Mesothelioma:
the rare disease that we need to know better

Radiotherapy: A controversial role in this disease

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DEPARTMENT OF
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5-18 April 2015, Geneva, Switzerland

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IASLC
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etop
Information | Research

- I have no conflicts of interest to disclose

What is the role of Radiotherapy in Malignant Pleural Mesothelioma?

Radiotherapy is (widely?) used in the treatment of patients with mesothelioma:

- In palliative setting
- In prophylaxis of port-site recurrence
- As an integral part of “curative” multimodality therapy for resectable disease

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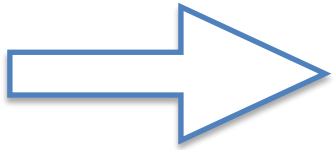
What is the role of Radiotherapy in Malignant Pleural Mesothelioma?

But…..

Where is the evidence to support the routine role of radiotherapy in patients affected with mesothelioma?



little supporting evidence

Annals of Oncology 21 (Supplement 5): v126–v128, 2010
doi:10.1093/annonc/mdq173

Malignant pleural mesothelioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

R. A. Stahel[1], W. Weder[2], Y. Lievens[3] & E. Felip[4]
On behalf of the ESMO Guidelines Working Group*

radiotherapy

The use of curative intent hemithoracic radiotherapy has been limited because of the difficulty of irradiating such a large target volume to high doses without exceeding the tolerance of the adjacent normal tissues, especially the (homolateral) lung. The exact role of definitive radiotherapy in the multimodality approach of MPM is currently under investigation. Nevertheless, in an attempt to improve local control after EPP, it has been shown feasible to deliver radiotherapy doses of >45 Gy with both 3D conformal (3D-CRT) and intensity-modulated radiotherapy (IMRT). However, caution must be exercised regarding the exposure of the contralateral lung to low-dose irradiation, especially when using IMRT [III, B].

In the palliative setting, radiotherapy can be delivered locally in view of pain control or prevention of obstructive symptoms [IV, C]. As mesothelioma invades the tracts made by chest instrumentation, prophylactic irradiation to the intervention tracts (PIT) has been advocated to reduce the incidence of port metastases. In the absence of unambiguous prospective data—the consequence of randomized trials with small patient numbers, different results according to histology and highly variable RT techniques—however, it remains impossible to draw definitive conclusions regarding its efficacy [II, C].

note

Levels of Evidence [I–V] and Grades of Recommendation [A–D] as used by the American Society of Clinical Oncology are given in square brackets. Statements without grading were considered justified standard clinical practice by the expert authors and the ESMO faculty.

Guidelines for the diagnosis and treatment of malignant pleural mesothelioma

Nico van Zandwijk, Christopher Clarke, Douglas Henderson, A. William Musk, Kwun Fong, Anna Nowak, Robert Loneragan, Brian McCaughan, Michael Boyer, Malcolm Feigen, David Currow, Penelope Schofield, Beth Ivimey Nick Pavlakis, Jocelyn McLean, Henry Marshall, Steven Leong, Victoria Keena, Andrew Penman

J Thorac Dis 2013;5(6):E254-E307

Recommendation	Grade*
34. Mesothelioma is sensitive to moderately high radiation doses and radiotherapy is advocated for palliation of symptomatic tumour masses arising from the pleural cavity or metastases in other locations.	C

*Grade of recommendation can be found on page

Recommendation	Grade*
35. For doses greater than 50 Gy, advanced radiotherapy technologies with strict constraints for contralateral lung doses are recommended to avoid excessive toxicity.	C

de of recommendation can be found on page E255.

Recommendation	Grade*
36. The administration of prophylactic radiotherapy following pleural interventions in patients with mesothelioma has no significant effect on changing the disease course and is not recommended.	C

*Grade of recommendation can be found on page E255.

*Grade of recommendation

A. Body of evidence can be trusted to guide practice;
B. Body of evidence can be trusted to guide practice in most situations;
C. Body of evidence provides some support for recommendation(s) but care should be taken in its application;
D. Body of evidence is weak and recommendation must be applied with caution.

Publication Approval

Australian Government
National Health and Medical Research Council

What is the role of Radiotherapy in Malignant Pleural Mesothelioma?

Radiotherapy is (widely?) used in the treatment of patients with mesothelioma:

- in the prophylaxis of port-site recurrence→

Table 3. Randomized trials of port-site prophylaxis

Study	No. entered	Radiotherapy dose (Gy/fractions)	Port-site failure without radiotherapy (%)	Port-site failure with radiotherapy (%)
Marseille [38]	40	21/3	20	0
Perth [39]	58	10/1	10	7
Beatson [40]	56	21/3	12	13

… has been concluded in two systematic reviews not to influence significantly the disease course

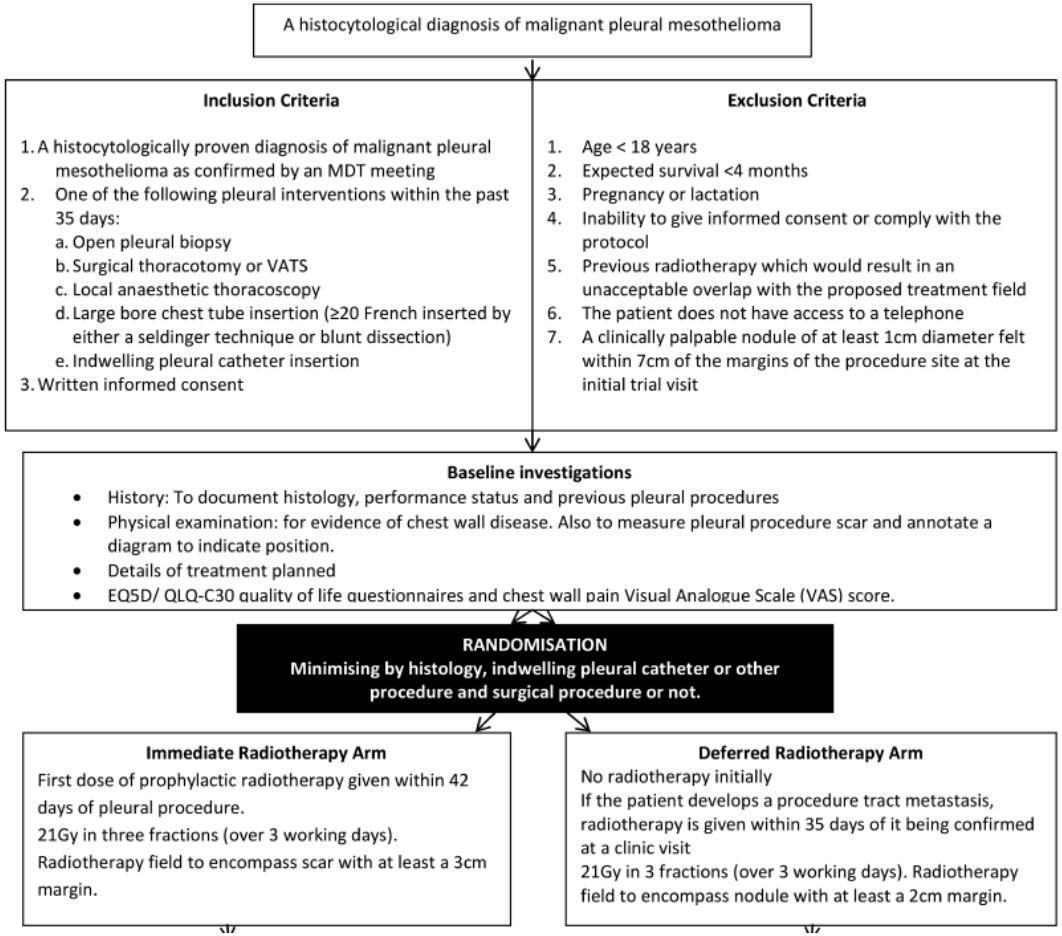
Strengths and limitations of this study

- Suitably powered multicentre, randomised controlled trial of prophylactic radiotherapy in malignant pleural mesothelioma.
- Robust 1 year patient follow-up.
- All large bore pleural interventions are eligible, including indwelling pleural catheters.
- Small bore chest tubes excluded.

BMJ Open

Protocol for the surgical and large bore procedures in malignant pleural mesothelioma and radiotherapy trial (SMART Trial): an RCT evaluating whether prophylactic radiotherapy reduces the incidence of procedure tract metastases

Amelia O Clive,[1,2] Paula Wilson,[3] Hazel Taylor,[4] Anna J Morley,[1] Emma de Winton,[5] Niki Panakis,[6] Najib Rahman,[6] Justin Pepperell,[7] Timothy Howell,[8] Timothy J P Batchelor,[9] Nikki Jordan,[1] Y C Gary Lee,[10] Lee Dobson,[11] Nick A Maskell[1,2]



The primary research question is to evaluate whether prophylactic radiotherapy prevents PTM following large bore pleural procedure in MPM

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Radiotherapy in palliation of MPM

- Is radiotherapy useful for treating pain in mesothelioma? A Phase II trial
  - 40 patients recruited from three UK Oncology Centres
  - 20 Gy in 5 daily fractions
  - Pain assessment at baseline, 5 and 12 weeks
  - 47% of 30 pts evaluable at week 5 had pain improvement
  - RT for pain control is an effective treatment in a proportion of patients

MacLeod N., JTO 2015

Multimodality treatment strategy
(Adjuvant RT after EPP)

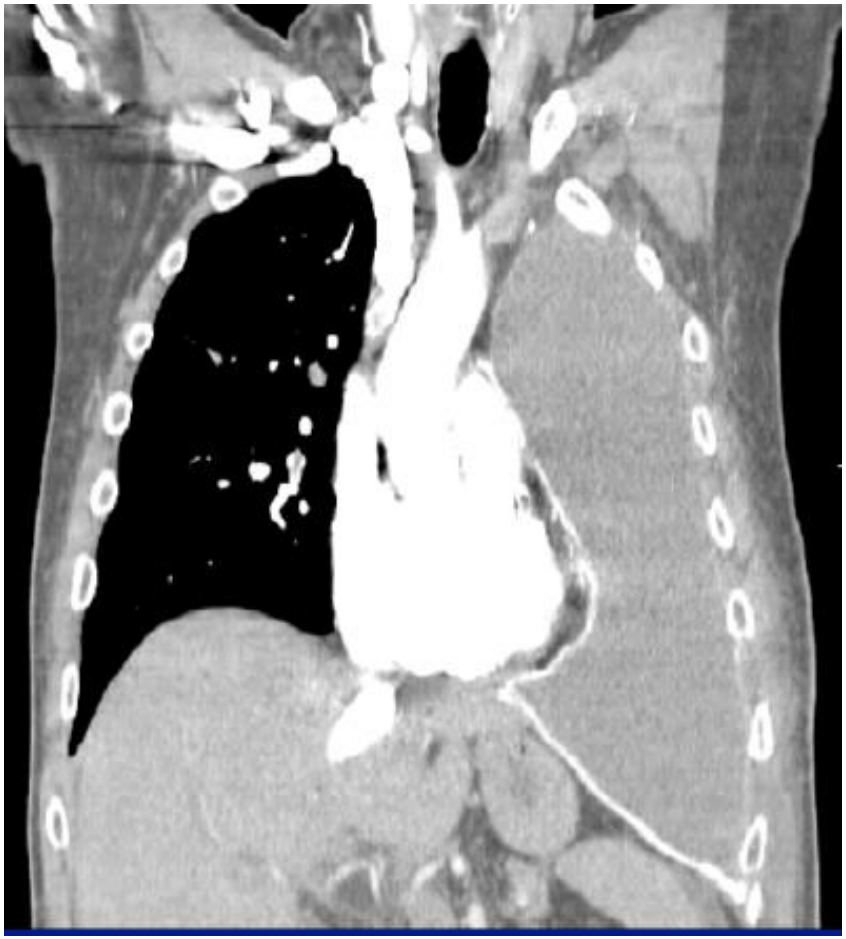
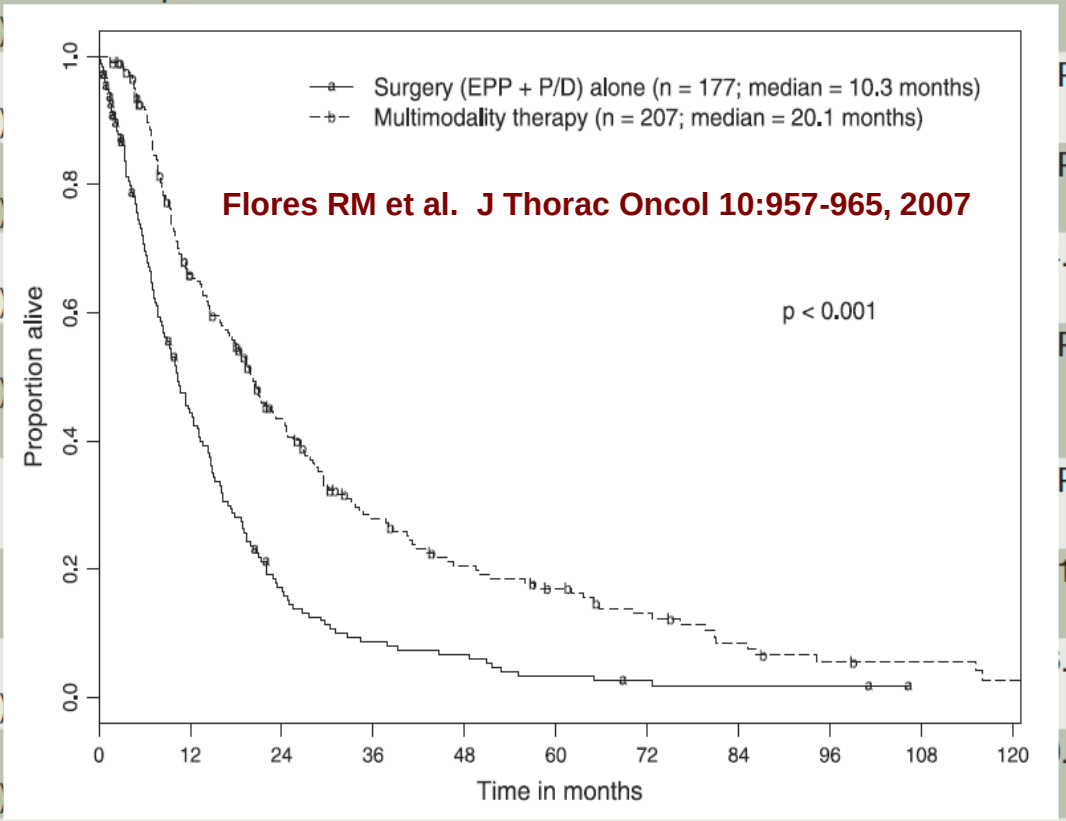


Table 2 Extrapleural pneumonectomy plus adjuvant therapy

Author, [year], (Ref)	Study design	EPP (n)	Modalities	Overall morbidity (%)	Major morbidity (%)	Mortality (%)	Median OS (mo)
Branscheid *et al.* [1991] (28)	Retrospective	76	CTX	NR	NR	11.8	9.3
Allen *et al.* [1994] (29)					R	7.5	13.3
Baldini *et al.* [1997] (30)					R	4.0	22
Sugarbaker *et al.* [1999] (31)					.5	3.8	19
Rusch *et al.* [1999] (32)					R	5.2	stage I 29.9, stage II 19, stage III 10.4, stage IV 8
Rusch *et al.* [2001] (33)					R	11.2	17
Aziz *et al.* [2002] (34)					1	9.0	35
Pagan *et al.* [2006] (35)					.3	4.5	20
Schipper *et al.* [2008] (36)					.7	8.2	16
Flores *et al.* [2008] (37)	Retrospective	385	CTX +/RT	10 (respiratory only reported)	NR	7.0	12
Luckraz *et al.* [2010] (38)	Retrospective	49	CTX +/RT	53	NR	8.2	19.5
Tonoli *et al.* [2011] (39)	Retrospective	56	CTX + RT	NR	NR	NR	46.9[b]
Rena *et al.* [2012] (40)	Retrospective	40	CTX + RT	62	NR	5.0	20 (stage I 28, stage II 18)

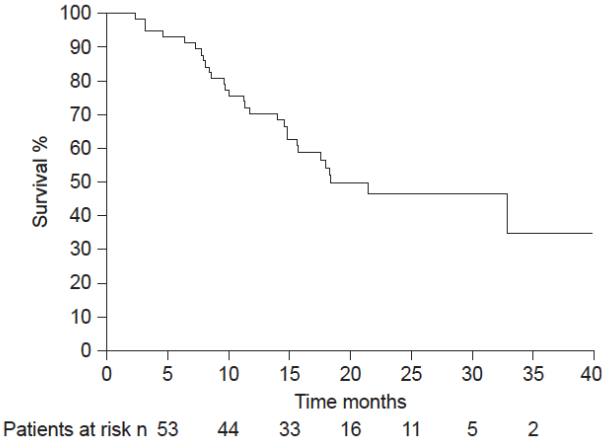


Studies with around 40 or more patients. EPP, extrapleural pneumonectomy; CTX, chemotherapy; RT, radiotherapy; OS, overall survival; NR, not reported. [a], Intention to treat; [b], selected patients.

Eur Respir J 2010; 36: 1362–1369
DOI: 10.1183/09031936.00039510

Trimodality therapy for malignant pleural mesothelioma: results from an EORTC phase II multicentre trial

P.E. Van Schil*, P. Baas#, R. Gaafar¶, A.P. Maat+, M. Van de Pol§, B. Hasanƒ, H.M. Klomp#, A.M. Abdelrahman¶, J. Welchƒ and J.P. van Meerbeeck** on behalf of the European Organisation for Research and Treatment of Cancer (EORTC) Lung Cancer Group



ABSTRACT: **The European Organisation for Research and Treatment of Cancer (EORTC; protocol 08031) phase II trial investigated the feasibility of trimodality therapy consisting of induction chemotherapy followed by extrapleural pneumonectomy and post-operative radiotherapy in patients with malignant pleural mesothelioma (with a severity of cT3N1M0 or less).**

59 patients were registered, one of whom was ineligible. Subjects' median age was 57 yrs. The subjects' TNM scores were as follows: cT1, T2 and T3, 36, 16 and six patients, respectively; cN0 and N1, 57 and one patient, respectively. 55 (93%) patients received three cycles of chemotherapy with only mild toxicity. 46 (79%) patients received surgery and 42 (74%) had extrapleural pneumonectomy with a 90-day mortality of 6.5%. Post-operative radiotherapy was completed in 37 (65%) patients. Grade 3–4 toxicity persisted after 90 days in three (5.3%) patients. Median overall survival time was 18.4 months (95% CI 15.6–32.9) and median progression-free survival was 13.9 months (95% CI 10.9–17.2). Only 24 (42%) patients met the definition of success (one-sided 90% CI 0.36–1.00).

Major technological advances in RT planning and delivery led to the widespread introduction of intensity-modulated radiotherapy (IMRT), which allows to better spare the healthy tissues and organs at risk

Toxicity:

- IMRT treatment: more fatal pneumonitis than 3D-CRT

Crucial points:

IMRT, toxicity and constraints

Author, Institution	RT Fatality Rate (%)	LR Recurrence Rate (%)	Median Dose (Gy)
After conventional RT and EPP			
de Perrot et al.[16], Toronto General Hospital	0/29 (0)	7	NR
Rea et al.[17], University of Padua (Italy)	0/15 (0)	35	45
Rusch et al.[11], MSKCC	0/54 (0)	13	54
Sugarbaker et al.[2], BWH	0/183 (0)	NR	50
After IMRT and EPP			
Allen et al.[8], BWH	6/13 (46)	NR	54
Kristensen et al.[18], Rigshospitalet (Denmark)	4/26 (15)	NR	50
Miles et al.[6], Duke	1/13 (8)	46	45
Rice et al.[19,20], MDACC	6/63 (10)	13	45

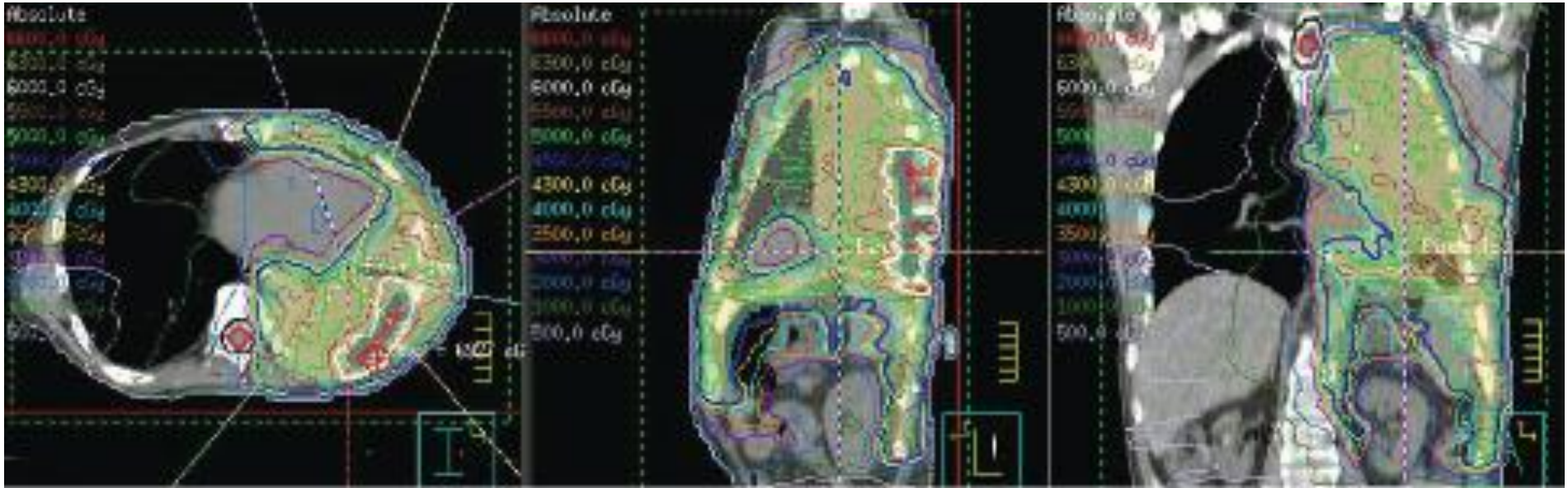
•Fatal Radiation Pneumonitis

Study	DVHs for controlateral lung	
	MLD	V20
Allen, BWH ’06	> 13 Gy	> 15%
Miles, Duke ’08	> 11 Gy	> 7%
Rice, MDACC ‘07	> 8.5 Gy	> 20%

Allen AM et al [Red Journal 2006;65:640-5]
Miles EF et al. [Red Journal 2008;71:1143-50]
Rice DC et al. [Red Journal 2007;69:350-7]

- ✓ Radiotherapy (RT) with modern techniques, within the context of a multimodality treatment, has potentially a role in the therapy of patients with malignant pleural mesothelioma

- ✓ Many data confirm the feasibility of 50-54 Gy post-operative RT in MPM patients with modern techniques, with a relatively low toxicity burden if strict constraints are applied



Open Questions

- Patients' selection for trimodality treatment
- Randomized trial on Adjuvant RT (SAKK trial)

SAKK - SWISS GROUP FOR CLINICAL CANCER RESEARCH

Protocol SAKK 17/04
Neoadjuvant chemotherapy and extrapleural pneumonectomy of malignant pleural mesothelioma (MPM) with or without hemithoracic radiotherapy. A randomized multicenter phase II trial

Activation date: 11.11.2005 EudraCT Nr. 2006000445-19

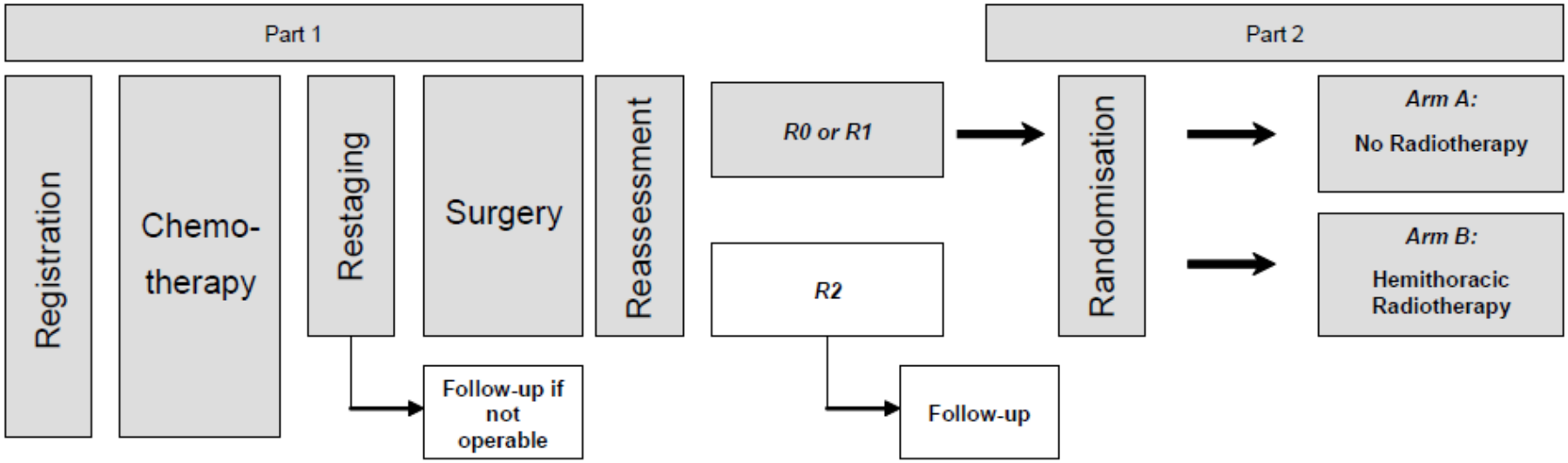
The objectives of the trimodality trial SAKK17/04 (NCT00334594) were to evaluate the time to loco-regional relapse with or without high dose hemithoracic radiotherapy in a prospective multicenter randomized phase II trial in patients with R0 and R1 resection after neoadjuvant chemotherapy and EPP

Eligible patients had pathologically confirmed MPM, surgically resectable

TNM stage (T1-3 N0-2 M0), PS0-1, ages 18-70 years

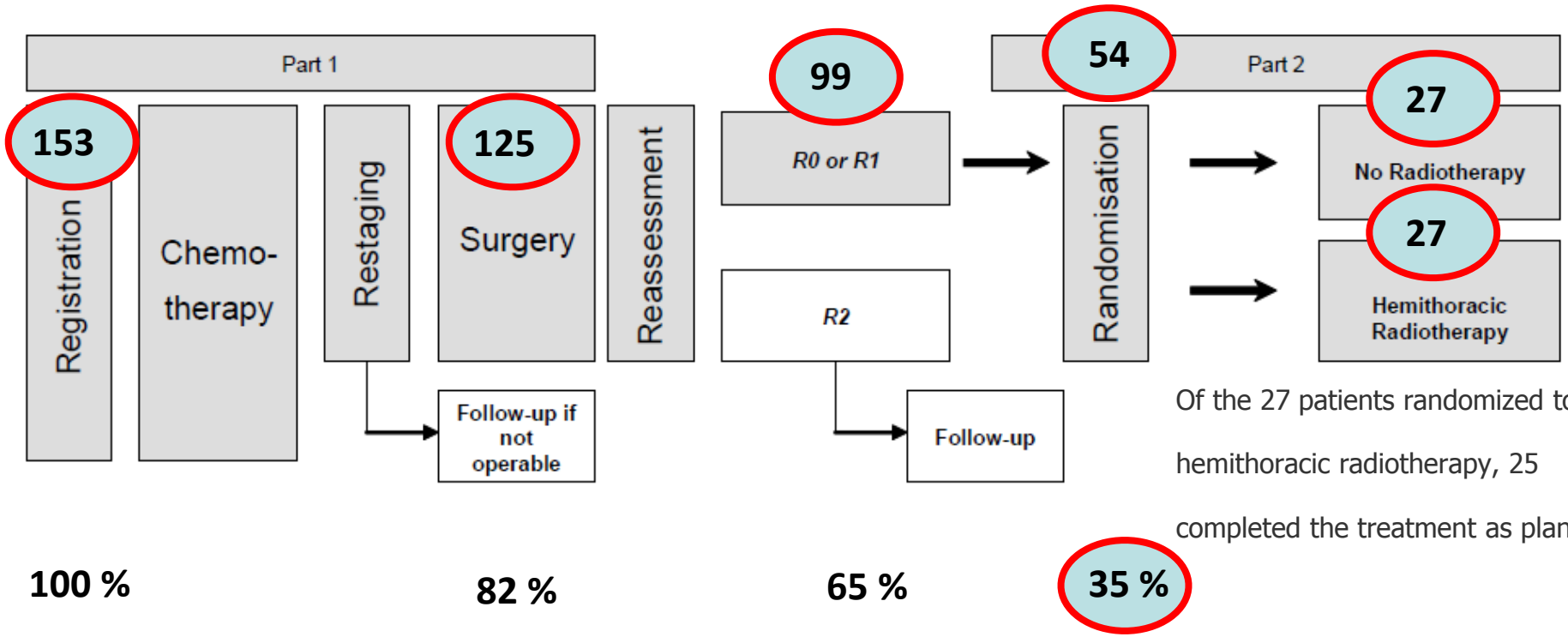
The primary endpoint of part 1 was complete macroscopic resection (R0-1)

The primary endpoint for part 2 was loco-regional relapse-free survival



Patient refusal: 24

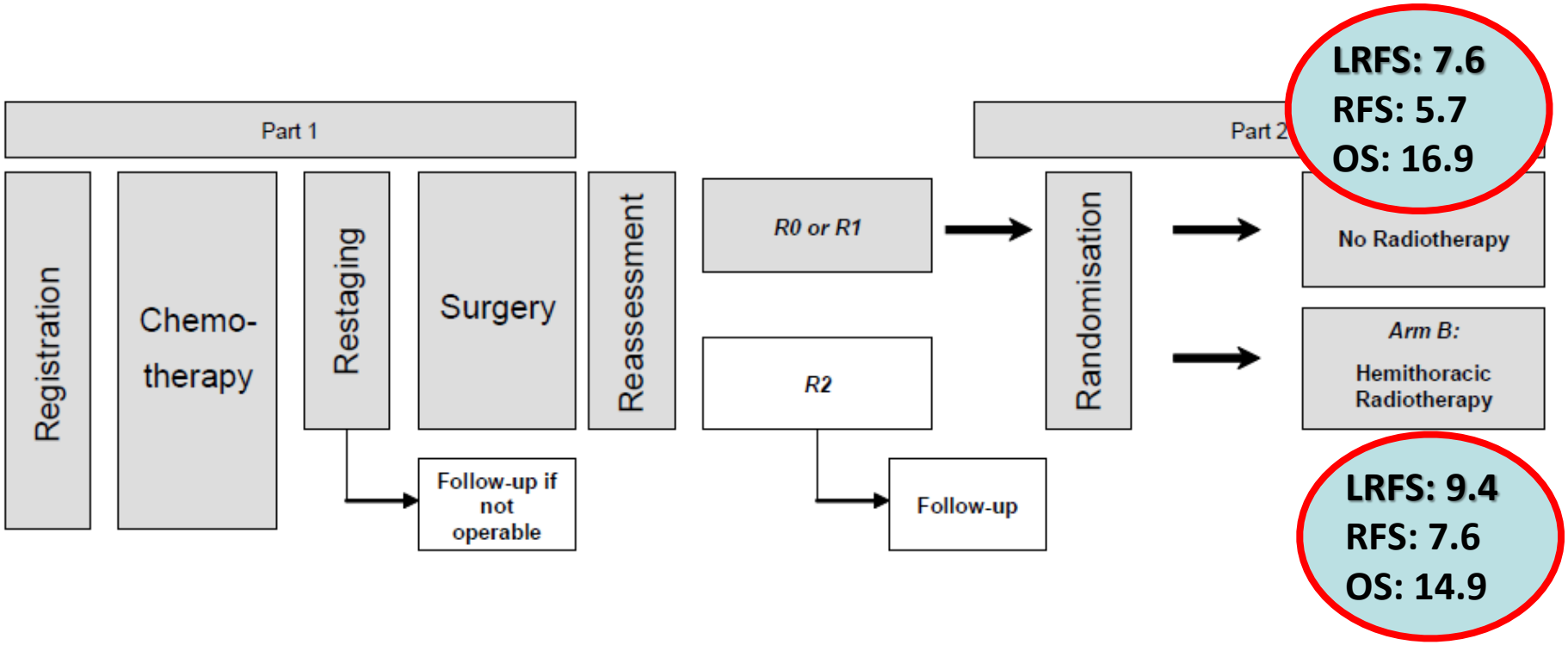
Inelegibility/protocol deviations: 21



Of the 27 patients randomized to hemithoracic radiotherapy, 25 completed the treatment as planned

100 % **82 %** **65 %** **35 %**

Relapse Free survival (Months)



Overall survival (Months)

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This study does not support the routine use of hemithoracic RT after neoadjuvant chemotherapy and EPP

- Accrual slower than planned and trial stopped in 2013: underpowered study (37 pts were needed)
- Even in upfront highly selected patients: 82 % EPP and only 35 % random for postoperative radiotherapy
- Still unsatisfactory local relapse-free survival:
  - 7.6 months with EPP
  - 9.4 months with postoperative radiotherapy
  - Nearly all patients: local relapse within 2 years
- Still unsatisfactory overall survival:
  - Median: 15.0 months
  - < 10 % 5-year survival

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Updated patterns of failure after multimodality therapy for malignant pleural mesothelioma

TABLE 2. Sites of first failure among 158 patients evaluable for recurrence: Some patients had failures in more than 1 site

Site of failure	N	% of all patients (n = 158)	% of all failures (n = 118)	% of all failures from 1997 report (n = 49)[10]
IHT +/or mediastinum (local failure)	85	54	72	67
Abdomen	62	39	53	50
CHT	45	28	38	33
Distant	8	5	7	8

IHT, Ipsilateral hemithorax; *CHT*, contralateral hemithorax.

Conclusions: The most common site of recurrence after extrapleural pneumonectomy and planned multimodality therapy remains the ipsilateral hemithorax (including mediastinum), and true distant failure (other than the abdomen or contralateral hemithorax) remains unusual. The distribution of recurrences is strikingly similar to our prior report. (J Thorac Cardiovasc Surg 2015;■:1-8)

TABLE 4. Multivariate analysis of time to local recurrence and local recurrence-free survival

	Time to local recurrence HR (95% CI)	Local recurrence-free survival HR (95% CI)
Non-epithelioid histology	2.2 (1.4-3.5)	1.6 (1.2-2.3)
HIOC	0.7 (0.4-1.1)	0.7 (0.5-1.0)
CTX	0.7 (0.5-1.1)	0.7 (0.5-1.0)
RT	0.3 (0.2-0.5)	0.4 (0.3-0.6)

HR, Hazard ratio; *CI*, confidence interval; *HIOC*, heated intraoperative chemotherapy; *CTX*, chemotherapy; *RT*, radiation therapy.

Among 158 evaluable patients, a recurrence developed in 118 (75%)

Median follow-up was 83 months, median time to recurrence was 13.1 months, and median survival was 15 months

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- ✓ EPP offers the benefit of complete resection of all gross tumor and permits the delivery of high-dose adjuvant hemithoracic radiotherapy, but is associated with greater morbidity and mortality than lesser operations

- ✓ Moreover, many of these patients experience rapid progression of disease and have a limited life expectancy

Surgery in Mesothelioma – Where Do We Go after MARS?

Birgitta I. Hiddinga, MD and Jan P. van Meerbeeck, MD, PhD*†*

Journal of Thoracic Oncology • Volume 8, Number 5, May 2013

TABLE 2. Extrapleural Pleuropneumonectomy and Pleurectomy/Decortication in Malignant Pleural Mesothelioma

Investigator (year)	No. of patients with EPP	No. of patients with P/D	Chemotherapy	Other modalities	MST EPP (months)	MST P/D (months)
Martini (1976)[28]	2	NS	Adjuvant	± PORT	2	21
Branscheid (1991)[29]	76	82	Adjuvant	–	9.3	10.4
Allen (1994)[30]	40	56	Adjuvant	RTX	13.3	9.0
Pass (1997)[31]	39	39	NS	Photodynamic therapy, immunotherapy	9.5	14.5
Pass (1998)[32]	25	23	NS	Adjuvant immunochemotherapy	14.4	22
Rusch and Venkatraman (1999)[33]	115	59	± adjuvant	± PORT	18.5	18.5
Martin-Ucar (2007)[34]	45	12	(Neo)adjuvant	PORT	15	16
Flores (2008)[14]	385	278	Adjuvant	PORT	12	16
Lucraz (2010)[35]	49	34	Adjuvant	PORT	26	30
Lang-Lazdunski (2012)[36]	22	54	Neoadjuvant	Hyperthermic pleural lavage, PORT	12.8	23
Rena (2012)[37]	40	37	(Neo)adjuvant		20	25
Rusch et al. (2012)[38]	1190	299	(Neo)adjuvant	Various	NS	NS
p stage I	75	57			40	23
p stage II	229	77			23	20
p stage III	762	97			16	19
p stage IV	124	68			12	15

EPP, extrapleural pneumonectomy; IMRT, intensity-modulated radiotherapy; IORT, intraoperative radiotherapy; MST, mean survival time; NS, not stated; P/D, pleurectomy/decortication; PORT, postoperative radiotherapy; RTX, radiotherapy.

Patients treated with P/D had an equal to better outcome than those treated with EPP

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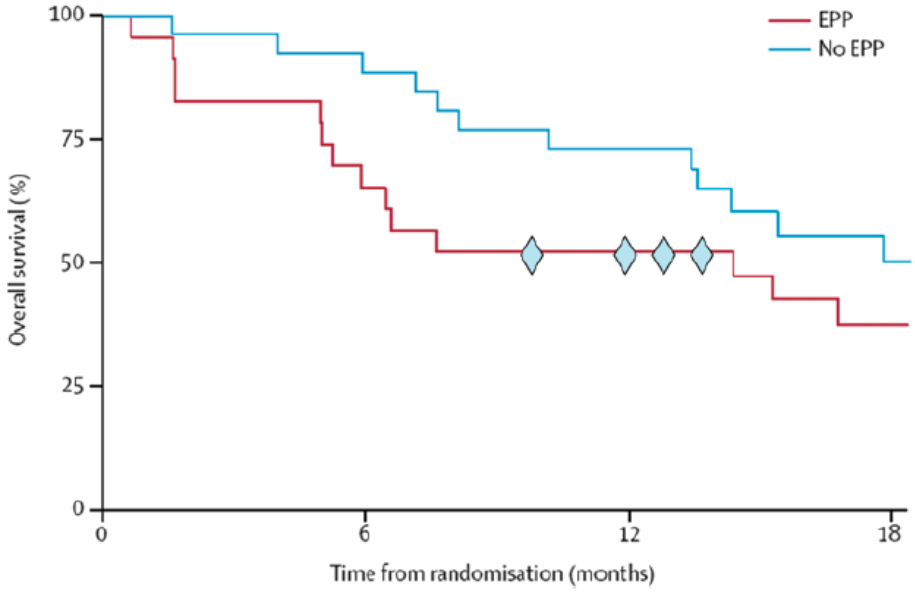
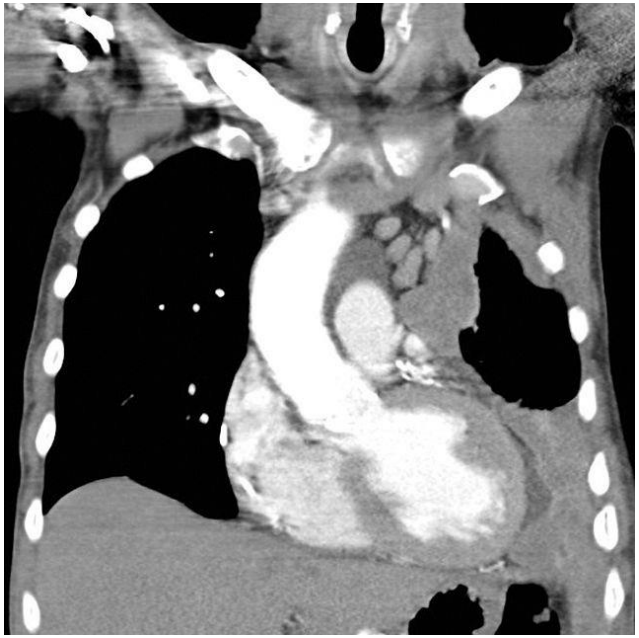


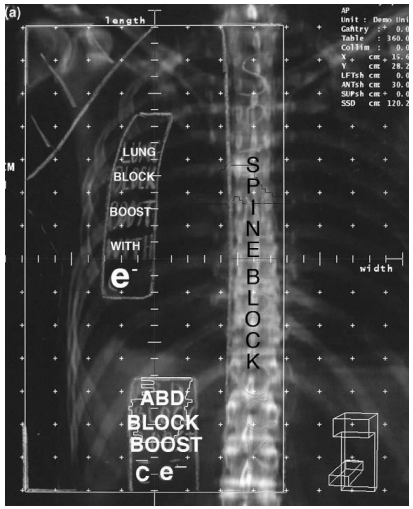


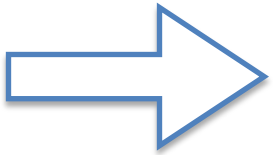
- ✓ The use of P/D is increasing, which poses a difficult problem for delivering adjuvant RT
- ✓ P/D is, by definition, a less complete resection than EPP and presumably carries a higher risk for locoregional recurrence
- ✓ Therefore, additional local treatment is critical

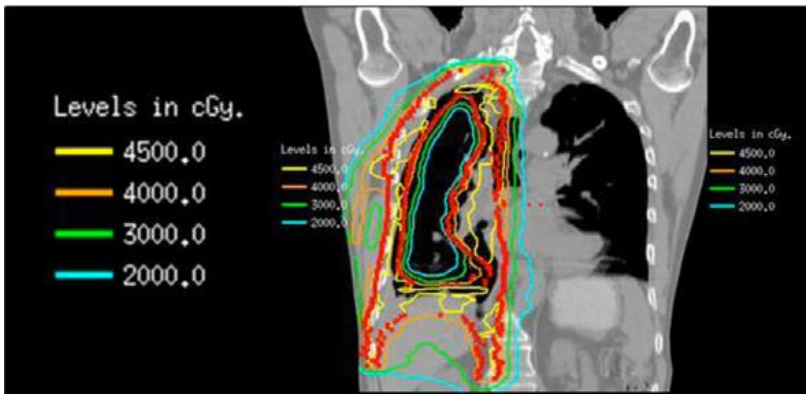
- An interesting challenge in MPM radiotherapy: to deliver a therapeutic RT dose to the hemithoracic pleura with intact lungs

- The use of pleural RT with conventional techniques has traditionally been limited by the difficulty of delivering an adequate RT dose without exceeding the tolerance of the adjacent normal structures, especially the lungs

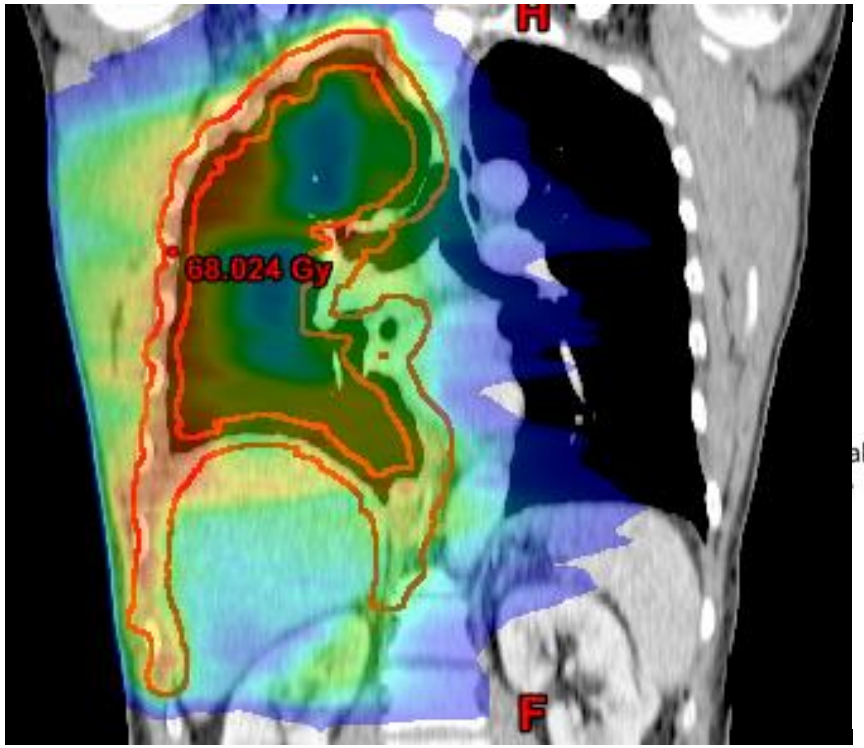
- Major technological advances in RT planning and delivery led to the widespread introduction of intensity-modulated radiotherapy (IMRT), which allows to better spare the healthy tissues surrounding the tumour

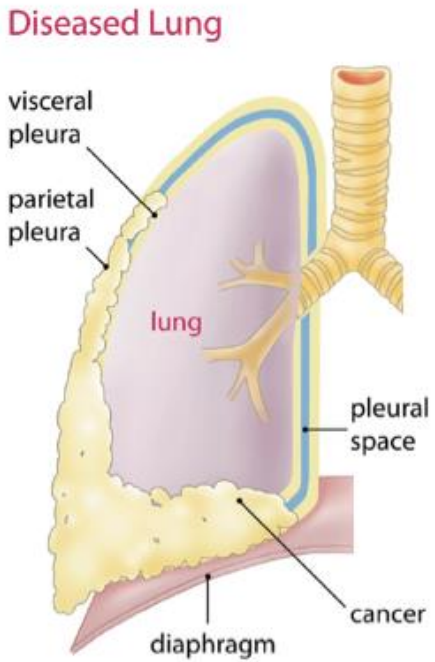


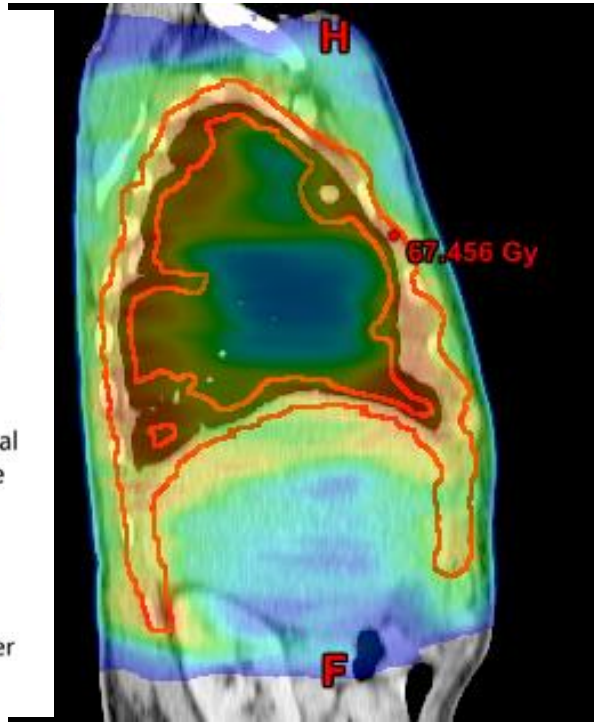


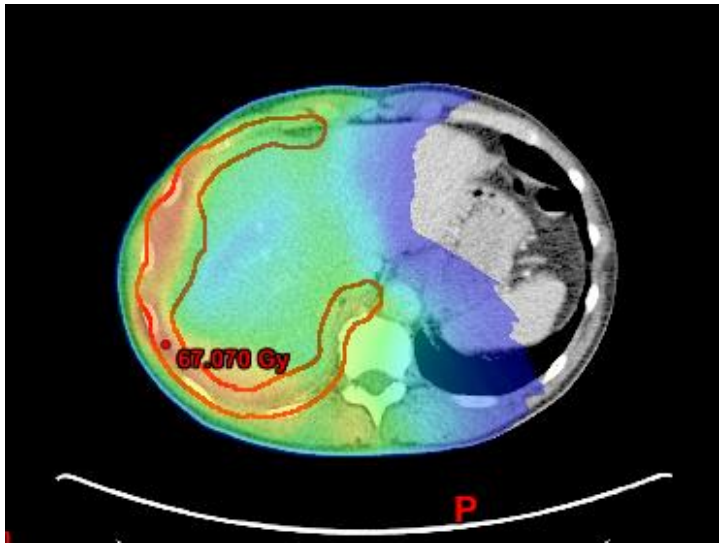


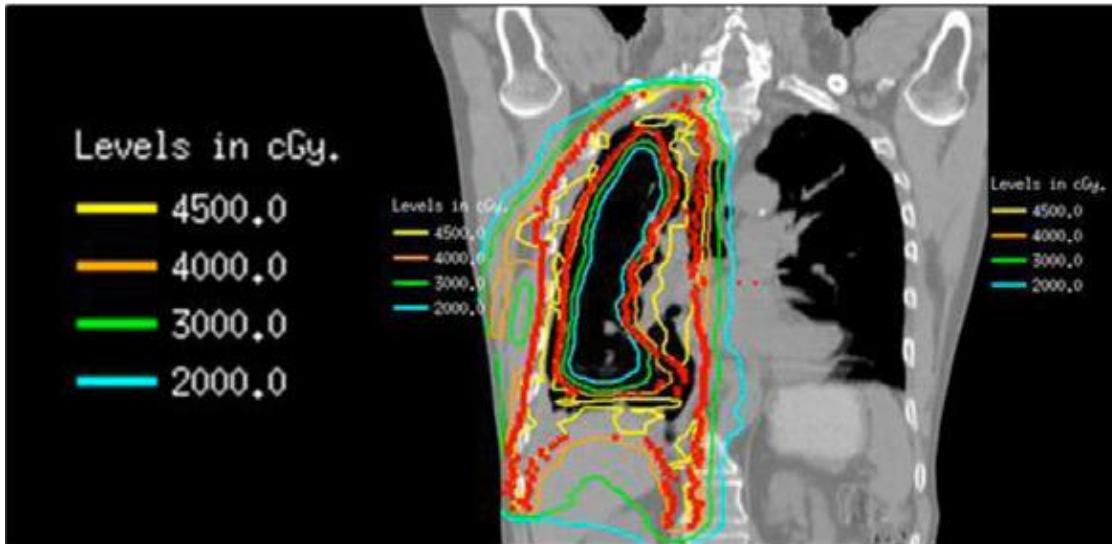
Lung sparing hemithoracic pleural IMRT







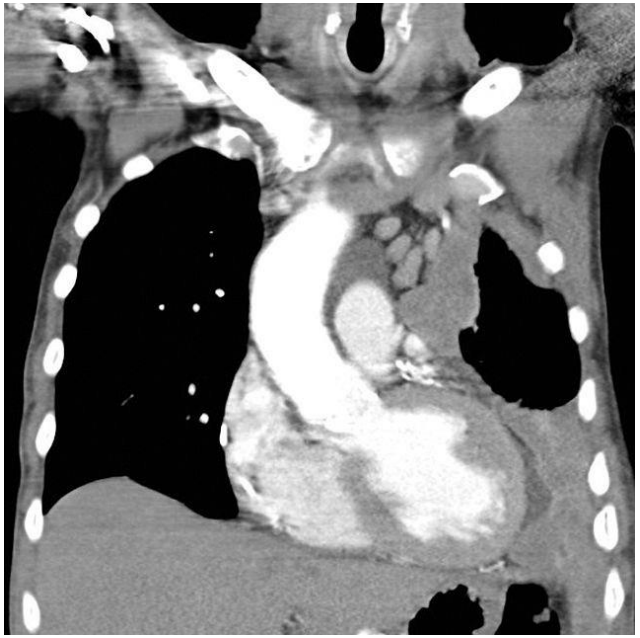


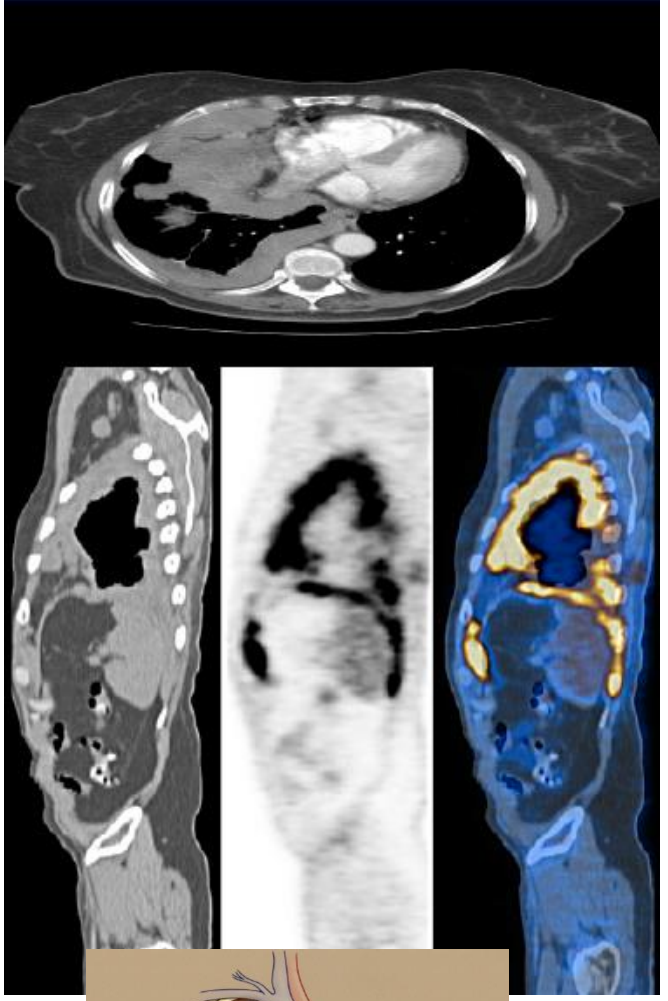


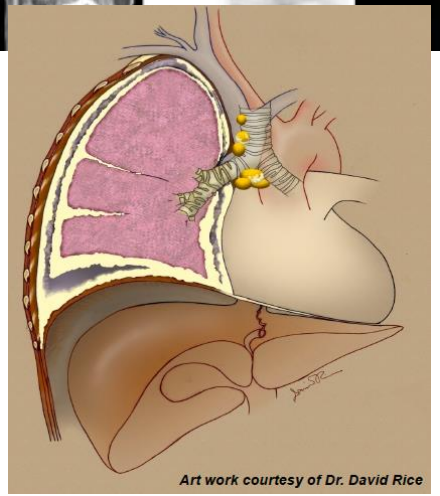
Adjuvant RT after P/D:
hemithoracic pleural IMRT

CTV defined as the entire hemithoracic parietal and visceral pleura including the entire diaphragm and involved lymh node stations (ipsilateral hilum), but without inclusion of the fissures

Optimal Imaging for target definition to be defined





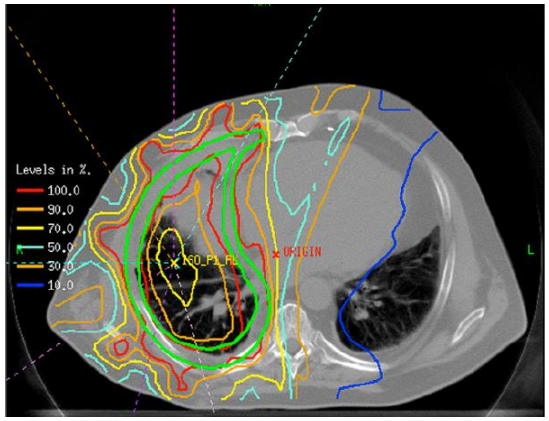


Pleural Intensity-Modulated Radiotherapy for Malignant Pleural Mesothelioma

Kenneth E. Rosenzweig, M.D.,* Marjorie G. Zauderer, M.D.,† Benjamin Laser, M.D.,‡ Lee M. Krug, M.D.,† Ellen Yorke, Ph.D.,§ Camelia S. Sima, M.D.,‖ Andreas Rimner, M.D.,¶ Raja Flores, M.D.,# and Valerie Rusch, M.D.**

Int J Radiation Oncol Biol Phys, Vol. 83, No. 4, pp. 1278–1283, 2012

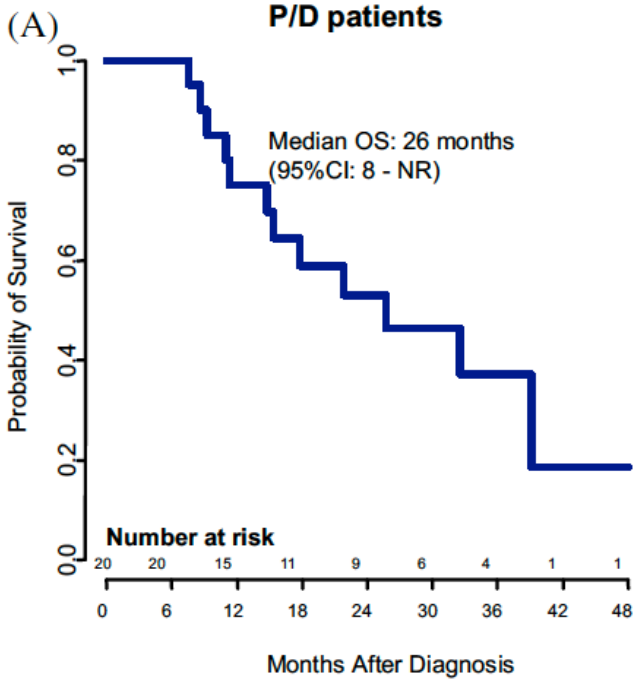
Characteristic	Value
Age (y)	
Median	67
Range	42–82
Gender	
Male	29 (81)
Female	7 (19)
Histologic subtype	
Epithelial	28 (78)
Sarcomatoid	2 (6)
Mixed	6 (17)
Surgery	
P/D or P	20 (56)
Nonoperative	16 (44)
Stage	
I	2 (6)
II	10 (28)
III	12 (33)
IV	12 (33)
Laterality	
Right	20 (56)
Left	16 (44)
Chemotherapy	
Yes	32 (89)
No	4 (11)

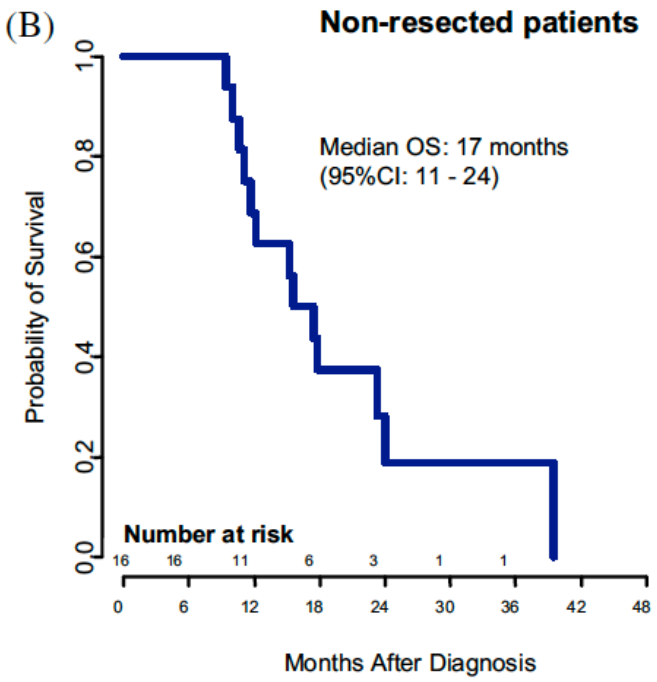


- 50.4 Gy in 30 fractions
- MLD < 20-21 Gy as dose constraint

Table 2 Acute toxicity (n = 36)

	Grade (n)					
Acute toxicity	0	1	2	3	4	5
Arrhythmia	36	0	0	0	0	0
Dermatitis	20	16	0	0	0	0
Dyspnea	4	20	5	5	1	1
Esophagitis	17	15	4	0	0	0
Fatigue	5	18	11	2	0	0
Nausea	21	7	8	0	0	0
Pericarditis/cardiac	36	0	0	0	0	0
Pneumonitis	24	5	0	5	1	1
Vomiting	33	3	0	0	0	0

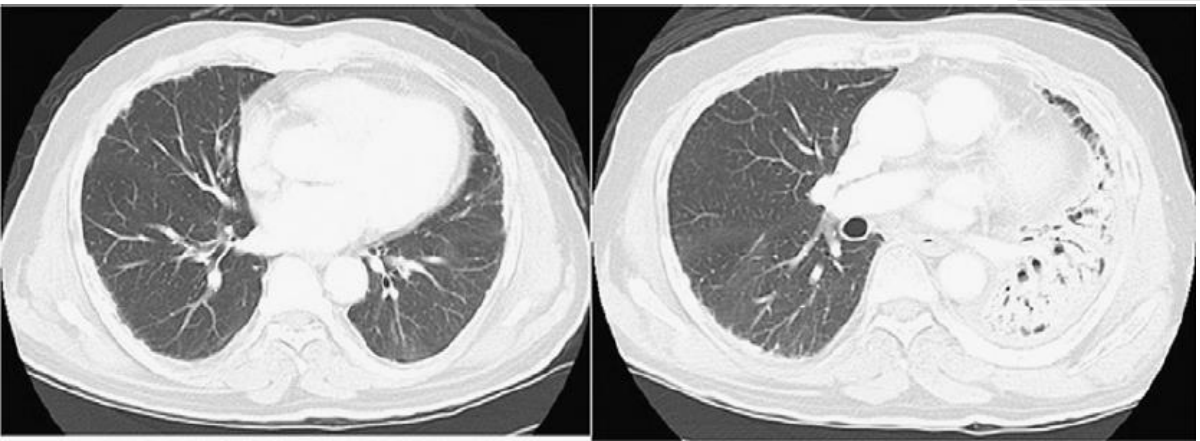




Treating the intact lung with pleural IMRT is a safe and feasible treatment option with an acceptable rate of pneumonitis. Additionally, the survival rates were encouraging, particularly for resected patients

Table 3 Late toxicity ($n = 30$)

	Grade (n)					
Late toxicity	0	1	2	3	4	5
Esophagitis	30	0	0	0	0	0
Pulmonary	9	12	4	5	0	0



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Failure Patterns After Hemithoracic Pleural Intensity Modulated Radiation Therapy for Malignant Pleural Mesothelioma

Andreas Rimner

Int J Radiation Oncol Biol Phys, Vol. 90, No. 2, pp. 394–401, 2014

Table 2 Failure types and patterns

	All patients (N=67)		Patients undergoing surgery (n=42)		Unresectable cases (n=25)	
	Number	%	Number	%	Number	%
Failure type						
Locoregional failures						
Total	44	66	25	60	19	76
In-field	43	64	24	57	19	76
Previous involved site	32	48	14	33	18	72
New site	11	16	10	24	1	4
Marginal	13	19	5	12	8	32
Out-of-field	25	37	13	31	12	48
Fissure	11	16	6	14	5	20
Distant	32	48	18	43	14	56
Failure patterns						
Local only	9	13	6	14	3	12
Local and regional	8	12	6	14	2	8
Local and distant	10	15	6	14	4	16
Local, regional, and distant	16	24	6	14	10	40
Regional only	1	1	1	2	0	0
Regional and distant	0	0	0	0	0	0
Distant only	6	9	6	14	0	0

Failure Patterns After Hemithoracic Pleural Intensity Modulated Radiation Therapy for Malignant Pleural Mesothelioma

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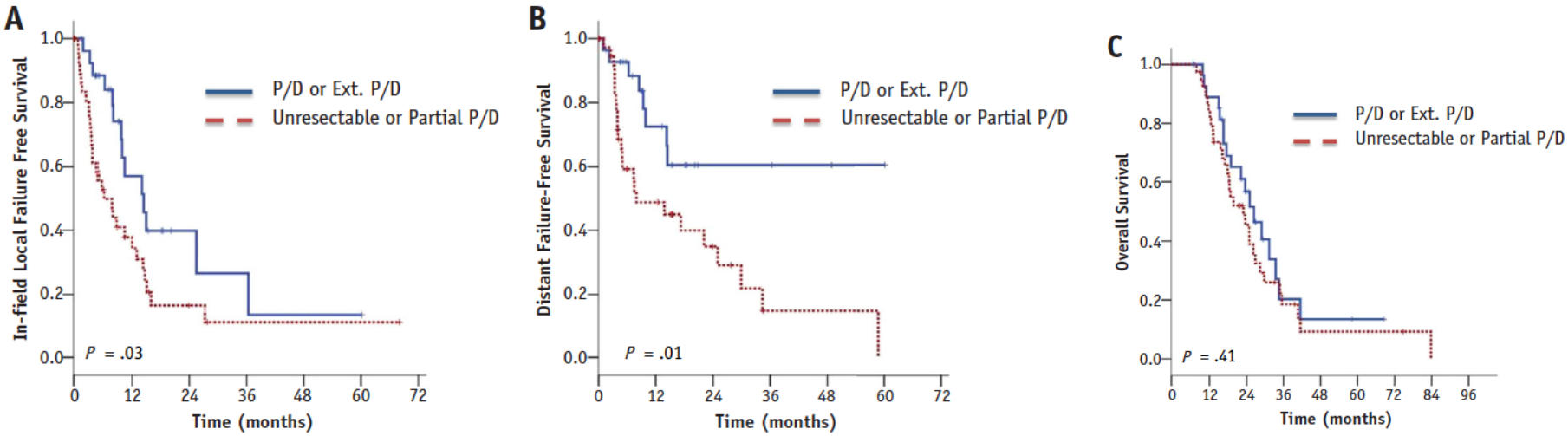
Int J Radiation Oncol Biol Phys, Vol. 90, No. 2, pp. 394–401, 2014



After hemithoracic pleural IMRT, most local failures occurred in sites of previous gross disease. Thus, macroscopic complete resection remains critical.

Increasing experience and improvements in target delineation combined with dose escalation will likely decrease the incidence of in-field and marginal failure rates with this new technique.

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Radical pleurectomy/decortication followed by high dose of radiation therapy for malignant pleural mesothelioma. Final results with long-term follow-up

Lung Cancer 83 (2014) 78–82

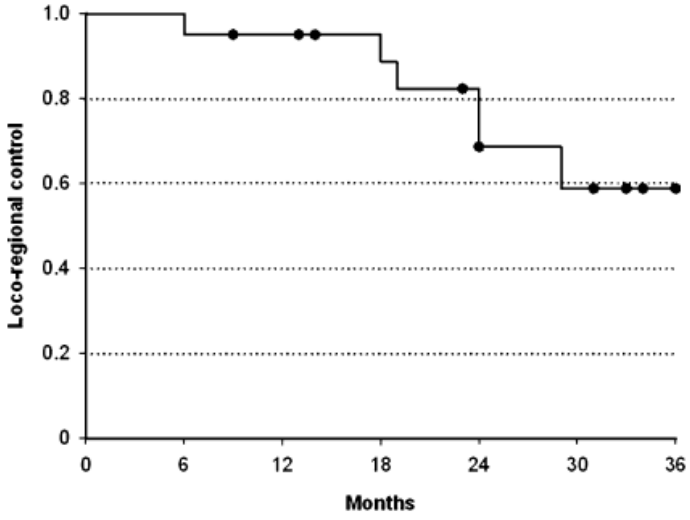
Emilio Minatel[a], Marco Trovo[a,*], Jerry Polesel[b], Tania Baresic[c], Alessandra Bearz[d], Giovanni Franchin[a], Carlo Gobitti[a], Imad Abu Rumeileh[a], Annalisa Drigo[e], Paolo Fontana[f], Vittore Pagan[g], Mauro G. Trovo[a]

Age median (y)	68 (52–80)
Gender	
Male	18
Female	2
Performance status	
0–1	12
2	8
Laterality	
Right	11
Left	9
Histology	
Epithelioid	18
Non-epithelioid	2
Stage	
I	3
II	5
III	11
IV (T4)	1
Nodal status	
N0	17
N1–2	3
Gross residual disease after surgery	
No	17
Yes	3
Chemotherapy	
Yes	19
No	1

The spinal cord, ipsilateral and contralateral kidney, contralateral lung and the dummy structure were the dose-limiting tissues. Specific dosimetric guidelines were the following: spinal cord maximum dose <45 Gy; ipsilateral and contralateral kidney V25 (percentage of kidney volume receiving 25 Gy) <40% and V10 < 10%, respectively; liver V30 < 40%; contralateral mean lung dose <7 Gy; dummy structure mean dose <36 Gy. No specific dosimetric constraints were required for ipsilateral lung or total lung. Dose-volume histograms (DVHs) were generated for all relevant structures for each of the 20 plans. Specific metrics were chosen to report dosimetric data in terms of dose distribution to the organs at risk (OAR) (Table 1).

Pattern of failure among study patients.

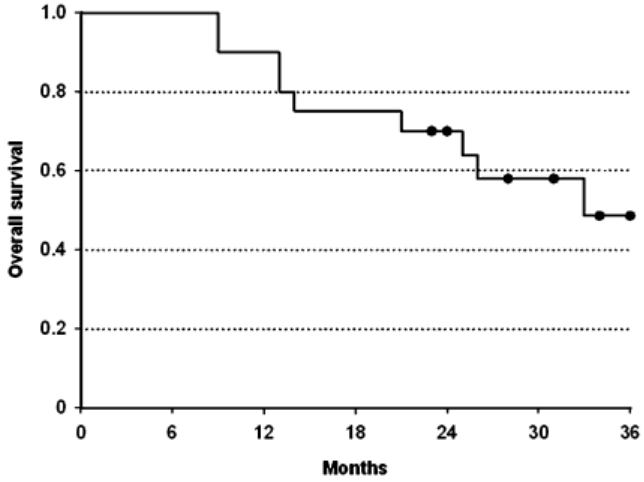
Local	4
Local only	1
Local and nodal	1
Local and distant	0
Local, nodal and distant	2
Nodal	5
Nodal only	1
Nodal and distant	1
Distant	7
Distant only	4



Patients at risk	20	19	17	14	9	6	2
Events	0	1	1	1	5	6	6

Main severe radiation adverse effects.

	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
Pneumonitis	3 (15%)	2 (10%)	–
Pericardial effusion	–	1 (5%)	1 (5%)
Thrombocytopenia	–	1 (5%)	–
Chest wall pain	–	1 (5%)	–



Patients at risk	20	20	18	15	12	7	2
Events	0	0	2	5	6	8	9

Hemithoracic Intensity Modulated Radiation Therapy After Pleurectomy/Decortication for Malignant Pleural Mesothelioma: Toxicity, Patterns of Failure, and a Matched Survival Analysis

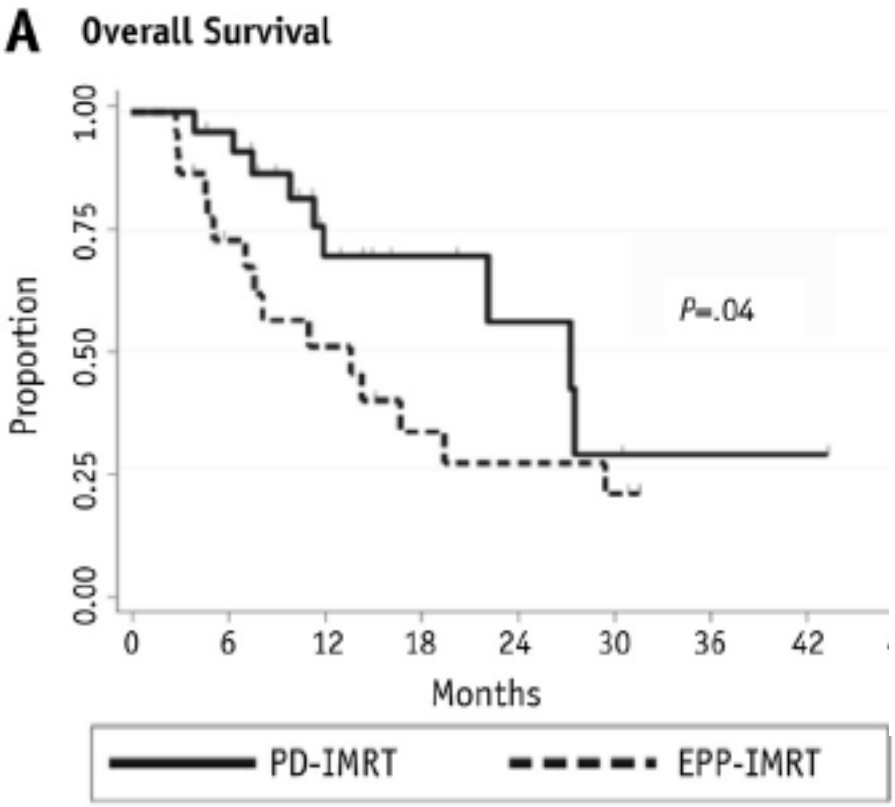
William W. Chance

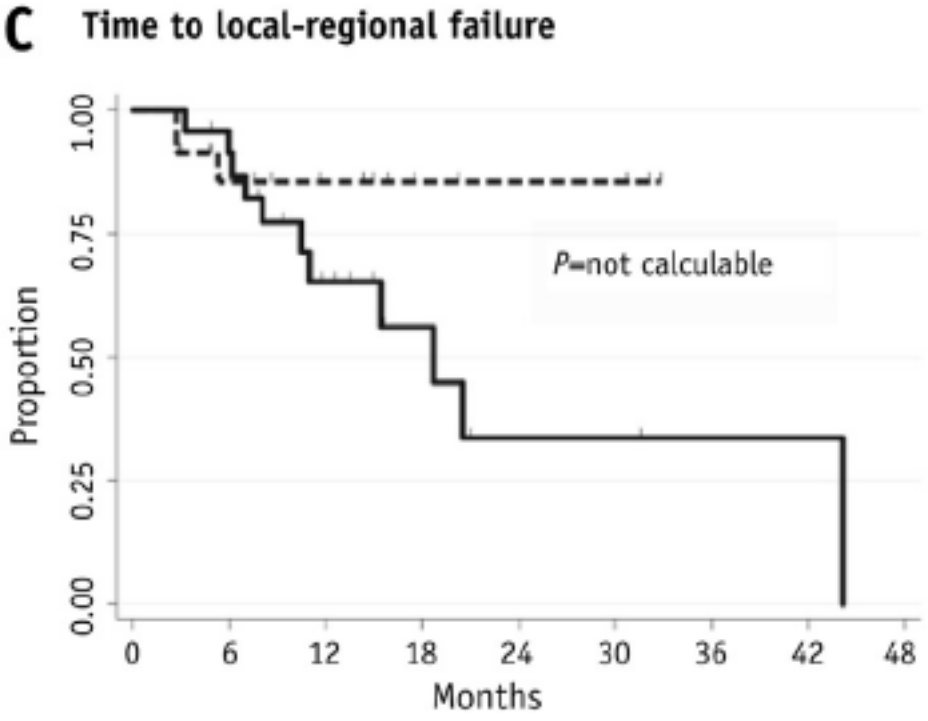
Int J Radiation Oncol Biol Phys, Vol. 91, No. 1, pp. 149–156, 2015

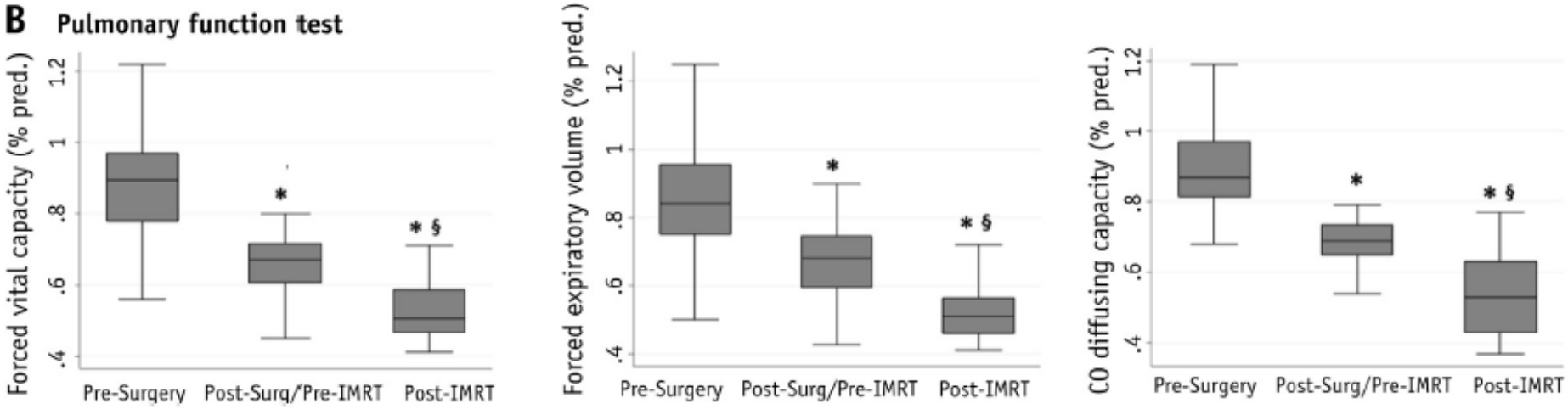
Characteristic	PD-IMRT (n=24)	EPP-IMRT (n=24)
Age (y), median (range)	65 (42-75)	64 (48-76)
Sex		
Female	7	1
Male	17	23
Disease location		
Left	14	8
Right	10	16
ECOG PS at diagnosis		
0	4	8
1	20	16
pT Status		
T1-T2	9	4
T3	11	18
T4	4	2
pN Status		
N0	16	16
N1	0	0
N2	8	8
Tumor histology		
Epithelioid	19	18
Sarcomatoid/biphasic	5	6
Chemotherapy		
None	2	2
Induction	17	17
Other	5	5

Table 2 Dosimetric variables by treatment group

Characteristic	PD-IMRT (n=24)	EPP-IMRT (n=24)
Total lung V_{20} (%)	35 (24-56)	-
Mean lung dose, total lung (Gy)	19.3 (19.3-27.8)	-
Mean lung dose, contralateral lung (Gy)	4.9 (0.2-8.7)	6.7 (4.3-8.4)
Mean lung dose, ipsilateral lung (Gy)	46.4 (38.0-52.0)	-
Heart V_{40} (%)	23 (7-38)	-
Mean heart dose (Gy)	26.2 (16.8-33.8)	26.5 (16.4-38.3)
Mean esophageal dose (Gy)	28.3 (14.3-41.1)	36.4 (29.5-44.9)
Liver V_{30}, right-sided tumors (%)	47 (23-51)	-
Liver V_{30}, left-sided tumors (%)	2 (0-4)	-


A
Overall Survival
Proportion
0.00
0.25
0.50
0.75
1.00
0
6
12
18
24
30
36
42
Months
P=.04
PD-IMRT
EPP-IMRT

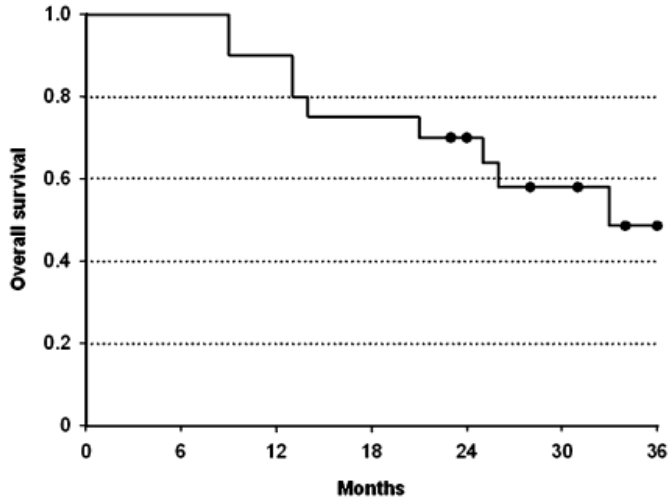

C
Time to local-regional failure
Proportion
0.00
0.25
0.50
0.75
1.00
0
6
12
18
24
30
36
42
48
Months
P=not calculable


B
Pulmonary function test
Forced vital capacity (% pred.)
Forced expiratory volume (% pred.)
CO diffusing capacity (% pred.)
.4
.6
.8
1
1.2
*
* §
Pre-Surgery
Post-Surg/Pre-IMRT
Post-IMRT

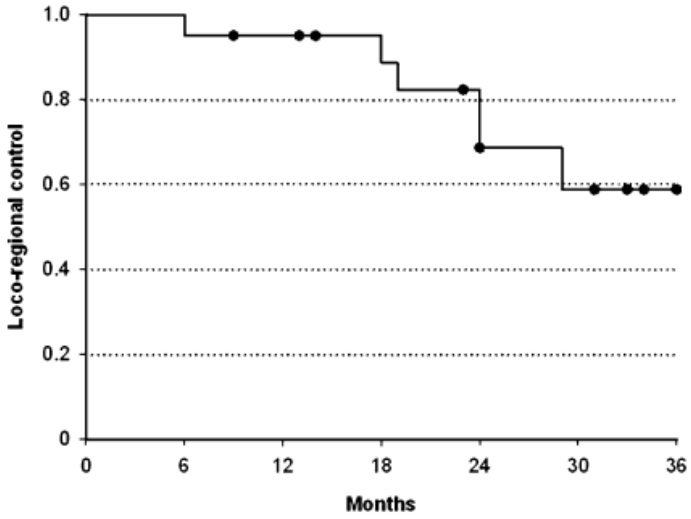
Hemithoracic Intensity Modulated Radiation Therapy After Pleurectomy/Decortication for Malignant Pleural Mesothelioma: Toxicity, Patterns of Failure, and a Matched Survival Analysis

Table 3 Toxicity by treatment group

Toxicity type and grade	PD-IMRT (n=24)	EPP-IMRT (n=24)
Gastrointestinal		
0-1	5	3
2	19	18
3	0	3
Dermatitis		
0-1	19	18
2	3	2
3	2	4
Pulmonary		
0-1	15	19
2	7	2
3	2	0
4	0	1
5	0	2
Fatigue		
0	5	-
1	9	-
2	10	-
Hematologic*		
0	8	-
1	2	-
2	3	-
3	2	-
4	1	-

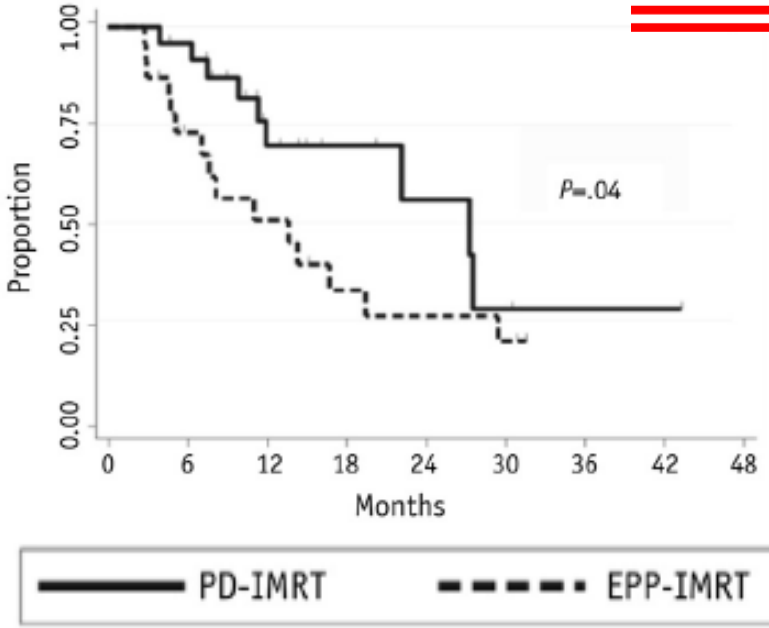


Patients at risk	20	20	18	15	12	7	2
Events	0	0	2	5	6	8	9

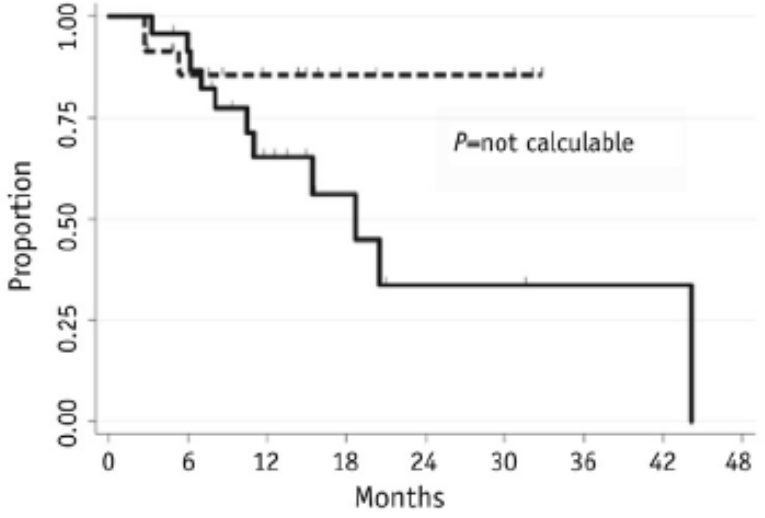


Patients at risk	20	19	17	14	9	6	2
Events	0	1	1	1	5	6	6

A Overall Survival



C Time to local-regional failure



Pleural IMRT

- Lung-sparing IMRT (alone or after P/D) has been proven feasible and safe, with delivered RT doses ranging from 47 to 55 Gy and grade $\geq$ 3 toxicity rates of 20-30%
- IMRT strictly required
- Adequate clinical endpoints (PFTs after lung sparing IMRT)
- Adjuvant irradiation after P/D is not recommended outside clinical trials (ongoing trials)

The "SMART" Approach for Resectable Malignant Pleural Mesothelioma

B. C. John Cho

Journal of Thoracic Oncology® • Volume 9, Number 3, March 2014

Study Schema

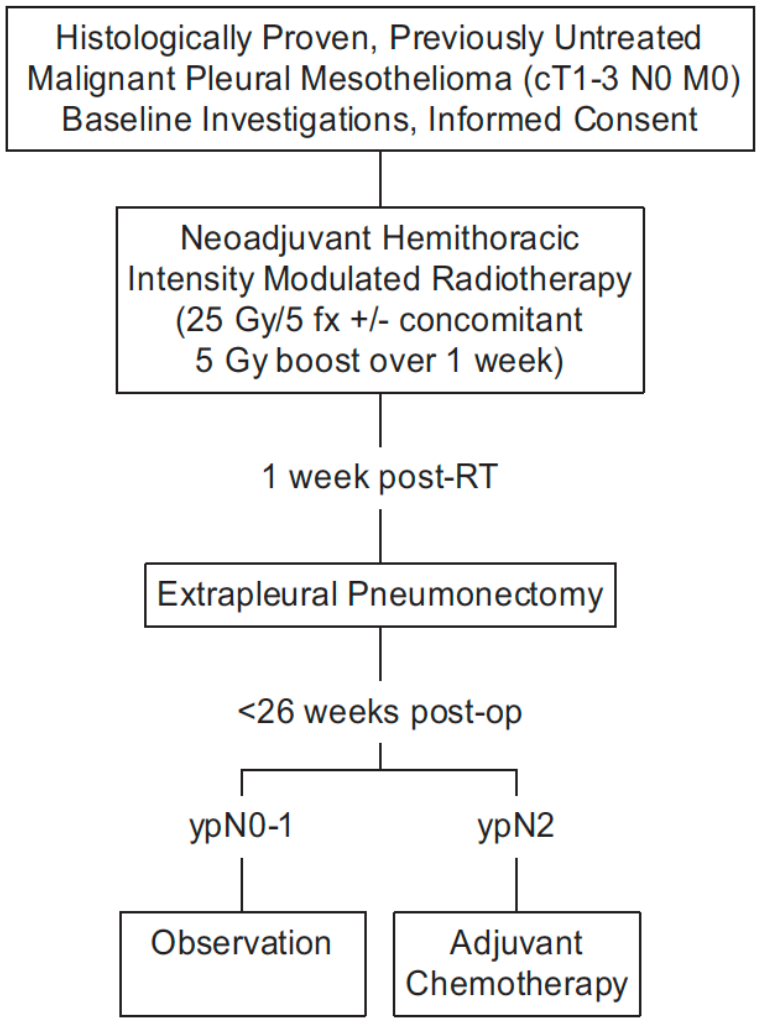
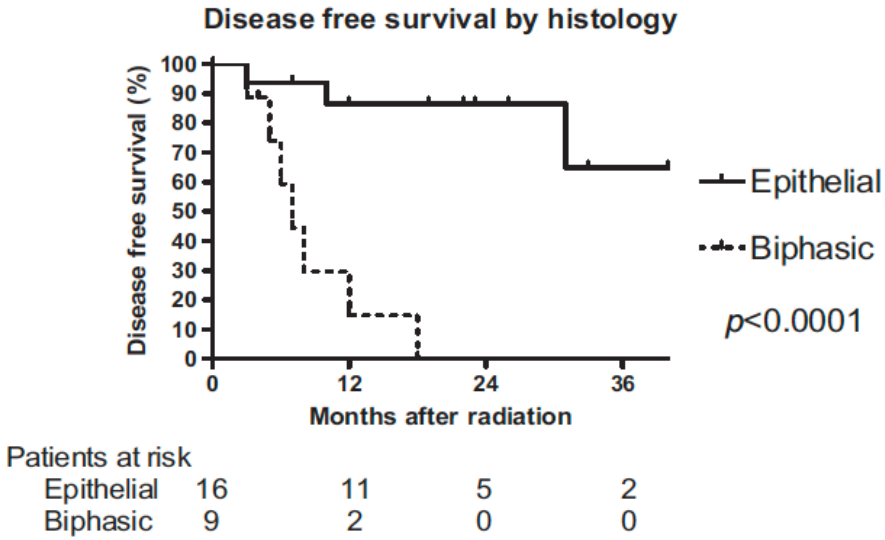


TABLE 2. Complications after SMART

Grade	0	1	2	3	4	5
Thromboembolic event	22	0	1	1	1	0
Atrial fibrillation	15	0	5	5	0	0
Wound infection	22	0	2	1	0	0
Chylothorax	23	0	0	2	0	0
Hemothorax	24	0	0	0	1	0
Wound dehiscence	21	1	2	1	0	0
Renal dysfunction	24	0	0	1	0	0
Pneumonia	24	0	0	0	1	0
Empyema	23	0	0	1	0	1

Some patients can present more than one complication.



Conclusions: RT and MPM

- Still dismal prognosis
- Unclear if any local treatment changes long-term survival
- No definitively “proven” effective local treatment
- Need for better local (radiosensitizing drugs) and systemic treatments

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Second Italian Consensus Conference on Malignant Pleural Mesothelioma: State of the art and recommendations

Carmine Pinto [a,*], Silvia Novello [b], Valter Torri [c], Andrea Ardizzoni [d], Pier Giacomo Betta [e], Pier Alberto Bertazzi [f], Gianni Angelo Casalini [g], Cesare Fava [h], Bice Fubini [i], Corrado Magnani [j], Dario Mirabelli [k], Mauro Papotti [b], Umberto Ricardi [l], Gaetano Rocco [m], Ugo Pastorino [n], Gianfranco Tassi [o], Lucio Trodella [p], Maurizio Zompatori [q], Giorgio Scagliotti [b]

Cancer Treatment Reviews xxx (2012)

- ✓ Systematic adjuvant irradiation of surgical tracts is not routinely indicated
- ✓ Positive role of palliative hypofractionated radiotherapy
- ✓ For patients with resectable MPM, who undergo EPP (after neoadjuvant chemotherapy), adjuvant radiotherapy can be recommended for selected and fit patients (50-54 Gy in 1.8-2 Gy daily fractions)
- ✓ IMRT: promising treatment technique (adequate experience required); special attention to reduce radiation exposure of the remaining lung (strict dose constraints)
- ✓ Adjuvant irradiation after P/D is not recommended outside clinical trials