP or PBSC was indicated, but the prognosis of MPM is extremely poor. Development of early diagnostic tools or establishment of advanced treatment strategy is urgently needed.

Number: 179

Abstract title:
Immunohistochemistry in distinguishing malignant mesothelioma from lung adenocarcinoma: comparison of new mesothelial and lung adenocarcinoma markers and conventional markers in malignant mesothelioma

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Keywords:
TTF-1, Napsin A, Calretinin, malignant pleural mesothelioma, lung adenocarcinoma

Abstract:

Aim: Distinction between primary lung adenocarcinoma and malignant pleural mesothelioma can be a major challenge. The present study analyzed the utility of new markers (Podoplanin, monoclonal Calretinin, new TTF-1's clone of SPT24, and Napsin A) for differential diagnosis of malignant pleural mesothelioma (MPM) and compared them with the conventional positive and negative MPM markers.
Materials: The materials for the present study were extracted from cases deposited in the pathology files of the National Cancer Center Hospital, Tokyo, between 1971 and 2005. This study was composed of 48 cases of MPM and 40 cases of primary adenocarcinoma of the lung.
Methods: The antibodies used in this study were calretinin (polyclonal and DAK -Calret1), Podoplanin (D2-40), WT-1 (6FH2), surfactant apoprotein A (PE10), thyroid transcription factor 1 (8G7G3/1 and SPT24), and Napsin A (TMU-Ad02). Immunohistochemical staining was scored independently by two observers (Y.K. and K.T).
Results: The positive immunostaining rate of polyclonal calretinin and DAK -Calret1 were both 93.8% in MPMs, whereas the rates were only 40% and 32.5% in adenocarcinomas of the lung, respectively. Immunostaining by Podoplanin was observed in 87.5% of MPMs, whereas in only 2.5% of the adenocarcinomas. Immunostaining by WT-1 was observed in 75% of MPM, but in 0% of the adenocarcinomas.
Immunostaining for the negative markers, SP-A and Napsin-A were observed in 0% of MPMs, but in 47.5% and 95% of the adenocarcinomas, respectively. Immunostaining by SPT24 and 8G7G3/1 were observed in 92.5% and 87.5% of the adenocarcinomas, respectively. However no immunostaining whatever was observed in any MPMs with SPT24 and 8G7G3/1.
Conclusion: The present study revealed that most sensitive mesothelial marker is calretinin (DAK -Calret1), and the most specific marker is WT-1. All lung adenocarcinoma markers were negative for MPM. The most sensitive marker for adenocarcinoma was Napsin-A.

Number: 180

Abstract title:
Caveolin-1 is a novel immunohistochemical marker of malignant mesothelioma and differentiates epithelioid mesothelioma from lung adenocarcinoma.

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Keywords:
caveolin-1; immunohistochemistry; mesothelioma; lung adenocarcinoma

Abstract:

The incidence of mesothelioma is increasing, and surgical pathologists are more and more frequently facing with the diagnostic problem in distinguishing epithelioid mesothelioma from lung adenocarcinoma involving pleura. The use of immunohistochemical panel that should include both positive and negative mesothelial markers is becoming a general rule. However, the immunohistochemical profile of the tumor in all cases is not always definitive, leading the continual search for new positive mesothelial markers. Caveolin-1, which is expressed in endothelial cells, alveolar type I pneumocytes, and mesothelial cells, seems to be one of such novel markers. We analyzed the expression of caveolin-1 in 130 cases of malignant mesothelioma, including 80 cases of epithelioid mesothelioma, 30 cases of sarcomatoid mesothelioma and 20 cases of biphasic mesothelioma. We found caveolin-1 expression in all cases except one. Sixty-three cases showed caveolin-1 expression in more than 50% of tumor cells, 55 cases with 5-50% of tumor cells and 12 cases with less than 5%. The caveolin-1 expression was also identified in non-neoplastic mesothelial cells, from flattened mesothelial cell to reactive mesothelial cells. We also studied expression of caveolin-1 expression in 80 cases of lung adenocarcinoma. Only 6 cases (7.5%) of lung adenocarcinoma showed weak or negligible expression and no more than 1% of tumor cells. We found that the sensitivity and specificity of caveolin-1 expression for differentiating epithelioid mesothelioma from lung adenocarcinoma was comparable or even superior to that of currently available positive markers. The inclusion of this novel marker of mesothelioma in the immunohistochemical panel used for the differentiation of epithelioid mesothelioma from lung adenocarcinoma is highly recommended.

Number: 181

Abstract title:
IMPACT OF OESTROGEN RECEPTOR BETA ON PROGNOSIS OF HUMAN MALIGNANT PLEURAL MESOTHELIOMA

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Keywords:
Oestrogen receptor beta, malignant pleural mesothelioma, gender difference, survival

Abstract:

Malignant Pleural Mesothelioma (MMe) is an asbestos related neoplasm with poor prognosis, refractory to current therapies, whose incidence is expected to raise in the next decades. Female gender was identified as a positive prognostic factor among other clinical and biological prognostic markers for MMe, yet a role of oestrogen receptors (ERs) has not been studied. Our goal was to investigate ERs expression in MMe and to assess whether their expression correlates with prognosis. Immunohistochemical analysis revealed intense nuclear ER staining in normal pleura that was reduced in tumour tissues. Conversely, neither tumours, nor normal pleura stained positive for ER. Multivariate analysis of 78 MMe patients with pathological stage, histological type, therapy, sex and age at diagnosis, indicated that ER expression is an independent prognostic factor of better survival. Moreover, studies in vitro confirmed that treatment with 17 -oestradiol led to an ER -mediated inhibition of MMe cell proliferation as well as p21CIP-1 and p27 KIP-1 up-regulation. Consistently cell growth was suppressed by ER over expression, causing a G2/M phase cell cycle arrest, paralleled by cyclin D1 and survivin down-regulation. Our data support the notion of ER acting as a tumour suppressor, and are potentially relevant to prediction of disease progression and to therapeutic response of MMe patients.

Number: 182

Abstract title:
Mesothelioma prevention by an antioxidant food supports an involvement of reactive oxygen species in asbestos carcinogenesis

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Keywords:
prevention, boysenberry, antioxidant, 8-OH-dG, rat

Abstract:

It has been well recognized that the dietary habits affect the incidence of malignant neoplasms, except mesothelioma. The aim of the study was to investigate the possibility to lower the risk of asbestos induced mesothelioma by ingestion of Boysenberry which is known as the high contents of antioxidants and other protective substances. Female F344 rats were divided into the 6 groups (n=20 each): asbestos i.p.+ standard diet (AS); asbestos i.p.+ 2% Boysenberry diet(A2B); asbestos i.p.+ 1% Boysenberry diet (A1B); asbestos i.p.+ 5% beef fat diet (ABF); saline i.p.+ 2% Boysenberry diet (S2B); saline i.p.+ 5% beef fat diet (SBF) and saline i.p.+ standard diet (SS). After i.p. administration of chrysotile asbestos (2 mg/ml in saline, 10 mg/rat), rats were followed for 2 years. The first case of mesothelioma was dissected at day 211 in the ABF, at day 239 in the AS, at day 248 in the 248 in the A1B and at day 292 in the A2B. No mesothelioma was developed in rats administered saline instead of chrysotile in the experimental period. Over the 2-years, survival rate of A2B was significantly extended in comparison with the control (AA). In contrast, survival rate of ABF was the worst in all groups with a statistical significance vs. A2B. Two percent Boysenberry diet corresponded to a human daily intake of 160 g of Boysenberry juice. This result supports the hypothesis that naturally occurring antioxidants and other protective substances in Boysenberry can delay and reduce the risk to develop asbestos induced mesothelioma. In addition to this preventive effect, serum 8-OH-Gua and urinary 8-OH-dG support that the asbestos carcinogenesis involves reactive oxygen species and its derived oxidative DNA damage.

Number: 183

Abstract title:
ASBESTOS-INDUCED MURINE MESOTHELIOMA IN DIFFERENT GENETIC BACKGROUND

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Keywords:
Asbestos mesothelioma, tumor suppressor genes

Abstract:

To better understand the role of tumor suppressor genes (TSGs) in malignant mesothelioma (MM) we have developed models of MM. Survival and MM characteristics were studied in 3 groups (204 mice) of FVB/N mutant mice injected intraperitoneally with 5 mg of crocidolite fibres (Cr-mice) or saline Ctrl-mice), in 3 independant studies. There were 25 Nf2+/-/P16+/- mice, 67 Nf2+/- and 53 WT Cr-mice, and 8, 27 and 24 Ctrl-mice respectively. Mice were sacrificed when signs of illness were detected. Genetic analyses were performed on early cultures of 22 tumour ascites from 7 Nf2+/-/P16+/- mice, 11 Nf2+/- and 4 WT mice.
Survival of all mice, post injection, was significantly different between the 3 groups (p= 0.0033), with the Nf2+/-/P16+/- mice having the shorter survival. Survival of Cr-mice was shorter than that of Ctrl-mice in all groups ((p=0.0126, 0.0001 and 0.0001 in Nf2+/-/P16+/-, Nf2+/- and WT) but not different between groups of Cr-mice. MM was observed in 25%, 38.2% and 15.7% of Cr-Nf2+/-/P16+/-, Cr-Nf2+/- and Cr-WT mice respectively (p= 0.02). Two MM were observed in Ctrl-Nf2+/-/P16+/- mice. No significant difference was found in the delay of tumour occurrence between the 3 groups of Cro-mice (p=0.16). The 3 main subtypes of MM were observed with a similar distribution in the 3 groups of Cr-mice (p=0.55). Sarcomatoid form was predominant. There was a link between ascites formation and MM occurrence in all groups. Genomic analyses showed Nf2 LOH in all but one of both Nf2+/-/P16+/- and Cr-Nf2+/- cultures from tumour ascites. Trp53 was mutated in 1Cr-Nf2+/-/P16+/-, 1 Cr-Nf2+/- and 1 Cr-WT. In contrast, genes at the INK4 locus were inactivated in most cell cultures from Cr-Nf2+/- and Cr-WT mice, although less in Cr-Nf2+/-/P16+/- cultures (3 out of 7).
Interestingly there were exclusive mutation between Trp53 and these genes.
In conclusion, mutations affecting the TSGs Nf2 and P16 increase the frequency of MM, but do not alter the pathological features of crocidolite-induced MM observed WT mice, and mimics human MM. The genomic similarities between human and murine MM underline the role of these TSGs in asbestos-induced MM.

Number: 184

Abstract title:
C. elegans as a model system to evaluate genetic alterations in MPM, and the genetic-environmental interactions/effects of asbestos

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Keywords:
C. elegans transgenics, c-Met receptor tyrosine kinase, juxtamembrane domain mutations, asbestos exposure

Abstract:

There are a large number of genetic abnormalities that occur in MPM. We have recently shown that the MET receptor tyrosine kinase is overexpressed, sometimes mutated and/or amplified in MPM tumor tissues and cell lines. In order to test the functionality of kinases, such as MET, we have developed a "high-throughput" system in the multicellular microscopic organism C. elegans. Chrysotile has been used more than any other type and accounts for about 95% of the asbestos found in buildings in the US. First, we have examined the toxic effect of this fiber in control (N2) C. elegans. C. elegans was cultured in M9 medium for 2 weeks with or without chrysotile fibers (asbestos), after which survival and rates of developmental defects were estimated. Chrysotile reduced survival and induced locomotion defects (as measured by time-lapse video microscopy). To examine the effect of human MET gene expression in C. elegans, cDNA constructs of human MET with the mammalian CMV promoter were micro-injected into the gonad syncytium. Wild-type MET cDNA and mutant MET (T1010I, juxtamembrane domain) cDNA were injected. Control animals (N2) were injected with vector alone. Progenies were isolated and examined for visible morphological abnormalities such as defects in vulval formation, body morphology and locomotion. Individually cloned transgenic animals were further analyzed for fecundity and viability. Expression of human wild type MET cDNA in C. elegans transgenic animals induced developmental abnormalities such as vulva defects, uncoordinated locomotion, and effects on viability of the progeny. A range of abnormalities in vulval development were observed, such as vulvaless, multi-vulva, protruding vulva, and ectopic vulval phenotypes. In order to confirm that transgenic animals with abnormal phenotypes expressed the human MET gene, MET expression was examined at the protein level by immunoblotting whole animal protein extracts against antibodies specific to human MET protein. An increase in developmental defects (vulva) was observed in T1010I mutant MET transgenic animals when compared to wild type MET and N2 control ($P<0.0001$). Currently, our studies on the various mutants of MET and the effects of asbestos are ongoing. Ultimately, this will serve as a new paradigm for high-throughput analysis of any gene (with or without mutations) and interactions with the environment (asbestos) in a multi-cellular organism.

Number: 185

Abstract title:
Identification of genes relevant for the development of murine malignant mesothelioma

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Keywords:
Mouse model, array CGH, expression array

Abstract:

Little is known about the genetic lesions contributing to the development of malignant mesothelioma. In a subset of tumors in man, inactivation of tumor suppressor genes such as the neurofibromatosis type 2 gene (NF2), INK4a and TP53 has been reported. We recently published a mouse model for malignant mesothelioma using conditional knockout mouse(1). Mesothelioma developed at high incidence in Nf2;Ink4a/Arf and Nf2;p53 conditional knockout mice and the tumors closely mimicked human malignant mesothelioma. Upon functional Ink4a loss in the latter mice, survival was significantly reduced and all tumors were highly invasive.
We analyzed these murine mesothelioma's with array CGH to identify genes that contribute to tumor progression in this model. Conditional Nf2;p53 mesotheliomas revealed multiple recurring chromosomal gains and losses, the most common aberration being gain of chromosome 15. A few small, high level amplifications point to the involvement of c-Myc en c-Met in the development of these tumors. Array CGH analysis of the mesotheliomas in the Nf2;Ink4a/Arf and Nf2;p53;Ink4a mice showed a more stable genome in these tumors with fewer genetic aberrations.
We are currently analyzing a representative subset of these tumors with expression arrays, to further investigate genes that are relevant for tumor development in this model.
(1) Jongsma J, van Montfort E, Vooijs M, Zevenhoven J, Krimpenfort P, van der Valk M, van de Vijver M, Berns A. (2008) A Conditional Mouse Model for Malignant Mesothelioma. Cancer Cell. 2008 March;13(3):261-271.

Number: 186

Abstract title:
Dietary vitamin A or E supplementation does not alter the rate of development of asbestos induced tumors in an accelerated model of mesothelioma

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Abstract:

Epidemiological studies suggest that dietary intake of -carotene can reduce the risk of lung cancer. The finding of an inverse relationship between serum -carotene levels and risk of lung cancer strengthened the validity of the observation. Vitamin A and other retinoids have been tested in clinical trials, and all-trans-retinoic acid is now an accepted treatment for acute promyelocytic leukemia. Similarly, Vitamin E has been scrutinized for its potential to reduce the risk of developing
cancer and in one study, -tocopheryl succinate, a semi synthetic vitamin E analogue increased survival >3-fold compared to untreated animals in an experimental model of peritoneal mesothelioma. The results from intervention studies, however, have been much less convincing. Alfonso and colleagues recently reported that there were no significant associations between carotene or vitamin E concentrations and incidence of mesothelioma in a cohort of at risk individuals in Western Australia. Here, we confirm these findings in a transgenic animal model of mesothelioma in which SV40 expression is directed to the mesothelial compartment. Untreated animals remain disease free, but inoculation of asbestos leads to accelerated tumour development with a median survival of 32 weeks. Animals fed vitamin-supplemented diets had identical survival, demonstrating that dietary vitamin A or E supplementation does not alter the rate of development of asbestos induced tumors.

Number: 187

Abstract title:
Adenovirus-mediated NK4 gene therapy for malignant mesothelioma

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Abstract:

Malignant mesothelioma (MM) is a highly invasive and metastatic malignancy. Despite diverse therapeutic approaches such as surgery, radiotherapy or chemotherapy, MM continue to have a very poor prognosis. Thus, new therapeutic modalities are urgently needed for patients with MM. Hepatocyte growth factor (HGF) and its receptor Met play a critical role in the pathogenesis of MM, and targeting HGF/Met signaling could be therapeutically important. NK4, a HGF antagonist and angiogenesis inhibitor, composes the N-terminal hairpin domain and four kringle domains of the -chain of HGF. The therapeutic potential of NK4 has been demonstrated in other tumor types. In this study, we generated an adenovirus-mediated NK4 delivering system for targeted therapy against HGF/Met in MM. Our results showed that NK4 significantly inhibited MM cell growth in culture dishes. NK4 also markedly reduced the number of MM cells that invaded through Matrigel, and decreased the rate of cell migration in wound healing assays. Furthermore, our pilot experiments showed that MM cells infected with NK4 adenovirus developed tumors much slower than MM cells infected with control adenovirus did in mice. These results suggest that molecular targeting of HGF/Met by NK4 could be an effective therapeutic approach for patients with MM.

Number: 188

Abstract title:
Measles Virus Induces Oncolysis of Mesothelioma Cells and Allows Dendritic Cells to Cross-Prime Tumor-Specific CD8 Response

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Keywords:
Mesothelioma - measles virus - virotherapy - cancer vaccine

Abstract content:

Despite conventional medical and surgical treatments, malignant pleural mesothelioma (MPM) remains incurable. Oncovirotherapy (i.e., the use of replication-competent virus for cancer treatment) is currently explored in clinical trials. In this study, we investigated the antineoplastic potential of a new oncolytic viral agent, a live-attenuated measles virus (MV) strain derived from the Edmonston vaccine lineage (Schwarz strain). We evaluated both oncolytic activity and immunoadjuvant properties of the MV vaccine strain on mesothelioma tumor cells. Infectivity, syncytium formation, and cytolytic activity of MV were studied on a panel of mesothelioma cells derived from pleural effusions of MPM patients. We observed that MV infected preferentially MPM cell lines in comparison with nontransformed mesothelial cells, leading to an efficient killing of a significant fraction of tumor cells. A cytoreductive activity was also evidenced through formation of multinuclear cellular aggregates (syncytia). The susceptibility of MPM cell lines to measles infection was assessed by the analysis of cell surface expression of the MV vaccine receptor (CD46). We also evaluated whether MV infection of mesothelioma cells could elicit an autologous antitumor immune response. We showed that MV Schwarz strain induced apoptotic cell death of infected mesothelioma cells, which were efficiently phagocytosed by dendritic cells (DC). Loading of DCs with MV-infected MPM cells induced DC spontaneous maturation, as evidenced by the increased expression of MHC and costimulatory molecules along with the production of proinflammatory cytokines. Priming of autologous T cells by DCs loaded with MV-infected MPM cells led to a significant proliferation of tumor-specific CD8 T cells. Altogether, these data strongly support the potential of oncolytic MV as an efficient therapeutic agent for mesothelioma cancer.

Number: 189

Abstract title:
Chemoimmunotherapy in mesothelioma

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Keywords:
cisplatin, pemetrexed, immunotherapy, murine, CD40

Abstract:

We previously demonstrated synergy between gemcitabine and immunotherapy in small syngeneic murine mesothelioma tumors. Since then, cisplatin and pemetrexed has become the clinical standard of care in mesothelioma. We aimed to investigate combinations of cisplatin and pemetrexed with immunotherapy. The murine mesothelioma cell line AB1-HA was generated through peritoneal asbestos inoculation and transfected with the hemagglutinin (HA) neo-antigen to allow analysis of antigen-specific anti-tumor responses using CD4+ or CD8+ lymphocytes from HA-specific TCR transgenic mice. In vitro growth inhibition was assessed by MTT assays. In vivo tumor growth was assessed using a subcutaneous flank model in athymic nude and wild-type (wt) BALB/c mice. Chemotherapy was given i.p. at the previously determined MTD. FGK 45 (activating anti-CD40 antibody) was given 3 times i.v. starting 2 days after the end of chemotherapy. AB1-HA was approximately 5-fold more sensitive to gemcitabine than pemetrexed in vitro. In vivo in athymic nude mice, gemcitabine decreased tumor outgrowth as compared with untreated control mice ($p < 0.001$) but cisplatin and pemetrexed did not (p=NS). However, in wt mice, both gemcitabine ($p<0.001$) and cisplatin and pemetrexed ($p=0.01$) decreased tumor outgrowth, suggesting a role of intact adaptive cellular immunity in the observed in vivo efficacy of cisplatin and pemetrexed. The adoptive transfer of HA-specific CD8+ T cells restored the wt phenotype of athymic nude mice treated with chemotherapy. No long term survival was observed with chemotherapy alone. Despite modest in vivo efficacy of chemotherapy alone, the combination of cisplatin, pemetrexed, and CD40 ligation with FGK45 resulted in long term survival and resistance to rechallenge in 40% of mice with large established tumors at the start of immunotherapy (5 x 5 mm). This contrasted with 0% long term survival in mice treated with gemcitabine and FGK45 when immunotherapy was started at the same tumour size (5 x 5 mm), although this combination cured smaller tumours (2 x 2 mm). In conclusion, this study supports an immune modulatory effect of cisplatin and pemetrexed and a rationale for combination studies of this regimen with CD-40 activating immunotherapy in human clinical trials.

Number: 190

Abstract title:
Malignant mesothelioma in Japan in relationship to asbestos exposure

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Keywords:
occupational asbestos exposure, diagnosis, therapy, survival

Abstract content:

The clinical features and therapy of malignant mesothelioma in Japan were investigated in relationship to asbestos exposure.
(Material and method) Retrospective study of malignant mesothelioma patients from 2000 to 2007 treated in 27 Rosai hospitals, Japan was performed. Gender, ages, primary sites, diagnostic motives, methodological procedures for diagnosis, histological types, clinical stages of IMIG classification, therapy and prognosis, occupational histories and radiological findings of asbestos-related changes were examined. The number of asbestos bodies in the lung was also counted.
(Results) Total 237 cases were examined and 221 were diagnosed of malignant mesothelioma and other 16 cases were not diagnosed as malignant mesothelioma. Two hundred and twenty-one patients consisted of 185 male and 36 female with the median age of 67 years. One hundred and eighty four originated from pleura and 29 from peritoneum, 4 from pericardium and 2 from tunica vaginalis. One hundred and thirty-five patients were diagnosed by the chief complaints and other 27 patients were diagnosed by regular health check-up etc. One hundred ninety-five patients were diagnosed by the histological examinations and 17 patients were by cytological examinations.
As for the histology, 112 patients exhibited epithelioid type, 52 for sarcomatoid type and 30 for biphasic type. According to the clinical stage, 40 patients were stage I, 13 patients stage II, 64 patients stage III and 62 patients were classified to stage IV.
Fifty patients were done by surgery, 99 by chemotherapy, 71 patients for best supportive therapy. Overall survival of 221 cases was 7.1 months Survival term for pleural mesothelioma was median of 7.5 months and peritoneal mesothelioma was 5.4months. For pleural mesothelioma, stage I + II were the median of 9.7 months survival, stage III were 9.4 months and stage IV were 5.2 months.
Eighty-four percent of 201 patients had occupational exposure to asbestos. Thirty-seven patients had occupational histories of shipyard work, 22 patients had in construction works, 19 patients were insulators, and the remainders were also employed in the asbestos-related works. The median duration of asbestos exposure was 30 years and the median latent period from the first asbestos exposure to the appearance of malignant mesothelioma was 43 years.
For the radiographical findings of asbestos-related changes, 9 patients exhibited asbestosis, 106 pleural plaques, 2 rounded atelectasis and 6 showed diffuse pleural thickening. Eighty-three percent of 45 patients had more than 1,000 asbestos bodies per 1g of dry lung tissue.
(Conclusion) More than eighty percent of malignant mesothelioma in Japan was induced by the occupational exposure to asbestos.

Number: 191

Abstract title:
Total antioxidant capacity in asbestos-related diseases in people exposed to crocidolite in Wittenoom

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Keywords:
antioxidant; vitamins; retinol; beta-carotene; crocidolite; mesothelioma; lung cancer

Abstract:

Background
Recent reports have shown increased mortality risks associated with intake of antioxidant vitamin supplements. Asbestos-related diseases (ARD) have been associated with an increase of oxidative activity. Vitamin A has been supplemented to people previously exposed to crocidolite at Wittenoom in an attempt to prevent ARD.
Methods:
Using plasma collected in the Vitamin A Program from workers exposed to crocidolite at Wittenoom, we have compared TAC levels in those who subsequently developed mesothelioma (n=63), or lung cancer (n=50) against 200 control workers. We have also examined the relationships between TAC levels and plasma levels of antioxidant vitamins previously measured into the Program.
Results: There were 3,107 measurements over 11.7 years of follow up, on average. After adjustment for age and smoking, plasma TAC levels were statistically similar among cases of mesothelioma and lung cancer, compared with controls (p0.13 and p0.85 respectively). There was a significant increase of plasma TAC levels over time in the non-diseased (0.011 units/year, p=0.05), while TAC levels in the mesothelioma and lung cancer groups showed no any significant trend over time prior to developing disease.
In a multivariate analysis, a positive association was found between plasma TAC levels and plasma retinol levels (p=0.08) and Vitamin E levels (p<0.01). An inverse association between beta-carotene and TAC was found (p<0.01). The significant effect of plasma retinol levels on TAC was lost after adjustment for plasma total albumin levels (p=0.75).
Conclusions:
Plasma TAC levels measured by AIOR method was not statistically associated with the development of mesothelioma or lung cancer in this study. Several reasons may explain this finding, including the lack of adjustment for diet and other lifestyle factors. The positive association between retinol and vitamin E and TAC levels is in agreement with their protective association with ARD and lung function previously observed in this cohort. The negative association between beta-carotene and TAC levels may help explain previous observations of deleterious effect of beta-carotene supplementation. This study suggests that measuring the oxidative capacity of supplemental vitamins may clarify their functional role in preventing these diseases.

Number: 192

Abstract title:
Asbestos Fiber Concentration in Lung Tissues Resected for Malignant Pleural Mesothelioma

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Keywords:
Asbestos concentration, Analytical electron microscopy

Abstract:

Background Although the association between asbestos exposure and the development of malignant pleural mesothelioma (MPM) is well recognized, the relationship between asbestos contents by fiber type and the development for MPM remains unclear.
Methods Asbestos fiber contents in the lung tissues and tumor were analyzed in 4 patients with MPM by transmission electron microscopy with energy-dispersive X-ray analysis using a low-temperature ashing procedure. The geometric mean content of total asbestos, crysotile and amphibole asbestos in the control subjects without asbestos exposure were used as reference, which was 1.8, 0.5 and 1.0 (x 106 fibers / g dry lung), respectively. (Reference: Sakai K et al. Asbestos Concentration and Fiber Size in Lungs of the Urban Residents. Japanese Journal of Public Health, 1991; 38: 762-770)
Results Four patients were analyzed in this study, which were Case 1: 50M, biphasic type, pT3N2M0, Case 2: 54M, biphasic type, pT2N0M0, Case 3: 56M, epithelial type, pT4N0M0 and Case 4: 65M, epithelial type, pT3N2M0. All patients had a history of asbestos exposure and underwent an extrapleural pneumonectomy with curative intent. Asbestos fibers were not detected in the tumor tissues in all. The geometric mean content of total asbestos in lung tissues were 1.8 (x 106 fibers / g dry lung), 54.2, 6.5 and 1.6 in the case 1, 2, 3 and 4, which ratios of case to control were 1.0, 29.6, 3.6 and 0.9, respectively. Ratios of case to control of chrysotile's content were 2.8, 58.2, 1.8 and 0.8, and those of amphibole asbestos were 0.4, 25.1, 5.6 and 1.2 in the case 1, 2, 3 and 4, respectively.
Conclusions Case 1 and 4 had MPM without high level exposure of total asbestos. On the other hand, case 2 and 3 showed higher concentration of total asbestos fiber in the lung tissues than control subject, which evidenced the high level exposure of asbestos. Those two patients also had a large proportion of amphibole asbestos, which might be associated with the development of MPM. To elucidate the relation between the pulmonary asbestos fiber contents by fiber type and development of MPM, further investigation is considered necessary.

Number: 193

Abstract title:
Clinical outcome, lung asbestos burden, and disease are predicted by epigenetic profiles in pleural mesothelioma

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Keywords:
Survival, prognosis, asbestos burden, epigenetics, methylation

Abstract:

Mechanisms of action of non-mutagenic carcinogens such as asbestos remain poorly characterized. As pleural mesothelioma is known to have limited numbers of genetic mutations, we aimed to characterize the relationships among gene-locus specific methylation alterations, disease status, asbestos burden, and survival in this rapidly-fatal and costly asbestos-associated tumor. Methylation of 1505 CpG loci associated with 803 cancer-related genes were studied in 158 pleural mesotheliomas and 18 normal pleura. After false-discovery rate correction, 969 CpG loci were independently associated with disease status (Q-value < 0.05). Classifying samples based upon CpG methylation profile with a mixture model approach, methylation classes discriminated tumor from normal pleura (permutation test P < 0.0001). In a random forests classification the overall misclassification error rate was 3.4%, with <1% (n=1) of tumors misclassified as normal (P < 0.0001). Among tumors, methylation class membership was significantly associated with lung tissue asbestos body burden (P < 0.03), and significantly predicted survival (likelihood ratio test P < 0.01). Consistent with prior work, asbestos burden was associated with an increased risk of death (HR = 1.4, 95% CI, 1.1 – 1.8). Our results have shown that methylation profiles powerfully differentiate diseased pleura from non-tumor pleura, that asbestos burden and methylation profiles are independent predictors of mesothelioma patient survival, and that cellular epigenetic dysregulation is a critical mode of action for asbestos in the induction of pleural mesothelioma. Importantly, these findings hold great promise for the use of epigentic profiling in the diagnosis and prognosis of human cancers in general.

Number:194

Abstract title:
AN ANATOMO-PATHOLOGICAL STUDY OF SPONTANEOUS MALIGNANT MESOTELIOMA (MM) IN DOMESTIC ANIMALS. ITS POSSIBLE USEFULNESS IN ENVIRONMENTAL MONITORING FOR THE PROTECTION OF HUMAN HEALTH IN ASBESTOS-POLLUTED

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Keywords:

mesothelioma, environment, domestic animals

Abstract:

Sixteen years after the ban on the industrial use of asbestos in Italy, there are still some geographic areas with a high incidence of MM deriving from environmental exposure to fibres. In these territorial contexts it would now be necessary to acquire data concerning asbestos-related tumour risk resulting from exposures chronologically closer than the traditional ones of occupational type, which cause MM in humans with induction-latency times of 20-40 years. For this purpose the study of spontaneous MM in domestic animals and pets, particularly dogs, has been suggested: MM would be an indicator of asbestos pollution, especially in the indoor environment. On this basis a preliminary anatomo-pathological study has been carried out, preparatory to the realization of a methodologically structured investigation with the recruitment of a statistically adequate number of small domestic animals in an area with high MM incidence, such as the district of Casale M.to. The aim was to define the gross and microscopic characteristics of spontaneous MM in a limited series of small domestic animals, such as dogs (n=8) and cats (n=2), which had been living in Casale M.to and, while still alive, had shown pleuro-pulmonary disease suggesting MM on the basis of the clinico-radiological and laboratory data. The key gross (multiple nodules, local growth with invasion of submesothelial tissues by continuity and metastases to loco-regional lymph nodes, but very rarely with systemic spread via the bloodstream) and microscope images (epitheloid pattern more frequent than biphasic, ferruginous bodies in the lung tissue) and the immunoreactivity (coexpression of cytokeratin and vimentin with strong and diffuse cytoplasmic staining) have suggested a close morpho-biological similarity between spontaneously-occurring MM in animals and humans. Thanks to the shorter induction-latency time of 8-9 years, the study of spontaneous MM in domestic animals can act as a comparative model in environmental health surveys. More generally, the study of the environment veterinary pathology probably does not provide data which can be used as the only determining factor in assessment of risk to human health due to environmental pollutants. However, it may be useful as support for further biological evidence in monitoring programmes of environmental decontamination.

Number: 195

Abstract title:

High Prevalence of Asbestosis Associated with Occupational Asbestos Exposure in Western Australia

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Abstract:

Background – Western Australia (WA) has the highest national rate of malignant mesothelioma in Australia. However limited information is available on the occupational risks of lung cancer and asbestosis in the workforce.

Objectives – To examine the risk of asbestos-related disease (ARD) from occupational asbestos exposure to asbestos in WA using job title as a surrogate for exposure

Methods – Participants were selected from a cancer prevention program for people exposed to asbestos. A cohort of 1399 males occupationally exposed to asbestos other than at the Wittenoom crocidolite mine were followed up from 1990 to 2005. Malignant mesothelioma and lung cancer incidence, and mortality with radiographic asbestosis represented ARD within the study. Rate ratios (RR) compared disease rates within the cohort over time and by industry and occupation.

Results – One hundred and two deaths with asbestosis, 28 incident cases of malignant mesothelioma (21 pleural and 7 peritoneal) and 48 incident cases of lung cancer were observed. Forty percent of the cohort (570 cases) had some level of asbestosis. Deaths coded as asbestosis represented 2% of total asbestosis prevalence. ARD incidence statistically increased over follow-up (p=0.0085). Asbestos manufacturing represented the greatest risk of ARD for industry and occupations followed by the marine industry and occupations, shipyard industry, process operators and firemen. Results were limited by the selective nature of the cohort and risk estimates could not be generalized to the WA workforce.

Conclusion – The presentation of occupational asbestosis was found to be far above that of any malignant ARD within the cohort. Examining radiographic asbestosis as well as malignant mesothelioma and lung cancer may allow a much better prediction of the extent and duration of ARD in Australia. Occupational risk estimates provided preliminary evidence towards job titles where asbestos disease and exposure maybe a priority.

Number: 196

Abstract title:
Panel of Tumor Markers for the Diagnosis of Malignant Pleural Mesothelioma

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Keywords:
tumor marker, early detection, ELISA

Abstract:

OBJECTIVE:
Most malignant pleural mesothelioma (MPM) patients present with advanced stage of disease when therapeutic options are limited. Tumor markers that define high-risk patients would enhance diagnostic capabilities and have clinical benefit for detection of MPM. In the current study, plasma concentrations of SMRP, osteopontin, CA-125, and transforming growth factor-β (TGF-β) in patients with MPM were compared against those from asbestos-exposed controls to determine the role of these markers in detection of MPM.
METHODS:
Prospective evaluation of plasma SMRP and osteopontin was conducted on patients with MPM (n = 38) and asbestos-exposed matched controls (n = 64). Matched factors were gender, age, and smoking history. Enzyme-linked immunosorbent (ELISA) assays were used to determine the values.
RESULTS:
Median SMRP, osteopontin, and CA125 were higher in the untreated MPM patients compared to those in asbestos-exposed controls (4.6 ± 5.7 vs. 1.4 ± 1.0 nM, p = 0.02; 500.1 ± 521.6 vs. 241.6 ± 94.8 ng/ml, p = 0.02; 37.3 ± 39.8 vs. 9.1 ± 8.0 U/ml, p < 0.001, respectively), while TGF-β showed no statistical difference between two groups (10.2 ± 8.9 vs. 14.8 ± 10.2 ng/ml, p = 0.1). In receiver operating curve analysis, the sensitivity and specificity of SMRP in differentiating the controls from untreated MPM patients were 94% and 75% (cut-off, 1.9 nM), those of osteopontin were 100% and 54% (cut-off, 247 ng/ml), and those of CA125 were 100% and 43% (cut-off, 7.1 U/ml), respectively. Among 17 patents who had their tumor markers measured before any type of therapy, 16 of them had all three markers (SMRP, osteopontin, and CA125) above their cut-off values (sensitivity, 94%). On the other hand, only 4 of 68 asbestos-exposed controls demonstrated higher values than their cut-off values for all three markers (specificity, 94%).
CONCLUSIONS:
The panel of three markers (SMRP, osteopontin, and CA125) is valuable in suggesting the diagnosis of MPM, and potentially useful in screening high-risk asbestos exposed populations for MPM.

Number: 197

Abstract title:
Potential value of soluble mesothelin-related protein in pleural fluid for diagnosis of malignant pleural mesothelioma

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Keywords:
mesothelin, diagnostic marker, benign asbestos pleurisy

Abstract content:

Malignant pleural mesothelioma (MPM) is a highly aggressive neoplasm strongly associated with asbestos exposure, primarily arising from the surface serosal cells of the pleura. Patients with MPM often develop pleural fluid as initial presentation. However, cytological diagnosis with pleural fluid is usually difficult and has limited utility. Useful molecular marker for differential diagnosis especially with lung cancer (LC) is urgently needed. The aim of the present study is to investigate the diagnostic value of soluble mesothelin-related protein (SMRP) in pleural fluid. Pleural fluids were collected from 23 patients with MPM, 38 with LC, 26 with benign asbestos pleurisy (BAP), 5 with tuberculous pleurisy (TP), and 4 with congestive heart failure (CHF), and SMRP concentration was determined. All data were analyzed by using non-parametric two-sided statistical tests. The mean concentration of SMRP in MPM, LC, BAP, TB, and CHF were 20.96 ± 23.99 (range, 0.90 - 82.80), 7.13 ± 6.66 (range, 0.05 – 36.40), 6.36 ± 2.83 (range, 1.45 – 11.25), and 3.79 ± 2.25 (range, 1.65 - 6.50), and 2.05 ± 0.69 (range, 1.35 – 2.80) nmol/L, respectively. SMRP concentration was significantly higher in MPM than in other diseases (P=0.001). The area under the ROC curve (AUC) values of MPM diagnosis was 0.75 for differential diagnosis from other groups. Based on the cut-off value of 8 nmol/L, the sensitivity and specificity for diagnosis of MPM were 70.0 and 68.4, respectively. These results indicate that SMRP concentration in pleural fluid would be a useful marker for diagnosis of MPM.

Number: 198

Abstract title:
Soluble mesothelin-related peptide (SMRP) in pleural effusion for the diagnosis of malignant pleural mesothelioma

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Keywords:
Soluble mesothelin-related peptide ,SMRP, pleural effusion

Abstract content:

Background: We have demonstrated that soluble mesothelin-related peptide (SMRP) in serum is highly specific and moderately sensitive biomarker for malignant pleural mesothelioma (MPM). Since most patients with MPM present with fluid retention, we investigate whether levels of SMRP were raised in pleural effusions.
Methods: Pleural fluid was collected from 80 patients with MPM. SMRP levels in effusion were determined by a double determinant ELISA using two antibodies (OV569 and 4H3).
Results: According to each histologic subtype of MPM, the mean levels of SMRP showed as follows; 75.9nM in epithelioid, 18.9nM in sarcomatoid, 43.8nM in biphasic, and 36.6nM in desmoplastic, respectively. The mean levels of SMRP in effusion of epithelioid subtype were significantly higher than those of non- epithelioid subtypes. According to each stage of MPM, the mean levels of SMRP showed as follows; 48.1nM in stage I, 48.6nM in stage II, 63.6nM in stage III, and 77.1nM in stage IV patients. SMRP levels in effusions were elevated not only in advanced stage, but also in early stage.
Conclusions: Measurement of SMRP levels in plural effusion may contribute to make an early diagnosis of MPM.

Number: 199

Abstract title:
Measurement of pleural fluid osteopontin level in diagnosis of malignant pleural mesothelioma

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Keywords:
pleural fluid, osteopontin

Abstract:

Previous studies reported that serum osteopontin levels were elevated in patients with pleural mesothelioma, indicating that osteopontin can be a useful biomarker in pleural mesothelioma. We examined pleural fluid osteopontin levels in 26 patients with pleural mesothelioma(PM), 15 with asbestos pleurisy (AP), 37 matastatic plreuritis (MP) and 28 with various nonmalignant diseases (NM). Average pleural fluid osteopontin level was 17907 ng/ml, 15550 ng/ml, 15126 ng/ml and 7332 ng/ml in PM, AP, MP or NM, respectively. There was a significant difference by Kruskal-Wallis test (P = 0.0003). Receiver-operating-characteristics (ROC) analysis showed an area under curve (AUC) of 0.641 between PM and the others. At a cutoff value of 8530 ng/ml, the sensitivity and specificity were 84.6% and 40.0%, respectively. ROC analysis showed an AUC of 0.805 between PM and NM. But ROC analysis showed AUCs of 0.479 between PM and AP and 0.585 between PM and MP, respectively. Average pleural fluid osteopontin levels were 17272 ng/ml, 9568 ng/ml, 36412 ng/ml in epithelioid, sarcomatoid and biphsic type, respectively. Measurement of pleural fluid osteopontin level is useful in differentiating PM from NM, hard in differentiating PM from AP or MP. Plueral fluid osteopontin level in patients with sarcomatoid type mesothelioma is lower than that with epithelioid or biphasic type mesothelioma.

Number: 200

Abstract title:
Potential value of DNA methylation profile in pleural fluid for differential diagnosis of malignant pleural mesothelioma and adenocarcinoma of the lung

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Keywords:
DNA methylation, Pleural fluid, Malignant pleural mesothelioma

Abstract:

Malignant pleural mesothelioma (MPM) is a highly aggressive neoplasm strongly associated with asbestos exposure, primarily arising from the surface serosal cells of the pleura. Patients with MPM often develop pleural fluid as initial presentation. However, cytological diagnosis with pleural fluid is usually difficult and has limited utility. Useful molecular marker for differential diagnosis especially with adenocarcinoma of the lung (AC) is urgently needed. The aim of the present study is to investigate the diagnostic value of DNA methylation profiles in pleural fluid. Pleural fluids were collected and DNA was extracted from 38 patients with MPM, 24 with AC, 14 with tuberculous pleurisy (TB), and 27 with benign asbestos pleurisy (BAP). The methylation status of Ras association domain family 1A (RASSF1A) and p16INK4a was examined with methylation-specific polymerase chain reaction (MSP). The relative level of two methylated genes in each sample was determined as the ratio of MSP-amplified two genes to ß-actin (ACTB), a reference gene. The mean ratios of MSP-amplified RASSF1A to ACTB in MPM, AC, TB, and BAP were -0.94 (range, -2.00 - 2.84), 0.21 (range, -2.00 - 3.14), -1.50 (range, -2.00 – 0.03), and -1.05 (range, -2.0 - 2.79), respectively. The mean ratios of MSP-amplified p16INK4a to ACTB in MPM, AC, TB and BAP were -1.73 (range, -2.00 - 2.67), -0.27 (range, 0 – 4.62), -2.00 (range, -2.00 - -2.00), and -1.62 (range, -2.00 - 3.94), respectively. In RASSF1A/ACTB and p16INK4a/ACTB methylation ratio , we found statistically significant differences between MPM and AC (P=.002; .007, respectively). These results indicate the potential usefulness of methylation analysis of pleural fluid DNA as a tool for differential diagnosis of pulmonary diseases presenting pleural fluids including MPM and AC.

Number: 201

Abstract title:
Mesothelioma Biomarkers in Pleural Effusions

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Keywords:
mesothelioma, biomarkers, pleural effusion

Abstract:

The analysis of hyaluronan in effusions has long been a useful adjunct for the diagnosis of a mesothelioma[1], giving diagnostic values in less than 60% of the cases. More recently mesothelin [2] and osteopontin [3] have both been recommended as mesothelioma biomarkers when analyzing effusions and/or serum.
These analyses were performed on 270 effusion supernatants, including fluids from 35 patients with mesothelioma. Logistic regression analysis clearly demonstrated that hyaluronan and mesothelin were diagnostically useful, while osteopontin had no additional information of diagnostic value. The analysis also provided an interpretation algoritm for the evaluation of the combined hyaluronan-mesothelin analysis to improve diagnostic sensitivity and specificity.
The study is now extended to the testing of further candidate biomarkers. For the upcoming meeting we hope also to present preliminary data regarding the utility of analyzing syndecan-1 and thioredoxin in effusion supernatants

Number: 202

Abstract title:
Refocusing on the hyaluronic acid concentration in the effusion of malignant pleural mesothelioma; a routine screening test for the epithelial type

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Keywords:
hyaruronic acid, epithelial mesothelioma, cytology, pleural effusion

Abstract:

[Purpose]: It is well known that hyaluronic acid (HA) concentration in pleural effusion of malignant pleural mesothelioma (MPM) is higher than in the other disease. But every effusion of MPM may not always have high concentration. The reason of this difference has not been well known. [Method]: The HA concentrations in the pleural effusion at the first thoracentesis of MPM were investigated retrospectively according to the cytology of the same sample and the histological type. HA concentration was measured by sandwich binding protein assay (SBPA), which is a widespread method in Japan to measure the serum HA for diagnosing liver fibrosis of chronic hepatitis patient (serum normal range; up to 50 ng/ml). The effusion HA level was so high that the sample was diluted before measurement. [Result]: There were 34 definite MPM patients fitting above criteria (1991-2006). A total of 22 epithelial and 7 biphasic type had significantly higher mean level of 383.7 mg/l (s.d.=463.3) and 232.7 mg/l (s.d.=257.6) respectively than 5 sarcomatous type, mean level of 27.1 mg/l (s.d.=11.0), $p<0.05$. A total of 16 cytological positive (Papanicolaou's class 5; epithelial 12, biphasic 4) cases had higher mean level of 511.6 mg/l (range 40.1-1600.0, s.d.=469.0) than the other ones, 112.2 mg (range 6.2-960.0, s.d.=218.6) ,which included all of sarcomatous type, $p<0.05$. [Conclusion]: The HA concentration of MPM effusion having epithelial component is higher than the other one. Cytologically positive cases show a tendency to higher effusion HA concentration. If the pleural effusion has high HA concentration and positive cytology, there is a strong probability of MPM, especilly epithelial type. The SBPA method for measuring HA is more convenient and has lower cost performance than the other methods. The routine analysis of the pleural effusion at the first thoracentesis is recommended for early detection of epithelial mesothelioma.

Number: 203

Abstract title:
SERUM MESOTHELIN VARIATIONS IN PATIENTS WITH ADVANCED MALIGNANT PLEURAL MESOTHELIOMA (MPM) TREATED WITH CHEMOTHERAPY: PRELIMINARY RESULTS

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Keywords:
chemotherapy, response, mesothelin

Abstract:

Background: The difficulties in assessing response to therapy in MPM, and the large variations of the prognostic factors, make the potential availability of serum tumor markers very useful. Mesothelin is a cell surface glycoprotein over-expressed in MPM. Aim of this study was to explore the role of serum mesothelin (sM) as predictor of response to chemotherapy (ChT) in patients (pts) with advanced MPM.
Methods: Pts with histologically proven MPM, treated with pemetrexed-based ChT in two different centers, were eligible for this study. sM levels were measured at baseline and after two cycles of ChT, using an ELISA assay (Mesomark). Radiological response was measured by spiral CT-scan according to MPM-modified RECIST criteria. Disease control rate (DC) was defined as complete response (CR) + partial response (PR) + stable disease (SD).
Results: Twenty-eight pts (23 male, 5 female) have been evaluated. Median age was 66 (range 63-78). Histology was epithelial in 26, sarcomatoid in 1, unspecified in 1 pts. Fifteen SD and 7 PR were observed, for an overall DC rate of 79%. Six pts had disease progression. Median baseline sM value was 1.8 nM (range 0.1-34.3); it was 1.79 in pts achieving DC and 1.71 nM in cases with progression (p=ns). Post-chemotherapy sM was available for 25 pts. After chemotherapy, median sM value was 1.53 nM (range 0.10-36.7), and was similar in pts with disease progression and in those achieving DC (1.53 vs 1.47 nM, p=ns). Mesothelin levels dropped in 13/25 pts (52%), with a mean reduction of 44% of baseline value. In particular, sM value was reduced after chemotherapy in 55% of pts achieving DC and in 40% of non-responders (p= 0.6).
Conclusion: The use sM levels in the assessment of treatment efficacy in MPM appears promising. However, no significant correlation with radiological response was observed in this series. Our preliminary observations need to be confirmed in a larger number of pts, with a correlation with survival outcomes.

Number: 204

Abstract title:
SOLUBLE MESOTHELIN-RELATED PROTEIN AND RENAL FAILURE: A CAVEAT

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Keywords:
SMRP, mesothelin, renal failure

Abstract:

BACKGROUND: The low-molecular weight protein (LWMP) soluble mesothelin-related protein (SMRP) (40kDa), as assessed by means of the ELISA-assay MESOMARKTM, has been shown to be increased in the serum of malignant mesothelioma (MM) patients [Robinson, 2003]. Therefore, it might be used as a biomarker for (early) diagnosis of MM in high-risk asbestos-exposed individuals and patients, monitor disease progression and response to treatment. One of the limitations of the assay is its dependency of renal function. The glomerular filtration rate (GFR) can confound the relationship between SMRP and MM, given that LMWPs accumulate in renal failure. GFR also declines with age, and since MM patients have a median age of 65 years, their kidney function can be impaired leading to falsely elevated SMRP levels. We have investigated the impact of renal function on SMRP levels in serum of patients with different grades of renal failure.
METHODS: 18 cancer patients and 2 non-transplant kidney patients, referred for 51Cr-EDTA clearance were included in this study. Renal function was assessed by determination of cystatin C and β–trace levels in sera. With the exception of SMRP, all measurements were performed using commercial reagents (Roche Diagnostics, Dade Behring).
RESULTS: Serum SMRP was found to correlate with renal function markers 51Cr-EDTA clearance (p=0,014), cystatin C (p=0,054) and β–trace protein (p=0,041).
CONCLUSION: The accumulation of serum SMRP in renal failure might cause a caveat for the application of the Mesomark assay as a biomarker for mesothelioma. Updated data will be presented at the meeting
This study was made possible by an unrestricted grant of the ‘Belgian Foundation against Cancer’

Number: 205

Abstract title:
Plasmatic osteopontin in subjects exposed to asbestos fibers and patients with Malignant Mesothelioma (MMe)

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Keywords:
Malignant Mesothelioma; Pasmatic Osteopontin; Early Diagnosis

Abstract:

Serum osteopontin (sOPN) and serum mesothelin (SMRP have been reported as promising markers of increased risk and/or early diagnosis of MMe.
Although the most important data regarding the role of OPN in MMs come out from their dosage in sera samples, the majority of the laboratory kits, commercially available, for osteopontin assay, are suitable for plasmatic dosage only.
We, therefore, measured osteopontin in 93 plasma samples (pOPN; 30 MMe patients, 45 healthy workers previously exposed to asbestos, 5 Benign Pleural Diseases; BPD) to:
a) validate their role in prevention and diagnosis
b) to disclose if any factor, i.e age, tobacco smoking, duration of asbestos exposure, can interfere with dosages of pOPN.
We also measured SMRP in the same samples in order to evaluate any correlation between the two markers in the populationa under investigation.
pOPN levels in both MMe and BPD were significantly higher than in healthy control group ($p<0.0001$, $p=0.048$ respectively), but no statistically significant difference was found between MMe and BPD ($p=0.070$).
The application of a ROC curve for the performance of pOPN resulted in a AUC value of 0.65 with a best cut-off of 995.02 ng/ml, associated with 56.3% of sensitivity and 80.6% of specificity.
A significant positive correlation was observed between age and pOPN ($p=0.002$, Rsquare=0.102), but no correlation was found with either duration of asbestos-exposure or with smoking habit. A positive significant correlation was seen between plasmatic osteopontin and serum mesothelin dosages ($p=0.001$, Rsquare=0.195).
Although based on a small-sized population these preliminary data suggest that pOPN may be useful in clinical and preventive application and further investigations are worth to be performed.

Number: 206

Abstract title:
Differentiate MPM from other causes using tumor markers

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Keywords:
smrp; cea; cyfra 21-1; MPM; NSCLC

Abstract:

Serum markers have been tested in patients with malignant effusions for their ability to differentiate malignant pleural mesothelioma from other causes. We have examined three different serum markers (Soluble Mesothelin Related Protein (SMRP), Cyfra 21.1, and Carcino Embryonic Antigen (CEA)) in a series of patients with different thoracic malignancies and a healthy controls.
This retrospective study consists of 179 patients and 50 healthy controls who visited our hospital. Seventy-four patients had a confirmed mesothelioma, and 106 patients had non small cell lung cancer (NSCLC), 55 had adenocarcinoma.
Cyfra 21.1 was the best single marker discriminating healthy from any malignant disease (AUC) 0.92, 95% confidence interval (CI) 0.89-0.96. By combining all three markers the discriminatory power improved marginally (AUC 0.95, CI 0.93-0.98, p=0.015). The combination of CEA and SMRP was most accurate in differentiating mesothelioma from NSCLC (AUC 0.94, 95%CI 0.90-0.97) and correctly identify 152 of 179 (85%) cases.
Conclusions: By using 2 serum markers (CEA and SMRP) we were able to discriminate mesothelioma from NSCLC with high sensitivity, while Cyfra 21.1 is useful in the discrimination of normal vs. malignancy.
Table : Results of logistic regression models to distinguish malignant pleural mesothelioma from malignant lung disease with the tumor markers as predictor variables

Tumor marker	*OR*	*95%CI*	*p-value*
Univariate analysis:			
Cyfra 21.1 (µg/l)	1.00	0.99-1.02	0.515
SMRP (nmol/l)	1.64	1.26-2.13	<0.001
CEA (µg/l)	0.45	0.33-0.61	<0.001
Multiple analysis:			
SMRP (nmol/l)	2.02	1.27-3.21	0.003
CEA (µg/l)	0.43	0.30-0.62	<0.001

Number: 207

Abstract title:
A pharmacokinetic study of pemetrexed administered intrapleurally in an animal model

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Keywords:
Chemotherapy; Intrapleural administration; Mesothelioma; Pemetrexed, Pharmacokinetics; Toxicity

Abstract:

Background: Pemetrexed is a key drug for the treatment of malignant pleural mesothelioma. The intrapleural administration of pemetrexed might increase its efficacy and decrease its toxicity in comparison with intravenous administration. The aim of this study was to assess in an animal model the pharmacokinetics of pemetrexed administered intrapleurally compared to intravenously.
Methods: Thirty Wistar rats were randomized into four groups according to the route of administration (intravenous or intrapleural) and the dose of pemetrexed (10 or 100 mg/kg). During the experiments, blood samples were harvested using a standardized protocol. Pemetrexed concentrations in plasma were analyzed by high performance liquid chromatography. The studied pharmacokinetics parameters were the maximum plasma concentration (Cmax), the area under the plasma concentration-time curve (AUC), and the total body clearance (CL).
Results: When pemetrexed was delivered at 10 mg/kg, neither the AUC nor the CL significantly differed according to the route of administration, but the Cmax was significantly lower after intrapleural administration than after intravenous administration (14.36 µg/mL versus 29.83 µg/mL; P=0.008). Similar results were found when pemetrexed was delivered at 100 mg/kg (Cmax after intrapleural administration, 70.64 µg/mL; Cmax after intravenous administration, 218.64 µg/mL; P=0.001).
Conclusions: While intravenous and intrapleural administration of pemetrexed yielded similar AUC and CL, the latter achieved significantly lower Cmax. As Cmax is a determinant of pemetrexed toxicity, intrapleural administration might offer a means of widening the effective therapeutic index of the drug by improving tolerability. Future studies are needed to confirm this hypothesis in malignant pleural mesothelioma patients.

Number: 208

Abstract title:
Validation of the biomarkers osteopontin and mesothelin in a multicenter prospective trial – Preliminary results of an ongoing study

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Keywords:
asbestos, exposure assessment, risk modelling, biomarkers

Abstract:

Purpose:
Formerly asbestos exposed workers in the power industry are at risk of developing asbestos related diseases, especially lung cancer and malignant mesothelioma. Recent reports suggest that the biomarkers like osteopontin and mesothelin might contribute to early diagnosis of mesothelioma.

Design:
In an ongoing survey of 8632 formerly or still active employees of a major provider of electrical power in Germany, general medical and occupational history, auscultation of the thorax, lung function testing and a standard chest X-ray is performed. For high risk individuals the surveillance included annual low dose spiral CT (LDSCT) and sputum cytology. Since 10/2005 osteopontin in plasma and mesothelin in serum samples is measured.. Cut off points were defined as 900ng/ml for osteopontin and 1,4 nM/L for mesothelin.

Preliminary results:
In 342 (4%) high risk individuals complete data inclusive LDSCT are available in 06/2008. The median age was 65 years (range 44 to 81 years). Median number of packyears was 26. Median cumulative exposure was 15 fibre-years. In a multiple linear regression model there was a significant association of osteopontin with benign asbestos-related findings in LDSCT (parenchymal p= 0.006; pleural p= 0.001) and age (p<0.0001), while mesothelin did not show significant results with the above mentioned potential confounding factors.
Median concentrations were 350 ng/ml (range 16 to 2204 ng/ml) for osteopontin and 0,589 nM/L (range 0,036 to 4 nM/L) for mesothelin. 11 (4%) resp. 18 (5%) cases exceeded the cut off values for osteopontin resp. mesothelin. So far one person developed malignant mesothelioma while another was already under treatment at the first examination within the study. Both cases had biomarker values below the cut off . In the incident mesothelioma case the blood sample was taken 16 months before diagnosis.

Conclusions:
Our preliminary results in 342 high risk employees suggest that only osteopontin levels in contrary to mesothelin levels are correlating with benign parenchymal and pleural changes in CT-scan. Moreover osteopontin concentrations are age-dependent. Therefore age and/or disease-status dependent cut-off values should be considered for this biomarker, to reduce “false positives” . For the interpretation of mesothelin concentrations the factors considered in our statistical analysis don`t seem to have influence on mesothelin levels.
The predictive values of both biomarkers should not be calculated so far on the basis of two cases. Due to the prospective design of our study it will be possible to describe the value of both biomarkers in the surveillance of asbestos workers .

Number: 209

Abstract title:
Down-regulation of chemokine receptor CXCR3 in peripheral T lymphocytes from patients with asbestos-related disease

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Keywords:
Asbestos, T cell, CXCR3, IFN-γ

Abstract:

[Introduction] As exposure to asbestos causes lung cancer and malignant mesothelioma (MM) after a long incubation period even if only slightly, we assume that an attenuation of antitumor immunity induced by immune cells exposed to asbestos is involved in the development of these diseases. To elucidate the influence of asbestos on the CD4＋ T cells, which activate tumor immunity, we examined the gene expression profile of human adult T cell leukemia virus-immortalized T cell line (MT-2Org) exposed to chrysotile-B of asbestos using DNA microarray method. [Methods] Six asbestos-induced, apoptosis-resistant sublines (MT-2Rst) were established by a long-term exposure (more than 8 months) to a low concentration of chrysotile-B (10 μg/ml). Total RNA from all cell lines were used for the microarray analyses. The clustering, pathway and network analyses were performed using GeneSpring and MetaCore as bioinformatics tools. Peripheral blood CD4＋ T cells from healthy donors were expanded by CD3/CD28 stimulation ex vivo, cultured in the presence of IL-2 and exposured to 50 μg/ml chrysotile-B for four weeks. The expression of chemokine receptor CXCR3 in expanded CD4＋ T cells and CD4＋ T cells from peripheral blood mononuclear cells (PBMC) of asbestos-related pleural plaque or malignant mesothelioma patients were examined by flow cytometry. [Results and Discussions] The DNA microarray analyses revealed an alteration of the expression of 162 genes, 102 genes were up-regulated and 60 genes were down-regulated respectively, was induced by a long-term, low concentration exposure to asbestos. Additionally a clustering analysis showed gene expression profiles of all asbestos-induced apoptosis-resistant sublines (MT-2Rst) to be very similar. Pathway and network analysis suggested that down-regulated chemokine receptor CXCR3 in MT-2Rst is involved in IFN-γ signaling. Furthermore, expanded CD4＋ T cells exposed to chrysotile-B exhibited a declining trend of CXCR3 expression. Finally, the results showed that the CXCR3 expression in CD4＋ T cells from PBMC decreased in patients with asbestos-related pleural plaque or malignant mesothelioma. These findings suggest that a decreased CXCR3 expression caused by a continuous exposure to asbestos may reduce the capacity of IFN-γ production, which may play a role in tumor immunity enhancement.

Number: 210

Abstract title:
Impairment in cytotoxicity and expression of NK-cell activating receptors on human NK cells caused by exposure to asbestos fibers

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Keywords:
tumor immunity, NK cell, cytotoxicity, NK-cell activating receptor

Abstract:

Malignant mesothelioma can result from exposure to asbestos, but the development of this disease requires a long period after exposure to asbestos, suggesting that asbestos might gradually affect anti-tumor immunity. Cytotoxicity of natural killer (NK) cells against tumor cells is controlled by NK-activating receptors such as NKG2D, 2B4 and NKp46, and involves components in cytotoxic granules such as granzyme and perforin. The present study explored the effect of asbestos exposure on NK cells by examining features of YT-A1 human NK cells exposed to chrysotile B (CB) asbestos, NK cells from patients with malignant mesothelioma (MM), and NK cells in PBMCs cultured with CB by flow cytometry. YT-A1 cells were continuously cultured with or without 5 μg/ml of CB, named YT-CB5 and YT-Org, respectively. Both sub-lines showed similar cytotoxicities a month after exposure to CB. However, at around 5 months after exposure to CB, the cytotoxicities of YT-CB5 against K562 cells and anti-2B4 antibody-coated P815 cells decreased compared with YT-Org. Furthermore, YT-CB5 exhibited significant decreases in cell surface NKG2D, 2B4 and intracellular granzyme A. The degradations stimulated with anti-NKG2D and anti-2B4 antibodies also decreased in YT-CB5. PBMCs from patients with MM exhibited decreased cytotoxicity against K562, the percentage of NK cells, and the expression of NKp46, but not NKG2D or 2B4, in NK cells. PBMCs cultured with CB showed a significant decrease in the expression of NKp46 on NK cells. In contrast, glass wool, which is a representative asbestos substitute, did not induce a decreased expression of NKp46. These results indicate that exposure to asbestos has the potential to impair the cytotoxicity of NK cells, and alter the expression of NK-cell activating receptors and perforin/granzymes. NKp46 seems to be particularly remarkable because its low expression was common to both NK cells of patients with MM and NK cells exposed to asbestos. Future studies concerning impairment in expressions of NK-cell activating receptors on NK cells exposed to asbestos will contribute to the prevention of the development of malignant mesothelioma.

Number: 211

Abstract title:
Establishment and characterization of new malignant pleural mesothelioma cell lines from Japanese patients

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Keywords:
array comparative genomic hybridization (CGH) analysis, cell line establishment

Abstract:

Malignant pleural mesothelioma (MPM) is an asbestos-related malignancy that is highly resistant to current therapeutic modalities. In addition to 4 cell lines that we reported in the previous meeting, we established another 8 cell lines (Y-MESO-9, Y-MESO-11B, Y-MESO-12, Y-MESO-14, Y-MESO-21, Y-MESO-22, Y-MESO-25, and Y-MESO-26B) from Japanese MPM patients. Mutation and expression analyses demonstrated that the NF2 tumor suppressor gene, which is known to be one of the most frequently inactivated in MPM, is mutated or deleted in Y-MESO-9, Y-MESO-12, Y-MESO-14, Y-MESO-22, and Y-MESO-26B, and down-regulated in Y-MESO-11B and Y-MESO-21. We detected homozygous deletion of p16INK4A/p14ARF in 11 of 12 cell lines. However, mutations of the TP53 tumor suppressor gene and other oncogenes, including KRAS, NRAS, BRAF, were not found in these 12 cell lines. We also performed array comparative genomic hybridization (CGH) analysis and found novel genomic alteration regions. Our new MPM cell lines are useful as new models for studying various aspects of the biology of human MPM as well as materials for the development of future therapies.

Number: 212

Abstract title:
Genetic alterations specific for malignant mesothelioma cells

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Keywords:
genetic alterations , p16 , malignant mesothelioma (MM)

Abstract:

To elucidate the genetic alterations specific for malignant mesothelioma (MM), we conducted array CGH analysis of 14 human MM cell lines established in our laboratory. Homozygous deletions were detected in various regions of 9q21 of all cell lines. Homozygous or heterozygous deletions were also detected in 22q regions of 12 cell lines. The minimum deletion of 9q21 common to all cell lines was 20 kb, involving the p16 gene, and several breakpoint hotspots were noted. We then analyzed deletion of the p16 gene at a single cell level by FISH method. Homozygous deletions were detected in 70 % of the cell lines used that were di-, tri-, or tetra-ploid. p16 deletions could not be detected in 30 %, which may be due to the large size (350kb) of the p16 probe not suitable for detecting small deletions. Based on these results, p16 deletions in tumor cells obtained from the pleural biopsy and pleural effusion were analyzed by real-time PCR targeting several regions of 9q21. Homozygous and heterozygous deletions of the p16 gene were detected in all samples, indicating that this method is useful for diagnosis of MM, although heterozygous deletions may be ascribed to contamination of normal cells.

Number: 213

Abstract title:
Cell Surface Proteomics reveals new protein markers for the discrimination of malignant pleural mesothelioma from lung adenocarcinoma

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Abstract:
Introduction: The correct diagnosis of malignant pleural mesothelioma (MPM) is still a major problem for clinicians as well as for the pathologists. The histopathological approach is complicated by a broad differential diagnosis and currently, a panel of histopathological marker are needed to discriminate MPM from anatomically related malignancies like lung adenocarcinoma. Therefore, we set out to identify cell surface protein patterns via mass-spectrometry (MS) which would allow for the discrimination of MPM from lung adenocarcinoma at tissue level .
Methods We investigated the cell surface subproteome of one epithelial MPM cell line (ZL55) in comparison to one adenocarcinoma cell line (Ca-Lu3) via the Cell Surface Capturing (CSC) technology. Relative quantification of the identified cell surface proteins was achieved by SILAC (Stable Isotope Labeling by Amino Acids in Cell Culture) labeling. Differentially expressed cell surface proteins were further investigated on the mRNA level by Low Density Microarray RT-PCR on a collection of MPM and adenocarcinoma cell lines. Confirmed classification marker candidates were further validated by IHC stainings on cell lines and frozen-tissue samples from patients affected by late-stage MPM or lung adenocarcinoma. Results : Over 130 bona fide cell surface glycoproteins were identified and quantified via CSC technology, among them 37 CD annotated proteins. 62 cell surface glycoproteins were found to be differentially expressed between the two cell lines at least two-fold. RT-PCR analysis of 29 differentially expressed protein candidates on 15 epithelial MPM and 6 adenocarcinoma cell lines revealed two glycoproteins as potentially good discrimination markers between MPM and adenocarcinoma. These two classification marker candidates were further investigated in antibody-based IHC experiments on patient samples. A commercially available antibody against one out of the two target cell surface glycoproteins discriminated MPM from adenocarcinoma in clinical relevant IHC stainings on biopsies from selected patients. Conclusion : By using cell surface capturing technology in a quantitative proteomics approach we were able to identify cell surface glycoproteins which are differentially expressed between mesothelioma and adenocarcinoma cells. Initial validation of two selected proteins on patient samples indicate their potential for aiding in the correct classification of MPM in contrast to adenocarcinoma.

Number: 214

Abstract title:
Selenite-induced apoptosis signalling in differentially sensitive mesothelioma cell lines

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Keywords:
malignant mesothelioma, selenite, apoptosis

Abstract:

Malignant mesothelioma cells may differentiate into an epithelioid or a sarcomatoid phenotype. The latter is usually more resistant to chemotherapy, and we have previously found that selenite is selectively toxic to sarcomatoid cells. Selenite is known to induce oxidative stress and apoptosis. In this paper we investigate which pathways of apoptosis signalling are activated by selenite. Treatment with selenite caused loss of mitochondrial membrane potential. Annexin-PI analysis was used together with JC-1 to examine the effect of inhibition of signalling enzymes. Chemical inhibition experiments showed that JNK had an anti-apoptotic role, while p38 had some mediatory effect in sarcomatoid but not in epithelioid cells. Inhibition of p53 made no difference. Selenite induced nuclear translocation of p53. However, less p53 was found in its active DNA-binding form after selenite treatment. Levels of thioredoxin decreased considerably in sarcomatoid cells after selenite treatment, indicating that p53 may be inactivated. Cathepsin B but not D and E showed proapoptotic activity that could be abrogated by chemical inhibition, although this did not increase the viability of the cells. Activation of caspase-3 was limited. As an alternative, we searched for autophagic vesicles, but found none. Bax was upregulated only in sarcomatoid cells and Bcl-XL was downregulated particularly in epithelioid cells. These phenotypic differences may partially explain the differing sensitivity of mesothelioma cells to selenite.

Number: 215

Abstract title:
Aberrant splicing and proteases involvement in mesothelin release from epithelioid mesothelioma cells.

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Keywords:
Mesothelioma - Soluble Mesothelin - Metalloproteases - Diagnosis

Abstract:

Elevated amounts of soluble mesothelin-related proteins (SMRP) have already been reported in sera or pleural effusions from mesothelioma patients, providing a useful diagnostic marker for malignant pleural mesothelioma (MPM). However, the origin of SMRP is not yet understood. Production of SMRP could be related to an abnormal splicing event leading to synthesis of a secreted protein (release) or to an enzymatic cleavage from membrane-bound mesothelin (ectodomain shedding). To test these hypotheses, we used a panel of mesothelioma cells established in culture from pleural effusions of MPM patients. Our in vitro results confirmed specific mesothelin expression and SMRP production in supernatants from epithelioid MPM cell lines, thus providing a relevant cellular model to study soluble mesothelin production mechanisms. Expression of mesothelin-encoding RNA variants was screened by RT-PCR experiments. Proteases involvement in mesothelin cleavage from cellular surface was investigated by treatment of MPM cells with GM6001, a broad-spectrum MMPs- and ADAMs- families inhibitor. GM6001 treatment significantly impaired SMRP production by MPM cell lines, in favour of an enzymatic-mediated shedding process. In addition, a splice variant transcript of mesothelin (variant 3) was detected in these MPM cell lines, in accordance with the release of a secreted part of the protein. So, our results indicate that both mechanisms could be implicated in soluble mesothelin production by epithelioid mesothelioma cells.

Number: 216

Abstract title:
D2-40 Utility for Differential Diagnosis between Pleural Sarcomatoid Mesothelioma and Lung Sarcomatoid Carcinoma

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Keywords:
D2-40, Immnohistochemistry, Sacrcomatoid mesothelioma, Sarcomatoid carcinoma

Abstract:

[OBJECTIVES]
The differential diagnosis of pleural sarcomatoid mesothelioma (SM) from lung sarcomatoid carcinoma (LSC) invading parietal pleura and chest wall is challenging issue. The purpose of this study is to elucidate the useful antibodies for differential diagnosis.
[MATERIALS & METHODS]
Forty-five pleural SMs and 27 LSCs were immunohistochemically analyzed using 15 commercially available antibodies, including D2-40, calretinin, thrombomodulin, WT1, CEA, Napsin A, TTF-1, pancytokeratin, CAM5.2, EMA, Ber-EP4, MOC-31, α-smooth muscle actin, h-caldesmon and desmin.
[RESULTS]
Only D2-40 positivity (86.7%) among pleural SM was significantly higher than that of LSC (25.9%). The proportion of staining grade of D2-40 in pleural SM were also higher than that of LSC. The positivity of “adenocarcinoma markers”, including CEA, Napsin A and TTF-1 was low. even in LSC.
[CONCLUSION]
These results indicated that evaluation of positive rate and positive degree of well-known mesothelial marker, “D2-40”, was applicable to differentiate pleural SM from sarcomatoid component of LSC along with clinical and radiological information.

Number: 217

Abstract title:
Analysis of EGFR, PDGFRA, PDGFRB and related pathways in malignant peritoneal mesotheliomas.

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Keywords:
EGFR; PDGFRA; PDGFRB; PI3KCA

Abstract:

Purpose. Little is known about receptor tyrosine kinase (RTK) activation in malignant peritoneal mesotheliomas (MPM), thus we performed EGFR, PDGFRA and PDGFRB analysis to ascertain if deregulation of RTK could offer useful alternative therapeutic targets in this tumor.
Experimental design. EGFR, PDGFRA and PDGFRB expression and phosphorylation were immunohistochemically and biochemically analysed in 15 MPM whose formalin-fixed paraffin–embedded and surgical frozen material was available. The tyrosine kinase domain (exons 18-21) of the EGFR gene were automatically sequenced, as well as the extracellular (exon 10) and juxtamembrane regions (exon 12) and the tyrosine kinase domain (exons 14 and 18) of PDGFRA and PDGFRB. The cognate ligand expression was investigated by real time PCR. Additionally, we explored the status of RTK downstream pathways through mutational and biochemical analysis of PI3KCA gene (exons 9 and 20)/PTEN/AKT, and ERK, along with mTOR and its effector S6.
Results. Immunohistochemical and immunoprecipitation/western blot analyses showed EGFR, PDGFRA and PDGFRB expression and activation in the most of the cases. In particular EGFR and PDGFRA resulted more frequently phosphorylated than PDGFRB. Autocrine loop activation of these receptors was suggested in all the cases by the expression of the related cognate ligands TGF-α, PDGFA and PDGFB, in absence of receptor gain of function mutations. No PI3KCA mutations were found, while all the MPMs showed expression of PTEN and expression/activation of AKT, ERK, as well as of mTOR and S6.
Conclusions. EGFR, PDGFRA and PDGFRB seem to be promising molecular targets for tailored treatments in MPM. Furthermore, the strong activation of the downstream signalling points out a role of mTOR inhibitors or analogous in MPM treatment.

Number: 218

Abstract title:
NOVEL SYNTHETIC INHIBITORS OF THE mTOR PATHWAY IN MALIGNANT MESOTHELIOMA

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Keywords:
malignant mesothelioma, mTOR, kinase activity, p70s6k, 4ebp1

Abstract:

Malignant Mesothelioma is an aggressive cancer with poor prognosis and low median survival, refractory to current therapies. Mammalian target of rapamycin (mTOR) promotes uncontrolled proliferation, through cell cycle progression, regulation of protein synthesis and protein degradation, playing a critical role in tumor cell survival and resistance to chemotherapy. The mTOR pathway becomes activated in most human tumors, including malignant mesothelioma. Rapamycin and its derivatives are known as mTOR inhibitors, however we aimed at testing novel small molecules, synthetized by the split-Ugi multi-component reaction, as selective inhibitors of this enzyme activity, to develop effective strategies for the treatment of this neoplasm. We evaluated cytotoxicity of the synthesized compounds on three mesothelioma cell lines: MPP-89, MSTO-211H and REN. After preliminary screenings we observed a marked decrease of cell viability in all three cell lines for two out of ten compounds, which displayed IC50 values about of 15 μM. Moreover, they inhibited the autophosphorylation of mTOR on Ser2481 as well as the phosphorylation of two mTOR downstream effectors 70-kDa ribosomal protein S6 kinase 1 (p70S6K) and the eukaryotic translation initiation factor 4E (eIF4E)-binding protein 1 (4EBP1). Conversely, no inhibition on Akt (Ser473) and mTOR (Ser2448) phosphorylation was observed.
Interestingly, the inhibition of mTOR kinase activity of both p70S6K and 4EBP1 was observed in MPP-89 cells, while in MSTO-211H cells was inhibited only the phosphorylation of p70S6K, which was slightly affected in REN cells. These preliminary data highlight these compounds as new inhibitors of the mTOR pathway, exerting cytotoxic effects on all mesothelioma cells examined and suggest selective effects, dependent on the different cell phenotypes.

Number: 219

Abstract title:
Our Surgical Techniques of Extrapleural Pneumonectomy for Diffuse Malignant Pleural Mesothelioma

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Keywords:
extrapleural pneumonectomy, malignant pleural mesothelioma, mesothelioma, surgery

Abstract:

Background: Multimodality therapy which includes surgery, radiotherapy and chemotherapy is needed to treat early stage diffuse malignant pleural mesothelioma. Many expert surgical techniques are required for excellent extrapleural pneumonectomy to keep patient condition good enough for radiotherapy and chemotherapy. Our surgical techniques of extrapleural pneumonectomy for diffuse malignant pleural mesothelioma are presented.
Surgical techniques: 1. A nasogastric tube is placed to confirm the esophagus and to prevent aspiration pneumonia. 2. Extended posterolateral incision along the 6th rib is made, and old incision site for the pleural biopsy is removed. The 6th rib is resected, and the extrapleural dissection is started. 3. Blood loss is reduced by hypotensive anesthesia and diluted epinephrine. Systolic blood pressure is kept around 90 mmHg. Towels which are soaked in 500 ml saline with 0.5 ml of epinephrine are packed in the dissected extrapleural space. 4. The costal arch is divided to create wider exposure. 5. The diaphragm incision is initiated at its anterior margin. The peritoneum is preserved when dissecting the diaphragm. 6. The pericardium incision is started at the apex cordis. 7. The pulmonary veins and artery are divided intrapericardially by staplers. 8. The main bronchus is divided by a stapler. 9. The mediastinal lymph nodes are resected. 10. The thoracic duct is ligated at the level of diaphragm in the right side case. 11. Dual mesh biomaterial (20 cm x 30 cm x 1 mm, W. L. Gore & Associates, Inc., AZ, USA) for the diaphragm reconstruction and preclude pericardial membrane (15 cm x 20 cm x 0.1 mm, W. L. Gore & Associates, Inc., AZ, USA) are soaked in antibiotics solution. 12. When the diaphragm is reconstructed, multiple sutures are tied outside the intercostal space. Some of them should be stitched around the 9th or 10th rib. 13. The pericardium is reconstructed to prevent cardiac herniation. 14. A chest tube is placed through the posterolateral incision.
Conclusion: Our surgical techniques of extrapleural pneumonectomy for diffuse malignant pleural mesothelioma are presented. Many expert techniques are required to perform excellent extrapleural pneumonectomy to keep patient condition good enough for radiotherapy and chemotherapy.

Number: 220

Abstract title:
Early detection of malignant pleural mesothelioma

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Keywords:
mesothelioma, pathology, early diagnosis, extrapleural pneumonectomy, thoracosopy, immunohistochemistry

Abstract:

Background. Pleural effusion is the only roentgenographical abnormal finding in patients with early stage malignant pleural mesothelioma (MPM), in which no nodules were detected roentgenographically. Computed tomography shows pleural effusion with slight pleural thickening. Histopathological finding of pleural biopsy with thoracoscope is thereby crucial for the diagnosis of mesothelioma. However, pathological diagnosis of mesothelioma with small biopsies is often difficult, because specific immunohistochemical test or other markers that discriminate between hyperplastic and neoplastic mesothelium are currently unavailable. Although a papillary architecture and necrosis of mesothelial cells favors mesothelioma in the pleura, invasion is the most decisive indicator of mesothelioma. The aim of this study was to elucidate the clinical data and the pathological findings on thoracoscopic biopsies of early stage MPM. Design. We investigated eight extrapleural pneumonectomy (EPP) cases of MPM without grossly visible tumor. We evaluated the clinical data and the pathological findings of thoracoscopic biopsies performed before EPP. Results. Levels of hyaluronic acid were extremely high (>90,000 ng/ml) in five cases and moderately high (>40,000 ng/ml) in one case. Cytological examination of pleural effusion revealed malignant cells in six cases and suspicious of malignancy in two cases. Multiple small maculas or nodules with diameter less than a few millimeters were observed on thoracosopy in some cases. However, there was no abnormal finding in two cases. Invasion into fat tissue was observed in three cases, papillary structure was observed in two cases, and expansile stromal nodules were observed in one case in thoracoscopic biopsies. Mesothelioma cells proliferated both on the parietal and visceral pleurae and invaded them in EPP specimens. They proliferated in solitary, trabecular, papillary, or solid patterns in epithelioid mesothelioma, and in patternless pattern in sarcomatoid mesothelioma. The lesions were discontinuous and multifocal. Conclusions. Pathological findings of stromal invasion were observed in less than half of the cases. Papillary proliferation and expansile stromal nodules are important pathological findings for the diagnosis of early stage MPM. Clinical data, such as levels of hyaluronic acid, cytological examination, and thoracoscopic findings, are helpful in diagnosing MPM in which thoracoscopic biopsies lack the findings of stromal invasion.

Number: 221

Abstract title:
Results of surgical treatment as part of multimodality treatment for malignant pleural mesothelioma.

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Keywords:
surgery, multimodality, radiotherapy, chemotherapy, early stage

Abstract:

Background. A minority of patients with malignant pleural mesothelioma are candidates for surgical treatment. It is virtually impossible to achieve a microscopically radical resection. Therefore, surgical therapy has been combined with other treatment modalities. The most effective combination is unknown. The objective of this study was to evaluate the results of surgical therapy as part of three different therapeutic regimens in our institute.
Patients. These groups form consecutive series of patients in good condition (WHO 0-1, no weight loss > 10%) with low-volume MPM (stage I-II, no hemithoracic retraction, epitheloid or mixed-type). Between January 1999 and December 2001, 20 patients underwent a combination of cytoreductive surgery - pleurectomy (12) or extrapleural pneumonectomy (EPP) (8) - and intraoperative hyperthermic intrathoracic chemotherapy (HITHOC), followed by radiotherapy to the thoracotomy scar and drainage tracts (24 Gy). Between January 2002 and September 2005, 15 MPM patients were treated with EPP and postoperative hemithoracic radiation (54 Gy). Between September 2005 and October 2007, 17 MPM patients were treated with induction chemotherapy (PC = pemetrexed, cisplatin), followed by EPP and postoperative hemithoracic radiation (54 Gy). Median duration of postoperative follow-up was 14 (8-80) months for HITHOC-patients, 30 (8-71) months for EPP+RT-patients, and 14 (5-32) months for PC+EPP+RT-patients.
Results. The three groups were comparable regarding age, sex, performance status, pulmonary function, and tumor histology. Median duration of hospital stay was 15 vs 14 vs 10 days (p=0.02), median ICU stay was 4 vs 2 vs 1 day (p=0.01). All but one HITHOC patient received radiotherapy according to protocol. Hemithoracic radiotherapy was delivered as planned in 12 of 15 EPP+RT patients. Four patients in the PC+EPP+RT group did not undergo surgical resection due to progression or embolic complications during induction chemotherapy. Hemithoracic radiotherapy was delivered as planned in 9 of 13 operated PC+EPP+RT patients Median recurrence-free survival was 11 months for HITHOC-patients, 23 months for EPP+RT-patients and 16 months for PC+EPP+RT-patients (0.09). The median time to local tumor recurrence was 12 vs 39 vs 19 months (p=0.008). Follow –up is too short for evaluation of overall survival.
Conclusions. The use of cytoreductive surgery with intraoperative chemoperfusion in the management of MPM is not supported. Local oncologic results of extrapleural pneumonectomy with adjuvant hemithoracic radiotherapy are encouraging. In our hands, induction PC chemotherapy is not associated with improved (locoregional) disease control.

Number: 222

Abstract title:
TARGETING OF SIGNALING PATHWAYS THAT ARE FREQUENTLY IMPLICATED IN MALIGNANT MESOTHELIOMA

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Keywords:
Mesothelioma, AKT, ERK

Abstract:

Malignant mesothelioma (MM) is highly resistant to conventional therapies. Activated kinases that are part of growth factor stimulated signaling pathways, such as PI3K/AKT/mTOR and Raf/MEK/ERK, are likely to contribute to a high rate of tumor growth, progression and resistance to treatment. Our hypothesis is that the effectiveness of MM therapy may be improved through anticancer agents that target multiple proteins in key signaling pathways to increase cell death. We are focusing on drugs that have been reported to block the enzymatic activity of AKT or ERK. We used a PDK1/AKT/Flt dual pathway inhibitor designated KP372-1, a known experimental inhibitor of MEK kinase named U0126 and a pharmaceutical currently in clinical trials called Sorafenib (Nexavar; Bayer Pharmaceuticals) that targets several kinases involved in tumor proliferation and progression including Raf, VEGFR, and other growth factor receptors. Analysis of phosphorylated proteins downstream in the respective pathways showed that Sorafenib was effective at inhibiting ERK activity in our panel of human MM cell lines, whereas KP372-1 did not induce the predicted effects. Sorafenib also inhibited the survival of human MM cells in MTT assays. Moreover, FACS analysis and DNA fragmentation assays showed that Sorafenib induced MM cell death. Testing of Sorafenib in mouse models of MM showed promise, delaying MM tumor progression. Studies are now underway with another mouse model that develops asbestos-induced MMs to determine if Sorafenib is efficacious in this preclinical model. Overall, insights derived from these studies are expected to provide important clues for the design of a therapeutic strategy targeting specific signal transduction pathways in MM.

Number: 223

Abstract title:
A Phase III, Randomized, Double-Blind, Placebo-Controlled Trial of Vorinostat in Patients with Advanced Malignant Pleural Mesothelioma (MPM) Previously Treated with Systemic Chemotherapy

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Keywords:
Vorinostat, HDAC inhibitor, advanced mesothelioma

Abstract:

Background: Malignant pleural mesothelioma (MPM) is an uncommon cancer associated with asbestos exposure that has a generally poor prognosis. Current treatments have a limited effect on survival. The standard first-line chemotherapy regimen is pemetrexed and cisplatin which improved median survival over treatment with cisplatin alone from 9 to 12 months. No standard second-line therapy exists and the benefits of chemotherapy for patients with progression after treatment with pemetrexed/cisplatin are unknown. In a prior Phase I trial of the oral histone deacetylase (HDAC) inhibitor, vorinostat, responses and disease stabilization were observed in several patients with previously-treated MPM, prompting further study.
Methods: This Phase III, randomized, double-blind, placebo-controlled, multicenter study aims to assess whether treatment with vorinostat improves survival for patients with advanced MPM and progressive disease after prior chemotherapy. Eligibility criteria include: pathologically confirmed diagnosis of epithelial, sarcomatoid, or mixed histology MPM, which has progressed or relapsed following treatment with pemetrexed and either cisplatin or carboplatin; no more than 2 prior systemic therapies (pemetrexed must have been part of the most recent regimen); measurable disease; and Karnofsky performance scale status ;70%. Patients are randomized 1:1 to receive vorinostat plus best supportive care (BSC) or placebo plus BSC. Patients are treated with 300 mg oral vorinostat twice daily for 3 consecutive days every 7 days, repeated weekly in a 21-day cycle. The primary objectives are to compare the overall survival of patients treated with vorinostat plus BSC to that achieved in patients treated with placebo plus BSC, and to assess the safety and tolerability of vorinostat. Secondary objectives include comparison of overall objective response rate; progression-free survival; dyspnea score; and percent change in forced vital capacity.
Results: Patient accrual is underway and approximately 660 patients will be enrolled to achieve 540 events for the survival analysis. The trial has passed the second interim analysis and current recruitment status will be presented.
Discussion: This is the largest trial ever conducted in patients with previously-treated MPM. If successful, vorinostat would fill an unmet need for this group of patients.

Number: 224

Abstract title:
COMBINED MODALITY TREATMENT FOR MALIGNANT PLEURAL MESOTHELIOMA (MPM)

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Keywords:
combined modality, extrapleural pneumonectomy, pemetrexed,

Abstract:

Purpose:
Guidelines for the treatment of MPM do not advocate either radiotherapy or surgery only. Since newer and more active chemotherapy became available for MPM, combined modality treatment for MPM by including neoadjuvant or adjuvant chemotherapy and postoperative radiotherapy, has been studied more frequently. We also started a feasibility study of combined modality treatment (CMT) for MPM patients, combining neoadjuvant chemotherapy, surgery and postoperative radiotherapy.
Patients and methods:
All consecutive MPM patients, selected for CMT between March 2003 and December 2007 were included. Treatment consisted of induction chemotherapy (IC) with cisplatin-pemetrexed (3 cycles, q 3 wks), extended pleuropneumonectomy (EPP), and radiotherapy (mostly by IMRT, intensity-modulated radiotherapy; 54Gy/1.8Gy). Inclusion criteria were: age < 65 years, WHO Performance Status ≤1, medically fit for pneumonectomy, staging of cT2N2M0 or less (epithelial subtypes) and cT2N1M0 or less (other histologic subtypes).
Results:
A total of 39 MPM patients were selected for CMT. Histologic subtypes were: epithelial (n=28); desmoplastic (n=2); sarcomatous (n=1); mixed (n=8). Five patients were either progressive after IC or estimated irresectable. Twenty-six patients underwent EPP (20 with R0 resection; 6 with R1 resection) while 7 patients had an exploratory thoracotomy (irresectable MPM due to chest wall or oesophageal invasion) and 1 patient refused surgery. Post-surgical complications included: postoperative mortality (n=3 or 11%), re-thoracotomy for bleeding (n=1), atrial fibrillation (n=8), ARDS (n=2), DVT (n=1) and empyema (n = 1). Because 1 patient was estimated ineligible for irradiation (unique kidney) and another developed bone metastases, 21 patients started postoperative radiotherapy. One patient didn't complete radiotherapy and another died after ending radiotherapy (BOOP). At the end, 20/39 patients completed CMT. Median survival (after MPM diagnosis) for all 39 patients who started CMT and for the 20 patients who completed CMT, was 24.7 months and 31.2 months, respectively.
Conclusions:
This study demonstrated that CMT with neoadjuvant chemotherapy, EPP and postoperative radiotherapy is feasible in our centre but for selected MPM patients only. The median survival for those patients who completed CMT is promising, but validation of these results in future randomized controlled trials will be of interest.

Number: 225

Abstract title:
The Insulin-Like Growth Factor (IGF-1) Pathway Influences Proliferation of Stem Cells Derived from Human Malignant Mesothelioma Cell Lines.

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Keywords:
Insulin-like growth factor; cancer stem cells; malignant mesothelioma

Abstract:

Stem cells exhibit extensive self-renewal capacity and the ability to differentiate into a wide variety of cell types. The potential role of stem cells in neoplasia has been a longstanding research topic, but in the last few years, a growing body of evidence supports the postulate that tumors are organized in a hierarchy of heterogeneous cell populations with different biologic properties and that the capacity to sustain tumor formation and growth resides exclusively in a small proportion of cells called cancer stem cells (CSCs). The CSC is defined as having the ability to self-renew, giving rise to another malignant stem cell as well as cells that develops into cancer cells with diverse phenotypes and genotypes. Human malignant mesothelioma (HMM) is an invariably lethal tumor of the pleura or peritoneum caused primarily by exposure to asbestos fibers. HMM remains weakly responsive to standard modalities of therapy. The insulin-like growth factor (IGF) signaling pathway is important in the regulation of cell proliferation, survival and apoptosis. The biological activities of IGF1 are mediated through the IGF1 Receptor. It has been shown that the IGF1 pathway and related genes are dysregulated in HMM and the blocking of this pathway suppresses mesothelioma cell growth in vitro and in vivo. Here we have used Hoechst 33342 staining to identify CSCs by flow cytometry at two emission wavelengths (red and blue). Low fluorescent cells appeared as a “side population” (SP) well separated from the non-side population (NSP) of high fluorescent cells. Stem cells were predominantly found in the SP fraction and were separated from three HMM cell lines. A breast cancer line was included as a positive control. “Stemness” genes such as NOTCH-1 and POU5F-1 were expressed 3-5 fold in SP cells over NSP cells. Treatment of the HMM cells with several specific kinase inhibitors blocked the IGF1R-pathway and showed dose-dependent reduction of cells in the SP fraction, while Cisplatin treatment increased the percentage of SP cells. We propose that further studies on the biology of CSCs in the SPs of HMM cells could provide new information on the response of these cells to potential therapeutic approaches.

Number: 226

Abstract title:
Severe complication after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy is a marker of poor prognosis in diffuse malignant peritoneal mesothelioma

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Keywords:
peritoneal mesothelioma, prognostic factors, local regional therapy

Abstract:

Background: The cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS+HIPEC) is actually considered the treatment of choice for diffuse malignant peritoneal mesothelioma (DMPM). Patient selection for the procedure should pursue not only maximum benefit in terms of survival and quality of life but also the identification of low risk groups for major morbidity. We assessed the correlation between procedure related morbidity and risk of disease progression, 2 adverse events that are usually taken as independent phenomena in the decision making for procedure indication.
Methods: Sixty three DMPM patients (27M/36F) submitted to CRS+HIPEC with a curative intent. We considered 2 main dependent variables surgical morbidity G3-5 and systemic toxicity G3-5 after the procedure. The adverse events were graded according to NCI CTCAE v3 criteria. We assessed the correlation of these variables with overall and progression free survivals (OS/PFS). We also tested the prognostic significance of the followings: previous surgical score, age, sex, carcinomatosis extension, completeness of cytoreduction (CC). The survival was calculated from the 14th postoperative day until the date of death or of the last contact. The median follow-up was 22.2 months (range: 1-118).
RESULTS: The postoperative surgical morbidity G3-5 and systemic toxicity G3-5 rates were 32% and 33%, respectively. Median OS and PFS were 39 months and 22 months, respectively. After multivariate analysis CC and surgical morbidity G3-5 were proven to be independently correlated with a shorter OS. Accordingly age, surgical morbidity G3-5 were significantly and independently correlated with a shorter PFS.
CONCLUSIONS: The indication of the procedure in high risk group for severe morbidity should be carefully tailored as outcome benefit is unlikely to be obtained in such circumstance. From a another point of view, this data could mean that once the DMPM patient is treated, the emergence of a serious morbidity could be a sign of a worse prognosis. The underlining mechanisms responsible for the correlation between the treatment morbidity and poor outcome is unknown.

Number: 227

Abstract title:
Simian virus-40 as a prognostic factor in malignant pleural mesothelioma

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Keywords:
SV40, Mesothelioma, Prognostic factors, Biological markers

Abstract:

Background: Malignant Mesothelioma is a highly aggressive neoplasm. In the past 50 years, the incidence of malignant pleural mesothelioma (MPM) has been increasing especially in developing countries, along with industrial development. The association between simian virus (SV40) and malignant pleural mesothelioma (MPM) suggests an etiological role for SV40. However, exact pathogenic mechanisms and possible prognostic value are not clear.
Methods: Fresh tumor tissues were obtained from 40 MPM Egyptian patients. All cases diagnosed as MPM were positive for mesothelioma markers (calretinine, mesothelioma antigen, keratin 5/6) and negative for epithelial membrane antigen and/or cytokeratin and/or CEA. Sarcomatoid cases were diagnosed by being positive for mesothelioma antigen and negative for vimentin. The samples were also investigated for the presence of SV40 DNA, altered Rb expression and p53 gene status using immunohistochemistry and molecular techniques. The relation between SV40, asbestos exposure, Rb, p53 and their contribution to clinicopathologic characteristics and overall survival (OS) were assessed.
Results: The age ranged from 20 to 69 years (mean= 45), 21 were males and 19 were females. SV40 DNA was detected in 20/40 cases and asbestos exposure in 31 cases; 18 of them were SV40 positive. Altered p53 and Rb expression were detected in 57.5% and 52.5% respectively with no p53 mutation. There was a statistically significant correlation between the presence of SV40 viral sequences and the pathological type of the tumor since 13 out of the 20 SV40 positive cases (65%) were of the sarcomatoid/mixed variants compared to 7 (35%) of the epithelioid variant (p.= 0.03). Similarly, there was a statistically significant correlation between the presence of SV40 viral sequences and a positive history of asbestos exposure (p. = 0.03). Multivariate analysis showed that when SV40 and asbestos exposure were considered together, only combined positivity of both is an independent prognostic factor affecting the OS (p = 0.001).
Conclusion: SV40 and asbestos exposure are common in Egyptian MPM denoting a possible etiological role and a synergistic effect for both agents. Our results prove that combined positivity for SV40 and asbestos exposure is an independent prognostic factor in MPM having a detrimental effect on OS.

Number: 228

Abstract title:
CT-determined tumor volume predicts survival in epithelial MPM following extrapleural pneumonectomy

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Abstract:

Pass et al (J Thorac Cardiovasc Surg 1998;115:310-318) reported an association of tumor volume with survival in surgically treated malignant pleural mesothelioma (MPM) patients with varying histology and extent of resection. Given the clinical importance of preoperative factors predictive of outcome, we sought to replicate this analysis using updated volumetric measurement techniques. To minimize competing influences on outcome we studied a homogeneous cohort of patients with epithelial MPM treated with extrapleural pneumonectomy (EPP).

DICOM files of CT images of the hemithorax were analyzed using a semiautomatic image-processing threshold technique to isolate the tumor from other tissues and structures (ImageJ Ver.1.39; http://rsb.info.nih.gov/ij/). Every third CT slice was visually segmented with area selection tools. Pixels between 5 to 150 HU within segmented areas were summed by the software and multiplied by 15 for conventional CT (slice interval 5 mm) or by 11.16 for PET-CT (slice interval 3.72). Tumor volume estimates were obtained by integration across slices. Apical disease was evaluated visually and scored as present or absent.
Eighty-three patients with epithelial tumors who underwent EPP and for whom DICOM images were available were evaluated. Among these, 58 were male and median age was 59 yrs. Median tumor volume was 423 cc (range 1-4236 cc). Thirty-eight patients with tumor volume <500cc experienced significantly longer survival duration than 45 patients with > 500cc tumor volume (37 versus 17 months; p<.0001). Forty patients with radiographic evidence of tumor in the apex of the chest had significantly shorter survival than 42 patients without (19 versus 27 months; p = .0147).
We conclude that preoperative radiographic estimation of tumor volume should be included in prognostic evaluation of patients being considered for primary surgery for epithelial MPM. If volumetric analysis is unavailable, evidence of apical disease involvement may be a reasonable surrogate.

Number: 229

Abstract title:
MicroRNA microarray analysis of malignant mesothelioma

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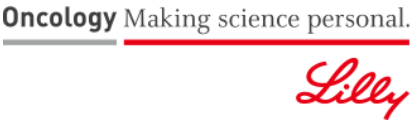
Keywords:
miRNA, microarray, Malingnant Mesothelioma

Abstract:

MicroRNA Microarray Analysis of Malignant Mesothelioma
Background. MicroRNAs have generated strong interest in the field of cancer research as a consequence of recent findings about their function. They have been shown to regulate gene expression at the level of mRNA. These small and noncoding RNAs can affect the stability of the mRNAs and can also initiate and /or inhibit the process of translation into proteins. More than 1000 miRNAs are known today with the rapidly increasing number . MiRNA has a variety of functions starting from cell death regulation to antiviral defenses in all living organisms. It is mainly involved in post-transcriptional gene regulation whereby it binds to the complementary sequence of the target mRNA. It has been speculated that miRNAs could regulate ~30% of the human genome. MiRNAs have been found to be responsible for the fine regulation of gene expression and adjusting cellular phenotype during vital processes, such as development and differentiation.
MiRNA are found to be conserved throughout the mammalian genome which further reaffirms their involvement in essential processes. Therefore miRNA gene mutations (inherited, somatic mutations, amplifications, deletions, epigenetic silencing) are likely to cause certain cancers while increasing susceptibility to others. Furthermore, significant amount miRNAs are shown to be in cancer associated genomic regions.
Aim. Little is known about the expression of miRNAs in malignant mesotheliomas. The aim of this study is to gain more insight into the possible role and function of these novel regulators of gene expression in this particular cancer.
It is becoming more evident that miRNAs play an essential role in the regulation of pathways that are involved in tumorigenesis of various tumors. It is therefore essential to combine potential miRNA data from this study with existing genomic and expression profiles of MM. Analysis of integrated data can further assist in understanding the fundamental mechanisms in the development and the progression of MM.
Materials and Methods. Fresh frozen samples from 23 MM patients were used in this study. Before extracting RNA, tumor content of each sample was determined. Total RNA was extracted using Agilent's miRNeasy mini kit and microarray experiments were performed using Agilent's miRNA microarray system.
Final results of the study will be presented at the conference.

ACKNOWLEDGEMENTS SPONSORS

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VERKORTE PRODUCTINFORMATIE HYCAMTIN®

Samenstelling: Hycamtin capsules bevatten 0,25 mg en 1,0 mg topotecanhydrochloride. Hycamtin poeder voor concentraat voor oplossing voor intraveneuze infusie bevat per injectieflacon 4 mg topotecanhydrochloride. **Indicatie:** Topotecan capsules en topotecan infusie worden toegepast bij de behandeling van: patiënten met recidiverend kleincellige longkanker (SCLC) voor wie opnieuw behandelen met een eerstelijnstherapie niet geschikt wordt geacht. Topotecan infusie wordt als monotherapie toegepast bij de behandeling van: patiënten met een gemetastaseerd ovariumcarcinoom als eerstelijnstherapie of daaropvolgende behandelingen niet aanslaan. Topotecan infusie in combinatie met cisplatine is geïndiceerd voor de behandeling van patiënten met cervixcarcinoom recidiverend na radiotherapie en voor patiënten met stadium IVB van de ziekte. Voor patiënten die eerder behandeld zijn met cisplatine is een ononderbroken behandelingsvrije periode vereist om de behandeling met de combinatie te rechtvaar-digen. **Dosering:** Kleincellig longcarcinoom: *Topotecan capsules, begindosis: Op dag 1-5 in een kuur van 21 dagen 2,3 mg/m2/dag; topotecan infusie,begindosis: Op dag 1-5 in een kuur van 21 dagen 1,5 mg/m2/dag* via intraveneuze infusie gedurende 30 minuten. Ovariumcarcinoom: Topotecan infusie, *begindosis: Op dag 1-5 in een kuur van 21 dagen* 1,5 mg/m2/dag via intraveneuze infusie gedurende 30 minuten. *Vervolgdoses:* Topotecan mag alleen opnieuw worden toegepast als de concentraties van neutrofielen ≥ 1 x 109/l, trombocyten ≥ 100 x 109/l en van hemoglobine ≥ 9 g/dl (eventueel na transfusie) bedragen. Neutropenie: Patiënten met ernstige neutropenie (< 0,5 x 109/l) gedurende 7 dagen of langer, of met ernstige neutropenie die gepaard gaat met koorts of infectie, of patiënten bij wie de behandeling werd uitgesteld vanwege neutropenie moeten als volgt worden behandeld: toedienen van een dosis topotecan capsules die met 0,4 mg/m2 is verlaagd tot 1,9 mg/m2/dag [of indien nodig verder wordt verlaagd tot 1,5 mg/m2/dag]; toedienen van topotecan infusie in een dosis verlaagd tot 1,25 mg/m2/dag [indien nodig verlaagd tot 1,0 mg/m2/dag) of profylactisch toedienen van G-CSF in de vervolg kuren te beginnen vanaf dag 6 van de kuur. Indien toedie-ning van G-CSF de neutropenie niet voldoende tegengaat, moet de dosis worden verminderd. Trombocytopenie: Gelijksoortige doseringsverlaging als bij neutropenie indien de trombocytenconcentratie < 25 x 109/l. In klinisch onderzoek werd behandeling met topotecan capsules gestopt als de dosis was teruggebracht tot beneden 1,5 mg/m2/dag of als dosis topotecan infusie was teruggebracht tot 1,0 mg/m2/dag en verdere verlaging noodzakelijk was om de bijwerkingen onder controle te houden. Verminderde nierfunctie: Voor topotecan capsules zijn geen dosisaanbevelingen vastgesteld bij patiënten met Cl_{cr} minder dan 60 ml/min. Voor topotecan infusie zijn onvoldoende gegevens beschikbaar om aanbevelingen te doen bij creatineklaring < 20 ml/min. Voorlopige gegevens duiden er op dat de dosis verlaagd moet worden bij een matig verminderde nierfunctie. Bij creatinineklaring van 20-39 ml/min is de aanbevolen dosering 0,75 mg/m2/dag. Cervixcarcinoom: *topotecan infusie, begindosis:* De aanbevolen dosis topotecan is 0,75 mg/m2/dag, toegediend als intraveneuze infusie gedurende 30 minuten per dag, dagelijks op de dagen 1, 2 en 3 van een kuur van 21 dagen. Cisplatine wordt toegediend als een intraveneuze infusie op dag 1 van de kuur in een dosering van 50 mg/m2/dag en na de dosering topotecan. Deze behandeling bestaat uit 6 kuren of tot progressie van de ziekte. *Vervolgdoses:* Topotecan infusie mag alleen opnieuw worden toegediend, als de neutrofielen concentratie ≥1,5 x 109/l, de trombocytenconcentratie ≥ 100 x 109/l en de hemoglobineconcentratie ≥9 g/dl is [na transfusie indien nodig]. Patiënten met febriele neutropenie [neutrofielenconcentratie < 1 x 109/l en een lichaamstemperatuur van 38°C of hoger] wordt vermindering aanbevolen van de dosis topotecan met 20%, tot 0,60 mg/m2/dag voor de volgende kuren. Als alternatief voor dosisvermindering wordt aanbevolen om in het geval van febriele neutropenie patiënten G-CSF te geven na de daarop volgende kuur (vóór gekozen wordt voor dosisvermindering) vanaf dag 4 van de kuur (tenminste 24 uur na het voltooien van de toediening van topotecan). Indien febriele neutropenie optreedt ondanks het gebruik van G-CSF, wordt aanbevolen de dosis topotecan voor daarop volgende kuren nog eens 20% extra te verlagen, tot 0,45 mg/m2/dag. Bij patiënten bij wie de trombocytenconcentratie onder de 10 x 109/l daalt wordt aanbevolen de dosis topotecan met 20% te verminderen, tot 0,60 mg/m2/dag. **Contra-indicaties:** Topotecan mag niet worden gebruikt bij patiënten:- waarvan bekend is dat zij ernstig overgevoelig zijn voor topotecan of een van de hulpstoffen, - die zwanger zijn of borstvoeding geven, - die reeds voor het begin van de eerste kuur ernstige onderdrukking van de beenmergactiviteit vertonen, zoals blijkt uit de baseline neutrofielen < 1,5 x 109 /l en/of een trombocytenconcentratie ≤ 100 x 109/l. **Waarschuwingen:** Ernstige myelosuppressie leidend tot sepsis is gemeld bij 5% van de patiënten behandeld met topotecan. Bij verzwakte patiënten (PS >1) wordt een lagere response rate gemeten en een verhoogde incidentie van complicaties zoals koorts, infectie en sepsis. Topotecan en topotecan in combinatie met cisplatine worden gewoonlijk geassocieerd met klinisch relevante trombocytopenie. Hiermee moet worden rekening gehouden bij een verhoogd risico op bloedingen van de tumor. Accurate evaluatie van de toestand op het moment dat de therapie wordt gegeven is belangrijk om er zeker van te zijn dat patiënten niet verzwakt zijn tot status 3 (PS= 3). Bij patiënten met ernstige nierfunctiestoornissen of leverstoornissen als gevolg van cirrhose wordt het gebruik van topotecan niet aanbevolen. Profylactisch management en behandeling van alle voortekenen en symptomen van (ernstige) diarree, gerelateerd aan behandeling met topotecan capsules is belangrijk. Kankerbehandeling geïnduceerde diarree (CTID) kan levensbedreigend zijn. **Interacties:** Topotecan remt humane P450-enzymen niet. Gelijktijdige toediening van granisetron, ondansetron, morfine of corticosteroïden heeft geen significant effect op de farmacokinetische eigenschappen van topotecan als totaal (actieve en inactieve vorm). In combinatie van topotecan met andere chemotherapie middelen, is reductie van de doses van elk geneesmiddel vereist om de tolerantie te verbeteren. Echter, in combinatie met platinum middelen, is een strikte sequentie-afhankelijke interactie ervan afhankelijk of het platinum middel is gegeven op dag 1 of dag 5 van de topotecan dosering. Topotecan is een substraat voor P-glycoproteïne en BCRP-enzym. Zorgvuldige controle ten aanzien van bijwerkingen is aanbevolen bij patiënten, die tegelijkertijd met topotecan capsules en remmers van deze enzymen worden behandeld. **Zwangerschap:** Topotecan is gecontraïndiceerd tijdens de zwangerschap en de borstvoedingsperiode. **Bijwerkingen:** *Hycamtin capsules,* Vaak: pancytopenie, abdominale pijn, constipatie, maagklachten, stomatitis, , asthenie, koorts, malaise. Soms: hyperbilirubinemie, onbekend: anafylactische reactie, angio-oedeem,urticaria; *Hycamtin infusie,* zeer vaak: abdominale pijn, constipatie, stomatitis, koorts, asthenie; vaak: hyperbilirubinemie; zelden: anafylactische shock, angio-oedeem, urticaria; zeer zelden: extravasatie. *Hycamtin infusie en capsules, zeer vaak:* Febriele neutropenie, neutropenie, trombocytopenie, anemie, leukopenie, anorexia, infectie, alopecia, fatigue, misselijkheid braken en diarree; vaak: overgevoeligheidsreacties (rash), pruritis, stomatitis, malaise, sepsis. Onbekend: interstitiële longziekte, Het bijwerkingenprofiel voor topotecan indien gegeven in combinatie met cisplatine bij klinische trials op het gebied van cervixkanker komt overeen met het profiel dat gezien wordt bij monotherapie met topotecan infusie. Aanvullende bijwerk-ingen werden gezien wanneer topotecan werd gegeven in combinatie met cisplatine, maar deze bijwerkingen werden ook gezien met cisplatine monotherapie en waren niet het gevolg van gebruik van topotecan. Voor de frequenties waarin de hematologische en niet-hematologische bijwerkingen optreden die gerelateerd of mogelijk gerelateerd zijn aan de topotecan therapie wordt verwezen naar de volledige productinformatie van topotecan capsules en van topotecan infusie. **Verpakking:** Een verpakking Hycamtin 4 mg wordt geleverd in 1x 5 ml injectieflacon (EU/1/96/027/003). Hycamtin capsules worden geleverd in een verpakking van 10 capsules à 0,25 mg (EU/1/96/027/006) en een verpakking van 10 capsules à 1 mg (EU/1/96/027/007). **Aflevering en prijs:** Hycamtin infusie: U.R. en voor de prijs zie G-standaard. Hycamtin capsules: U.R. wordt niet vergoedt.

Voor medische vragen over dit product belt u met het Medical Customer Support CenterTel. (030) 6938123.
Voor de volledige productinformatie zie de geregistreerde samenwatting van de productkenmerken van Hycamtin infusie (21 juni 2007) en van Hycamtin capsules (18 maart 2008).

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Literatuurreferenties:
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