SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Parma

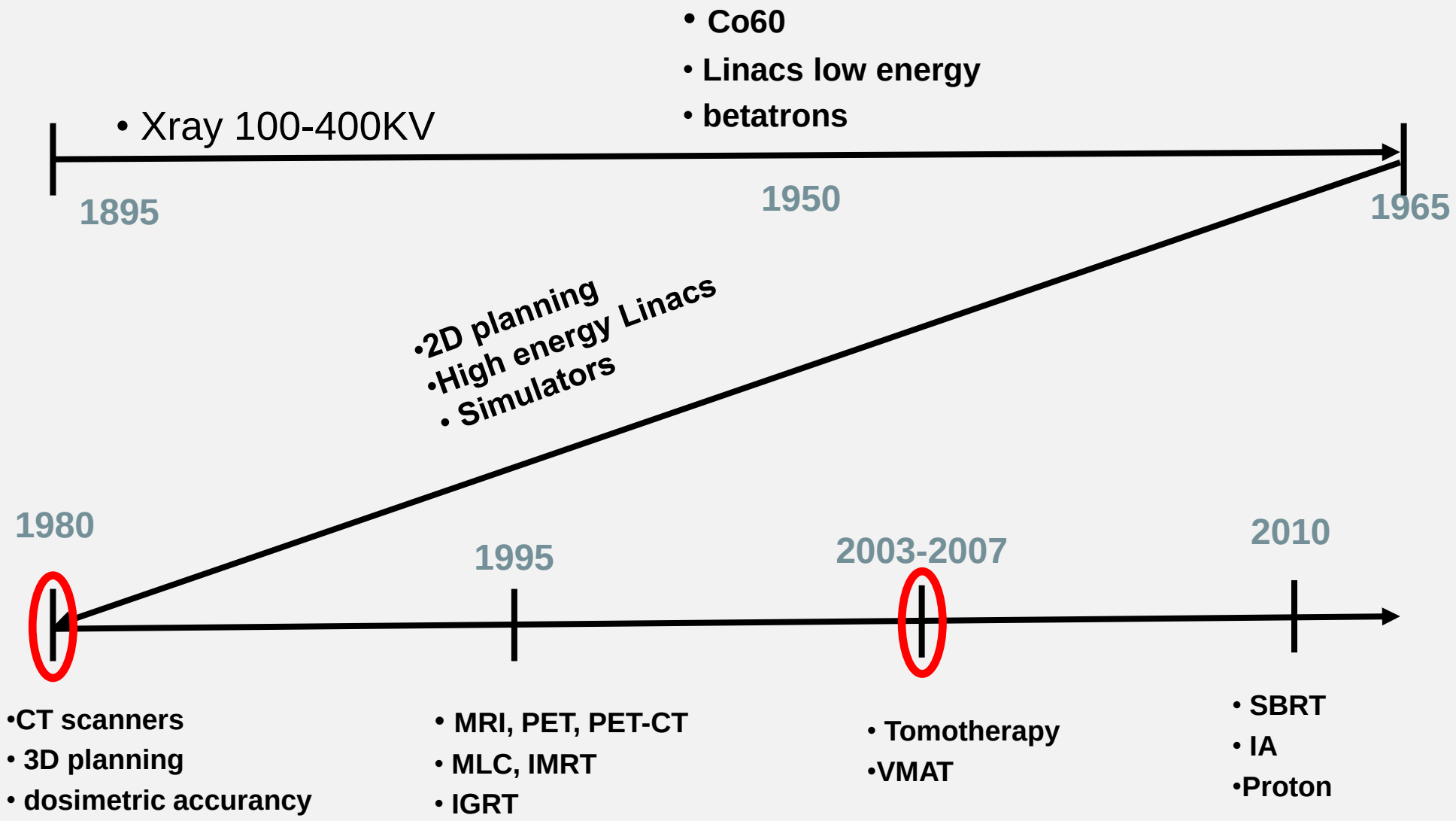
IL PERCORSO ASSISTENZIALE E LE PROSPETTIVE TERAPEUTICHE PER IL MESOTELIOMA PLEURICO NELLA REGIONE EMILIA ROMAGNA

QUANDO LA RADIOTERAPIA

Dr.ssa N. D'Abbiero Direttore UOC di Radioterapia

BOLOGNA 2 MARZO 2022

RADIOTHERAPY FROM THE BEGINNING UNTIL TODAY



GUIDELINES

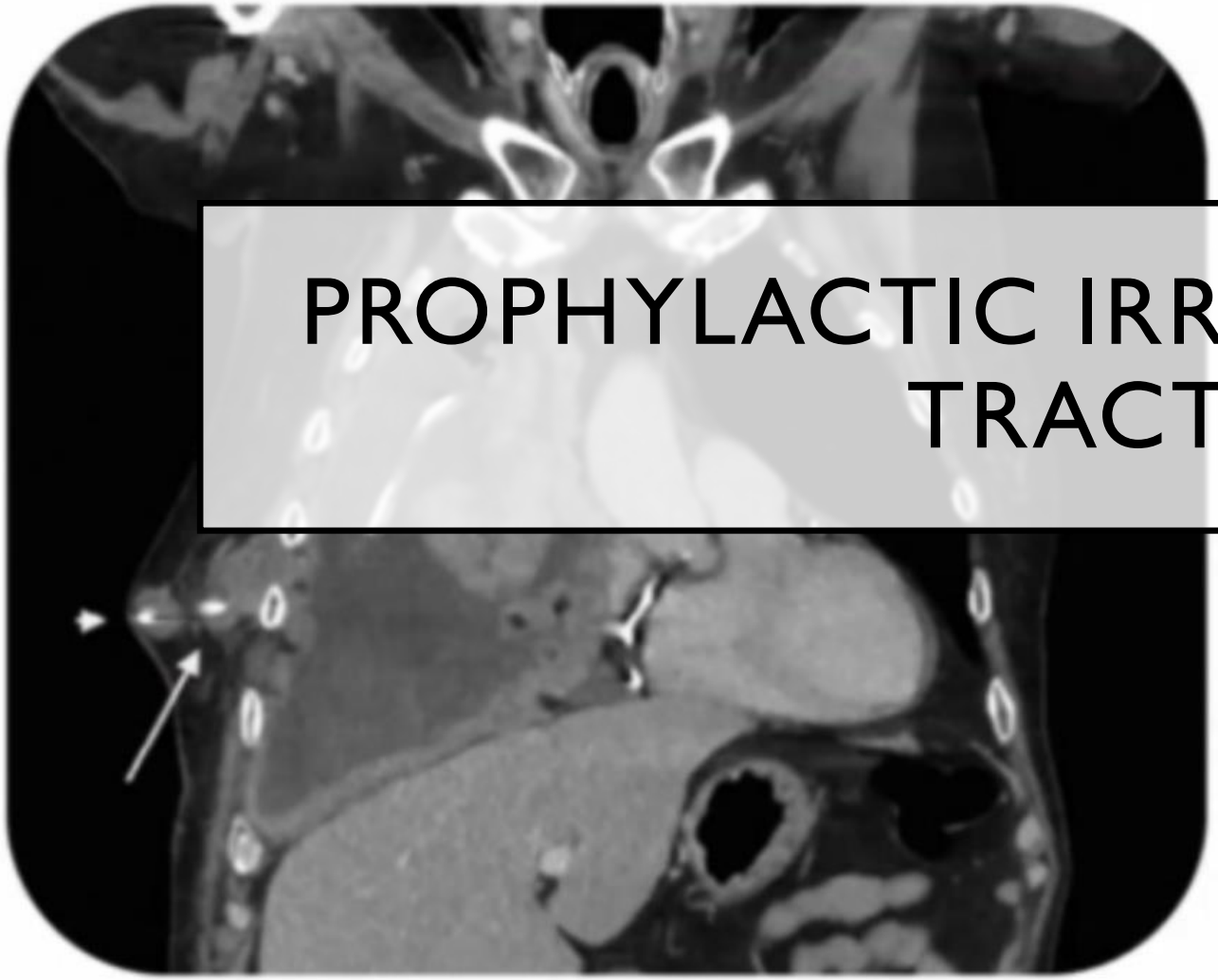
British Thoracic Society Guideline for the investigation and managementy of malignant pleural mesothelioma
Thorax 2018

Treatment of malignant Pleural Mesothelioma: American Society of Clinical Oncology – Clinical Practice Guideline
JCO 2018

ERS/ESTS/EACTS/ESTRO guidelines for the management of malignant mesothelioma.
Eur Resp J 2020

Malignant pleural mesothelioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up
TBP 2021

PROPHYLACTIC IRRADIATION OF TRACTS



A LOT OF CLINICAL STUDIES…

Table 1 Summary of randomised studies of prophylactic radiotherapy to procedure tract metastases

Lead author	Year	Sample size (n)	Radiation therapy field used	Prescribed radiation dose	Primary endpoint	Key result
Boudin, *et al.* (14)	1995	40	2.5 to 15 MeV electrons with 1 cm bolus	21 Gy in 3 fractions	Incidence of tract metastases	0% (RT) *vs.* 40% (non-RT), P<0.001
Bydder, *et al.* (16)	2004	43 (but 58 tract sites analysed)	Direct 9 MeV electrons	10 Gy single fraction	Incidence of tract metastases (median follow-up 8.7 months)	7% (RT) *vs.* 10% (non-RT), P=0.53
O'Rourke, *et al.* (17)	2007	61	6 cm circle, direct electrons	21 Gy in 3 fractions	Incidence of tract metastases (median follow-up 8 months)	12.9% (RT) *vs.* 10.0% (non-RT), P=0.748 (negative)
Clive, *et al.* (18)	2016	203	2 cm all directions	21 Gy in 3 fractions	Incidence of procedure tract metastases at 12 months	9% (immediate RT) *vs.* 16% (deferred RT), P=0.14
Bayman, *et al.* (19)	2019	374	3-cm Lateral/inferior borders; variable superior border, direct electrons	21 Gy in 3 fractions	Incidence of ipsilateral chest wall metastases at 6 months	3.2% *vs.* 5.3%, P=0.44 (negative)

Poor evidence

SMART TRIALS: INCIDENCE OF CHEST WALL METASTASES

	Immediate RT N (%)	**Deferred RT N (%)**	**Treatment effect % (95% CI)**	**P-value**
Primary ITT analysis Number of patients developing CWM within 7 cm of procedure @12 months	9/102 (8.8)	16/101 (15.8)	7 %	0.141
Number of patients developing a chest wall nodule anywhere on the ipsilateral hemitorax	13/102 (12.8)	16/101 (15.8)	3.1 %	0.554

Clive, Lancet Oncol 2016

Incidence of CWM within 7 cm of the margins of the procedure site at 12 months **N=203**

PIT TRIALS: INCIDENCE OF CHEST WALL METASTASES

Time from radomisation	PIT (n= 186)	NO PIT (N=189)	OR p-Value
6 months	6 (3.2%)	10 (5.3 %)	0.60 p=0.44
12 months	15 (8.1 %)	19 (10.1 %)	0.79. p= 0.59

Incidence of ipsilateral CWM al 6 months
N= 374

Bayman JCO 2019

SMART AND PIT COMPARISON

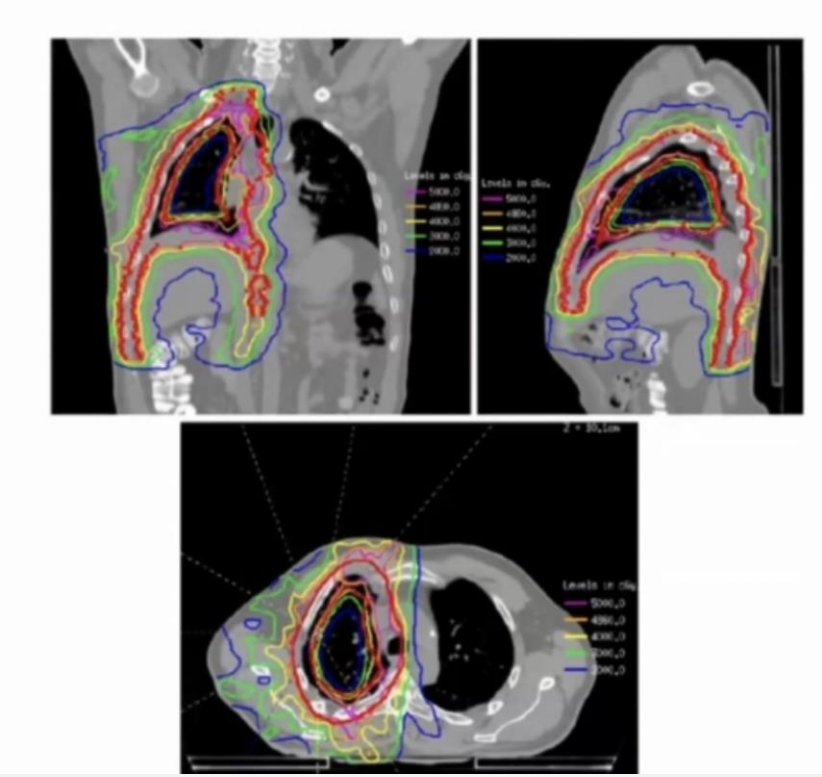
Characteristic	**PIT**	**SMART**
Sample size	374	203
Open Thoracoscopy	NO	YES
Toracoscopy	YES	YES
Indwelling pleural catheters	NO	YES
RT field size	3 cm lateral/inferior borders, variable superior border	2 cm all directions
RT dose	21 Gy in 3 fractions/3 days	21 Gy in 3 fractions/3 days
Primary end point	Incidence of ipsilateral CWM at 6 months	Incidence of CWM within 7 com of the margins of the procedure at 12 months

ERS/ESTS/EACTS/ESTRO GUIDELINES

Should radiotherapy be used to prevent procedure-tract metastases in patients with MPM ?

Recommendation: we do not recommend prophylactic drain site radiotherapy in routine clinical care (strong recommendation, moderate quality of evidence)

POST/PERIOPERATIVE RADIOTHERAPY

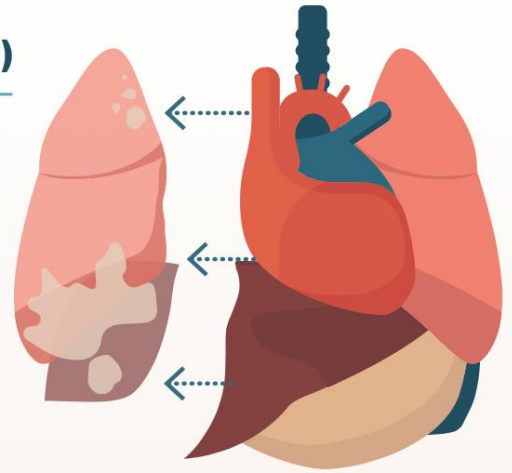


Most of the studies done in the contest of EPP
No longer a standard surgical procedure

Extrapleural Pneumonectomy (EPP)

EPP removes:

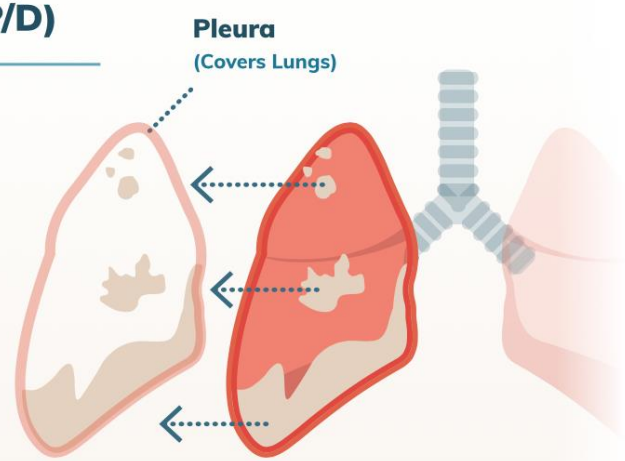
- the affected lung
- the lung lining (pleura)
- any cancerous portion of the diaphragm or pericardium.



Pleurectomy /Decortication (P/D)

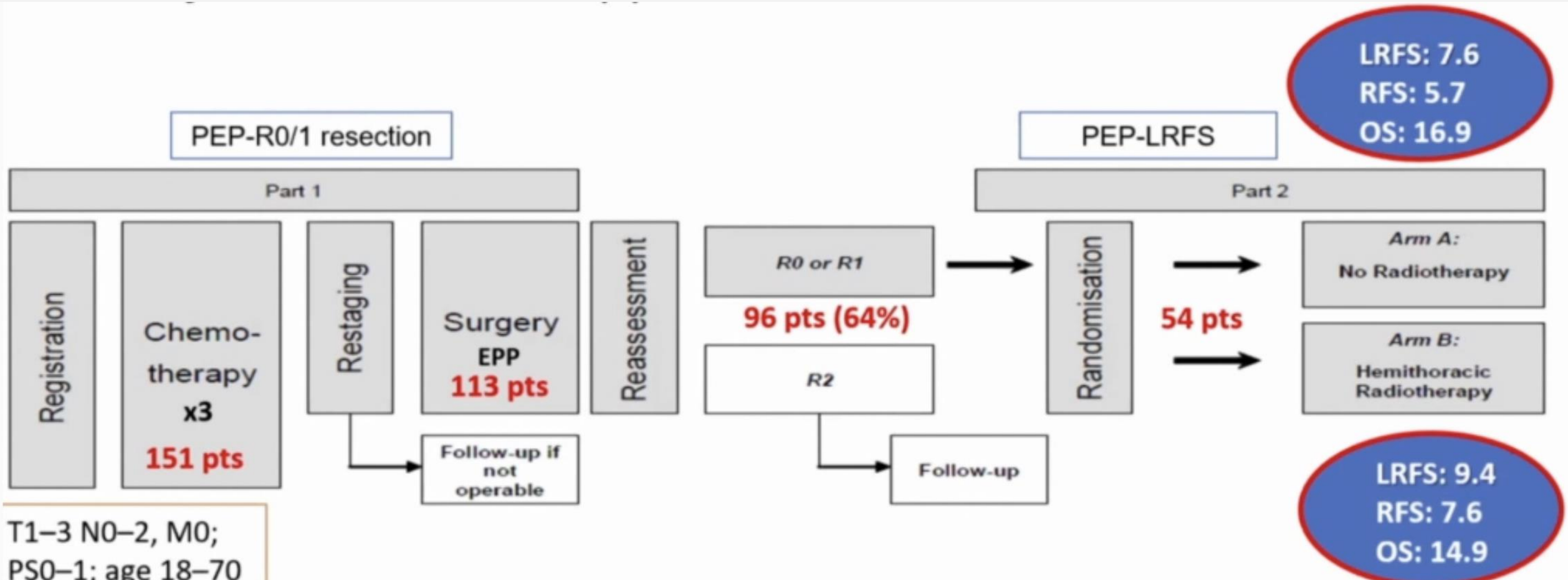
P/D removes :

- the tissue covering the affected lung (the pleura)
- a portion of the diaphragm
- a portion of the tissue covering the heart (the pericardium)



Neoadjuvant chemotherapy and extrapleural pneumonectomy of malignant pleural mesothelioma with or without hemithoracic radiotherapy (SAKK 17/04): a randomised, international, multicentre phase 2 trial

Lancet Oncol 2015



- Primary endpoint was locoregional relapse-free survival (LRFS)
- No significant difference observed between the two arms (9.4 months versus 7.6 months)
- Closed early due poor accrual and was therefore underpowered

Clinical Trial > Lancet Oncol. 2015 Dec;16(16):1651-8. doi: 10.1016/S1470-2045(15)00208-9. Epub 2015 Nov 2.

Neoadjuvant chemotherapy and extrapleural pneumonectomy of malignant pleural mesothelioma with or without hemithoracic radiotherapy (SAKK 17/04): a randomised, international, multicentre phase 2 trial

Rolf A Stahel [1], Oliver Riesterer [2], Alexandros Xyrafas [3], Isabelle Opitz [4], Michael Beyeler [5], Adrian Ochsenbein [6], Martin Früh [7], Richard Cathomas [8], Kristiaan Nackaerts [9], Solange Peters [10], Christoph Mamot [11], Alfred Zippelius [12], Carlo Mordasini [13], Clemens B Caspar [14], Katrin Eckhardt [5], Ralph A Schmid [15], Daniel M Aebersold [16], Oliver Gautschi [6], Wolfgang Nagel [17], Michael Töpfer [18], Jerome Krayenbuehl [2], Karin Ribi [19], Ilia Ciernik [20], Walter Weder [4]

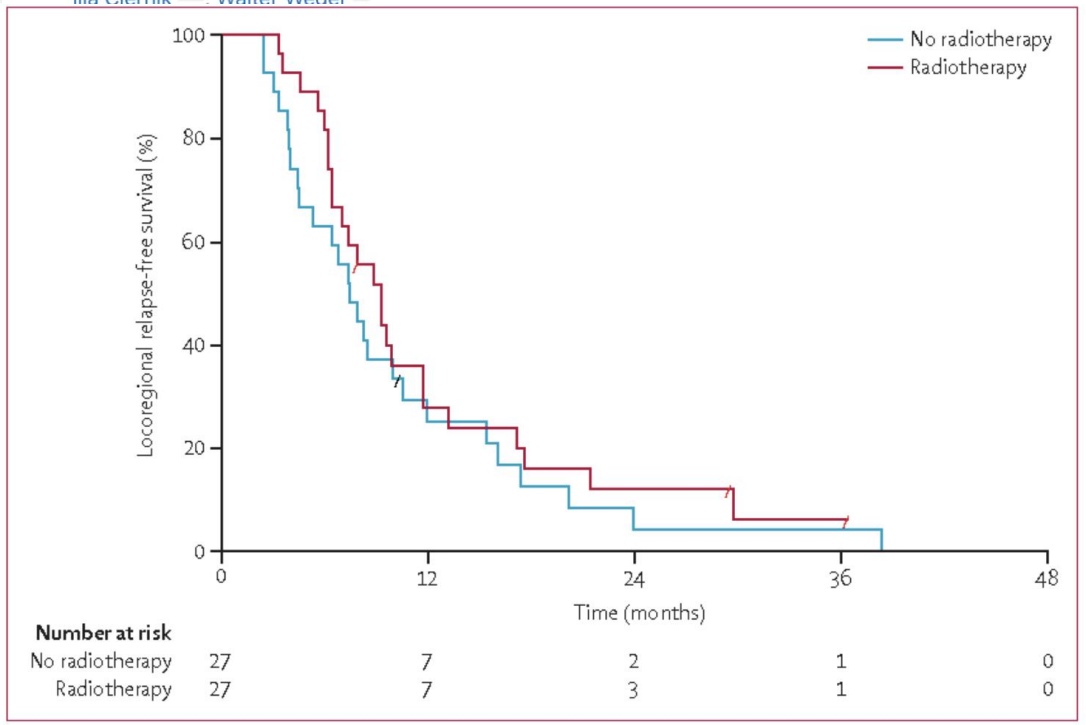
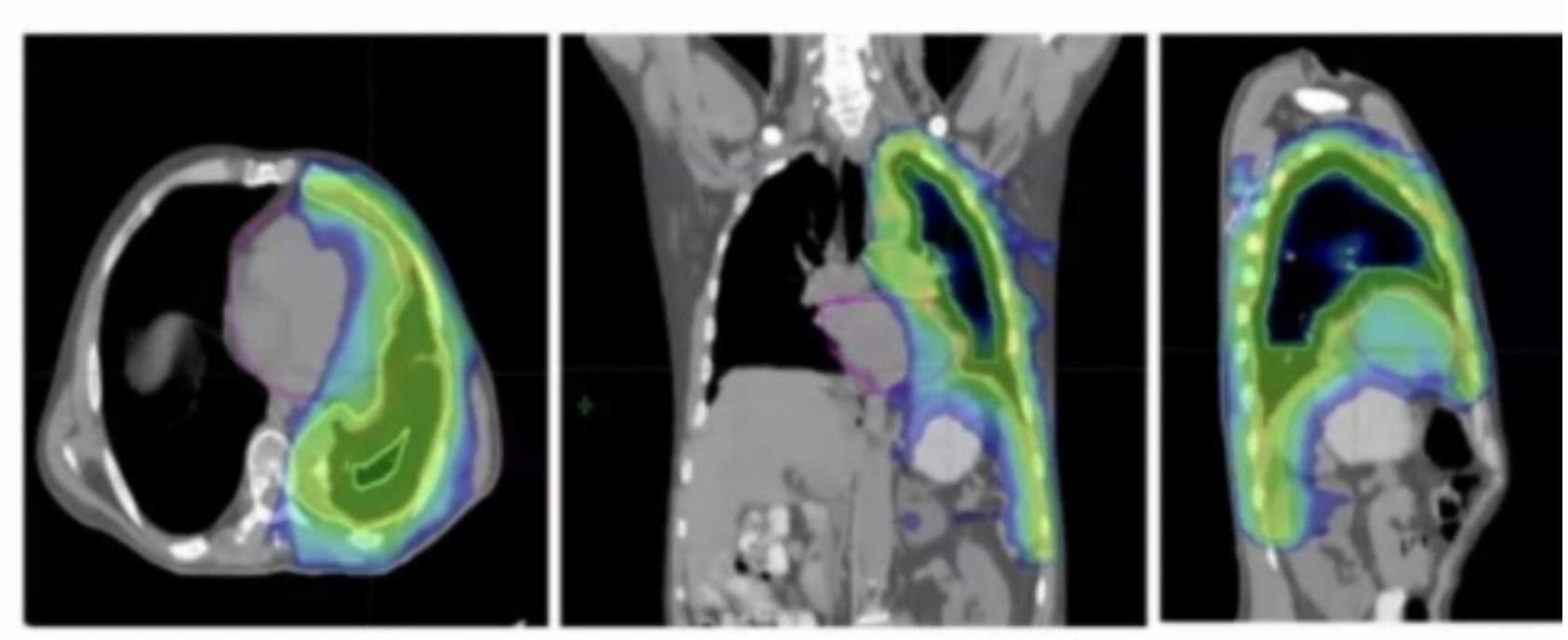


Figure 2: Kaplan-Meier analysis of locoregional relapse-free survival from surgery



RT AFTER PLEURECTOMY/DECORTICATION (P/D)

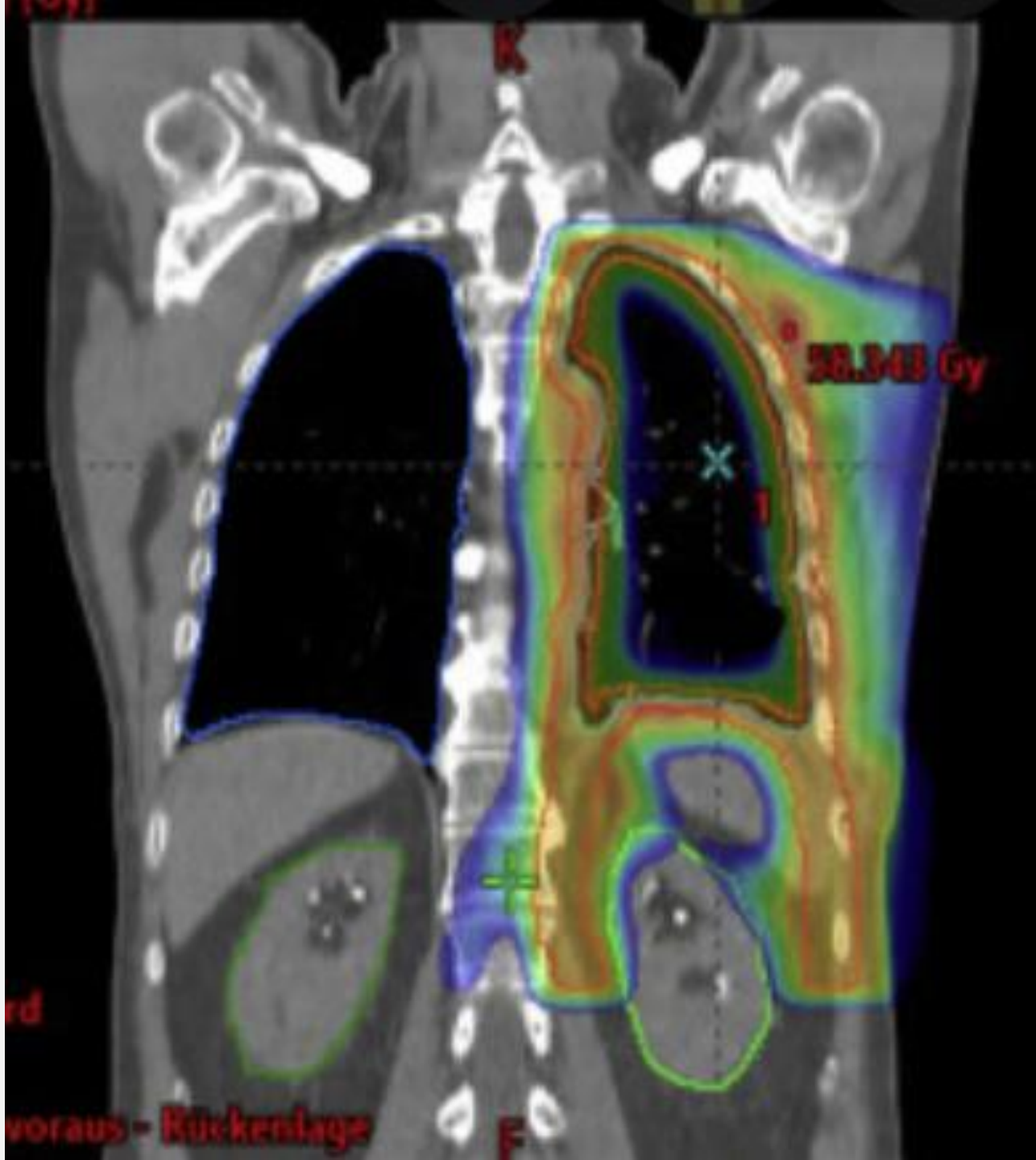
P/D HAS BECOME A COMMON SURGICAL APPROACH (LUNG SPARING)

Two prospetcive studies demonstrated that hemithoracic pleural IMRT:

- Is feasible
- Has an accepatable toxicity profile
- Median survival up to 26 months

Minatel E. Red J 2015

Rimner A. JCO 2016



«RADIOTHERAPY DOUBLES SURVIVAL FOR PATIENTS WITH MESOTHELIOMA»

Radical Hemithoracic Radiotherapy Versus Palliative Radiotherapy in Non-Metastatic Malignant Pleural Mesothelioma: Results from a Phase 3 Randomized Clinical Trial

Radical Hemithoracic Radiotherapy Versus Palliative Radiotherapy in Non-Metastatic Malignant Pleural Mesothelioma: Results from a Phase 3 Randomized Clinical Trial

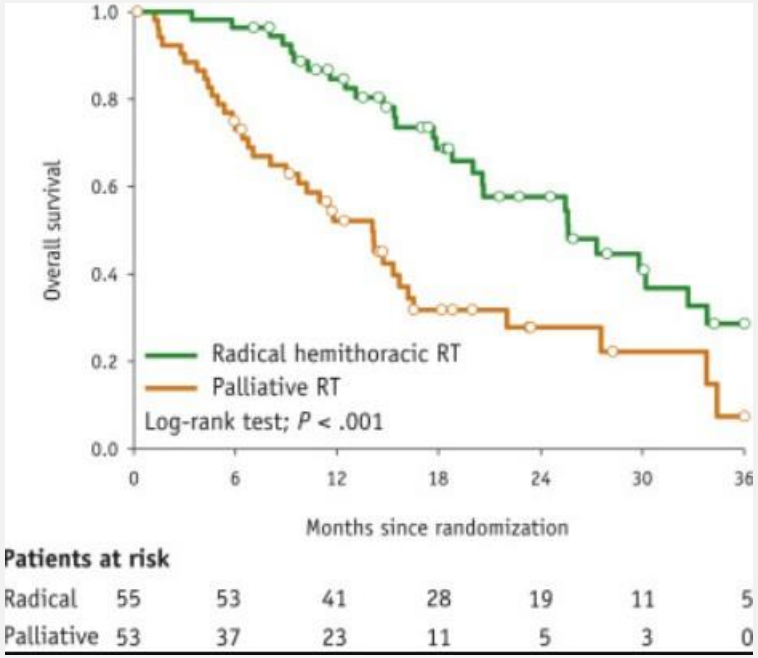
Hypotesis: local control will translate into survival advantage

Histologically confirmed MPM, lung sparing surgery (proven gross residual disease) and chemotherapy
PS 0-2

RHRT arm (55 pts)
Radical hemitoracic VMAT
50 Gy in 25 fr to pleural cavity + SIB of 60 Gy to gross disease

PRT arm (53 pts)
Palliative radiation therapy
20-30 Gy in 3-10 fr

Trovò, Red J 2021



- **108 pts randomized.** Median follow-up 14.6 months
- **2-year OS** 58 % in the RHRT arm vs 28 % in the PRT arm (HR 0.54; 95% CI, 0.31-0.95; P= 0.031
- **Median OS** 25.6 months in the RHRT arm vds 12.4 months in the PRT arm (P< .001)
- **Toxicity**
  - RHRT arm: 11 pts experienced acute toxicity grade 3+ (20%), 17 pts had grade 3-4 late toxicity (31%) 2 pts had grade 3 pneumonitis (4%) and 1 grade 5 (2%)
  - PRT arm: no grade 3+ toxicity

Phase III Randomized Trial of Pleurectomy/Decortication Plus Chemotherapy With or Without Adjuvant Hemithoracic Intensity-Modulated Pleural Radiation Therapy (IMPRINT) For Malignant Pleural Mesothelioma (MPM)

On going

Eligibility:
- Stage I-III MPM
- Resectable by lung-sparing P/D
- Epithelioid or biphasic subtype
- Age ≥18 and ≤80 years
- KPS ≥80%
- FEV1 ≥40%, DLCO ≥40% predicted

P/D (MCR)

Pemetrexed (500mg/m2) + Cisplatin (or carboplatin) (75mg/m2)

q21 days x4 cycles

R

1:1
n=150

IMPRINT (50.4/60 Gy in 28 fractions)

No adjuvant IMPRINT

Permissible alternatives:
- Neoadjuvant chemo → P/D
- Intensity-Modulated Proton Therapy

Andreas Rimner, MD
Radiation Oncologist
Memorial Sloan Kettering Cancer Center

Stratification
Cell type: Epithelioid vs biphasic
Macroscopic complete resection: R0/R1 vs R2
Center patient volume: ≤ 10 vs > 10 P/D per year

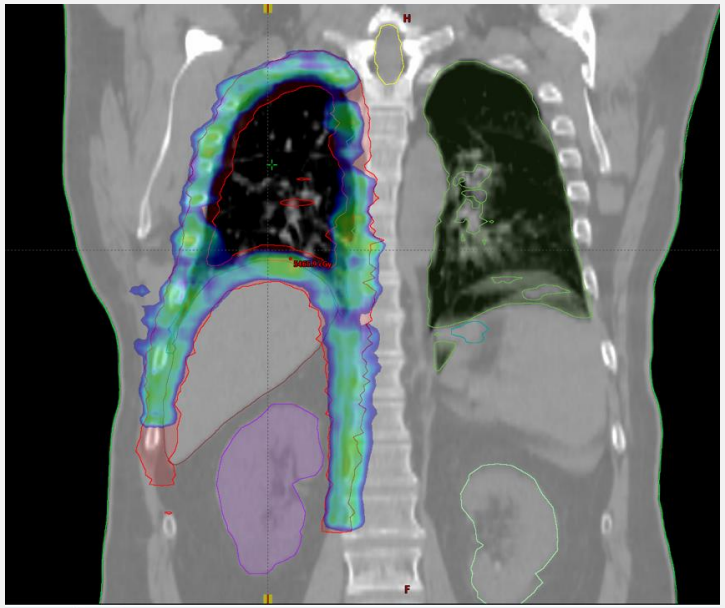
Primary Objective:
Improvement in median OS from 12 months (null hypothesis) to 20 months (alternative hypothesis)

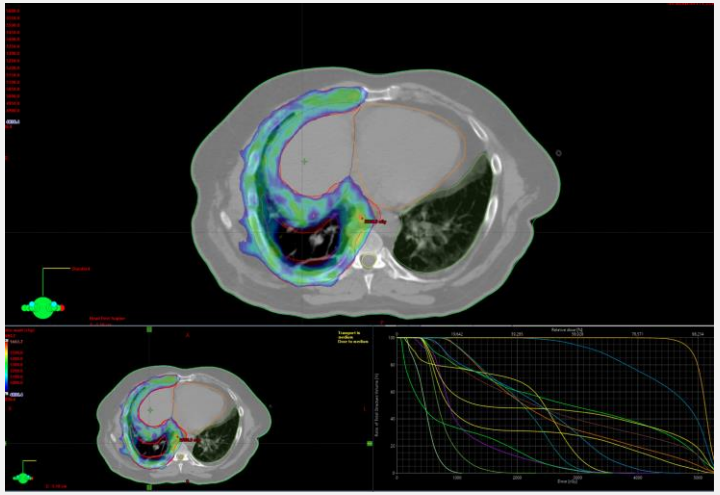
ERS/ESTS/EACTS/ESTRO GUIDELINES

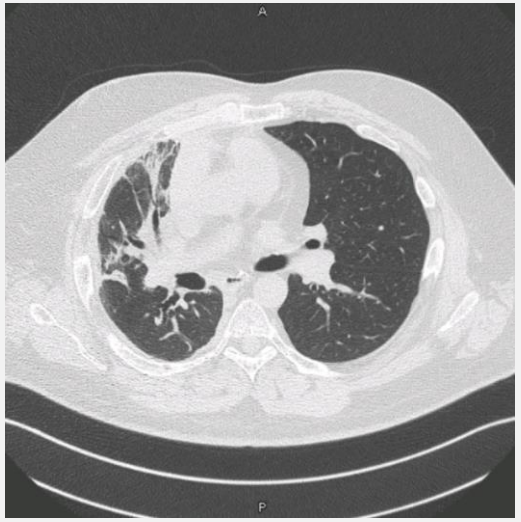
Should adjuvant post-operative radiotherapy be used in patients with MPM?

Recommendation: Radiotherapy after pleurectomy/decortication or after EPP should only considered within the context of clinical trials and/or included in national/international registries

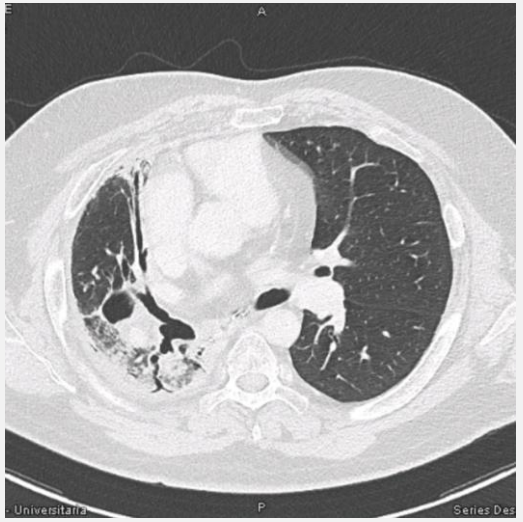
PARMA EXEPERIENCE (1)





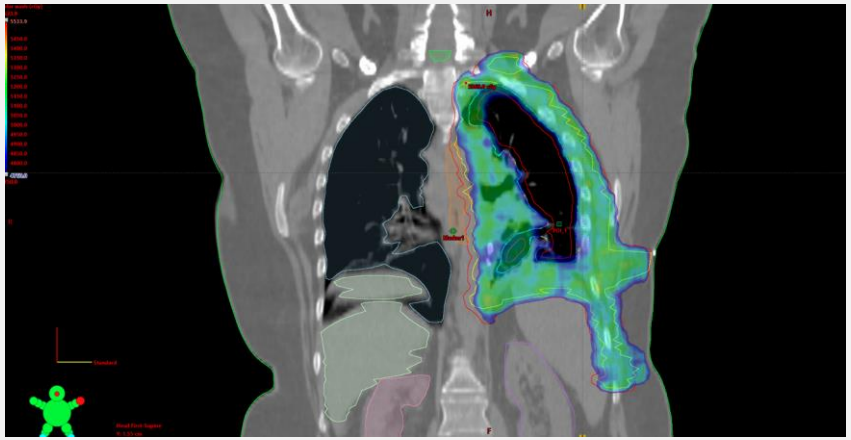


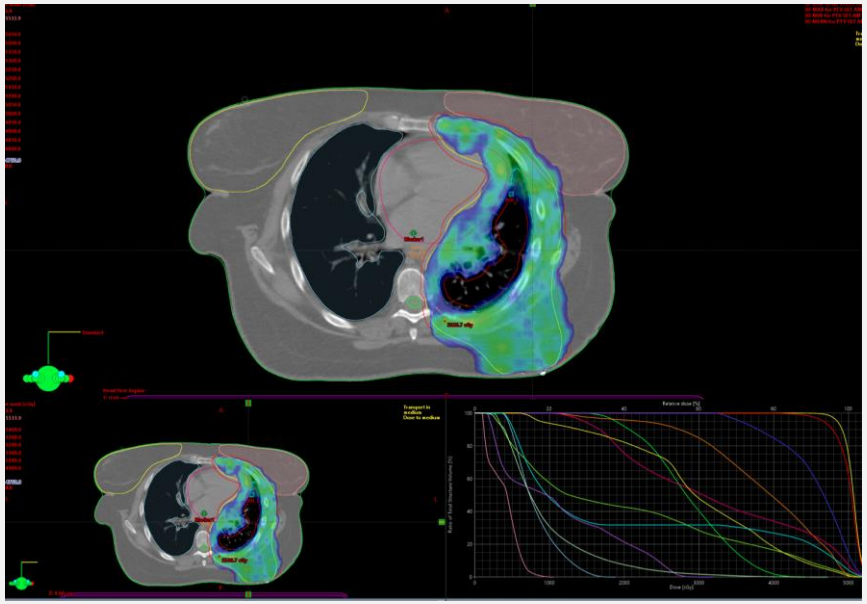
Jan 2021

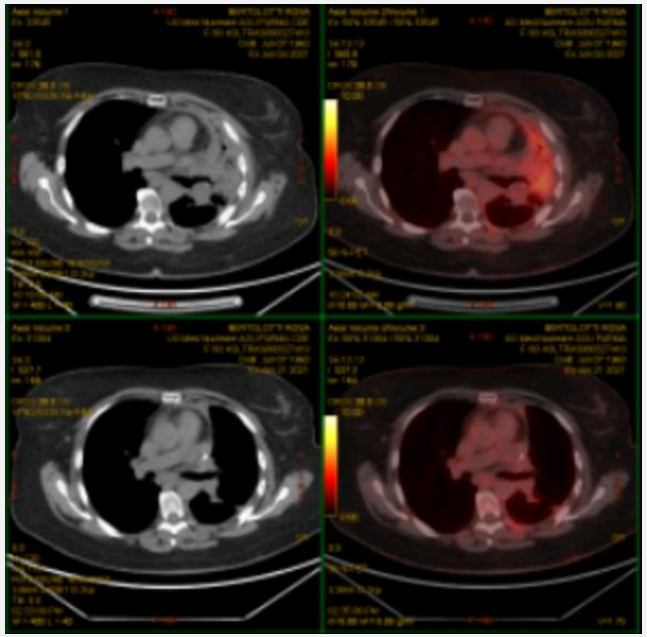


Nov 2022

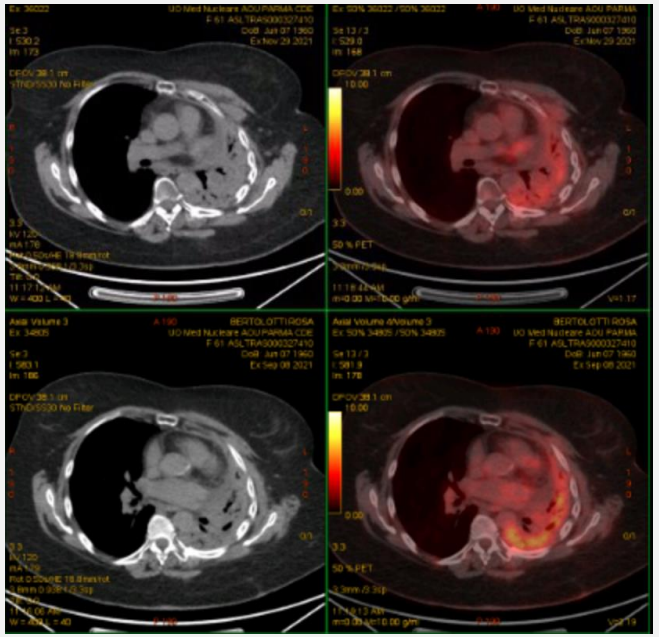
PARMA EXEPERIENCE (2)







Jan 2021



Jun 2021

PREOPERATIVE RT

Surgery for malignant pleural mesothelioma after radiotherapy (SMART): final results from a single-centre, phase 2 trial

B C John Cho, Laura Donahoe, Penelope A Bradbury, Natasha Leighl, Shaf Keshavjee, Andrew Hope, Prodipto Pal, Michael Cabanero, Kasia Czarnecka, Karen McRae, Ming-Sound Tsao, Marc de Perrot

- Phase II feasibility
- PS 0-2, histologically proven, resectable, cT1-3 N0M0
- 25 Gy in 5 fr to the entire ipsilateral hemithorax with concomitant 5 Gy boost to high risk areas
- EPP at a median of 5 days (2-12) after RT
- 102 pts enrolled, 96 treated with SMART
- Feasibility – numer of patients with grade 3-5 within 30 days of surgery (prespecified thereshold of 35%)

EPP

- ✓ 47 patients had 30 day perioperative grade 3-4 events
- ✓ 1 patiens died (1%) within 30 days periop (pneumonia)
- ✓ Median overall survival 24.4 months

Cho, Lancet Oncol, 2021

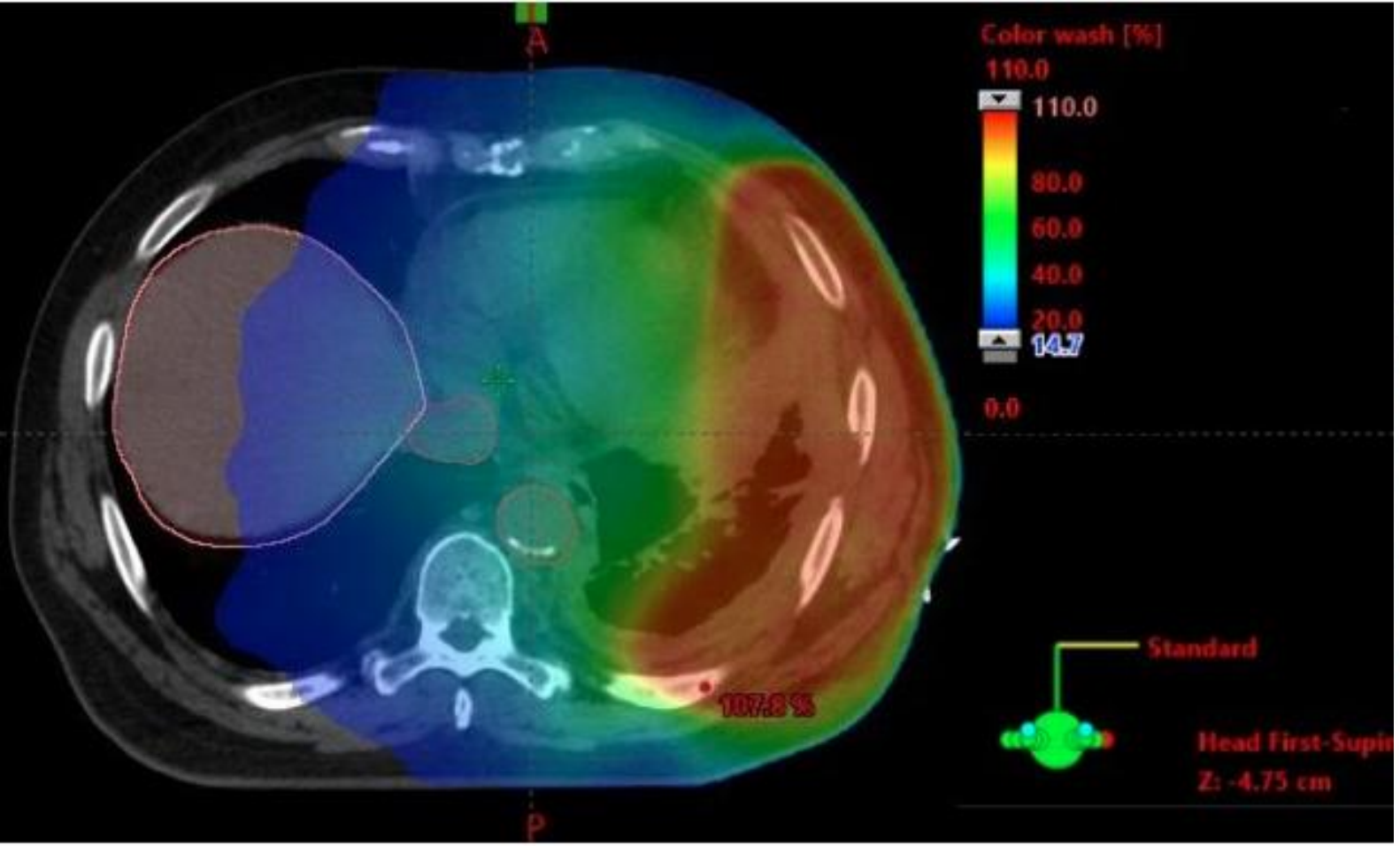
RESEARCH & CLINICAL TRIALS

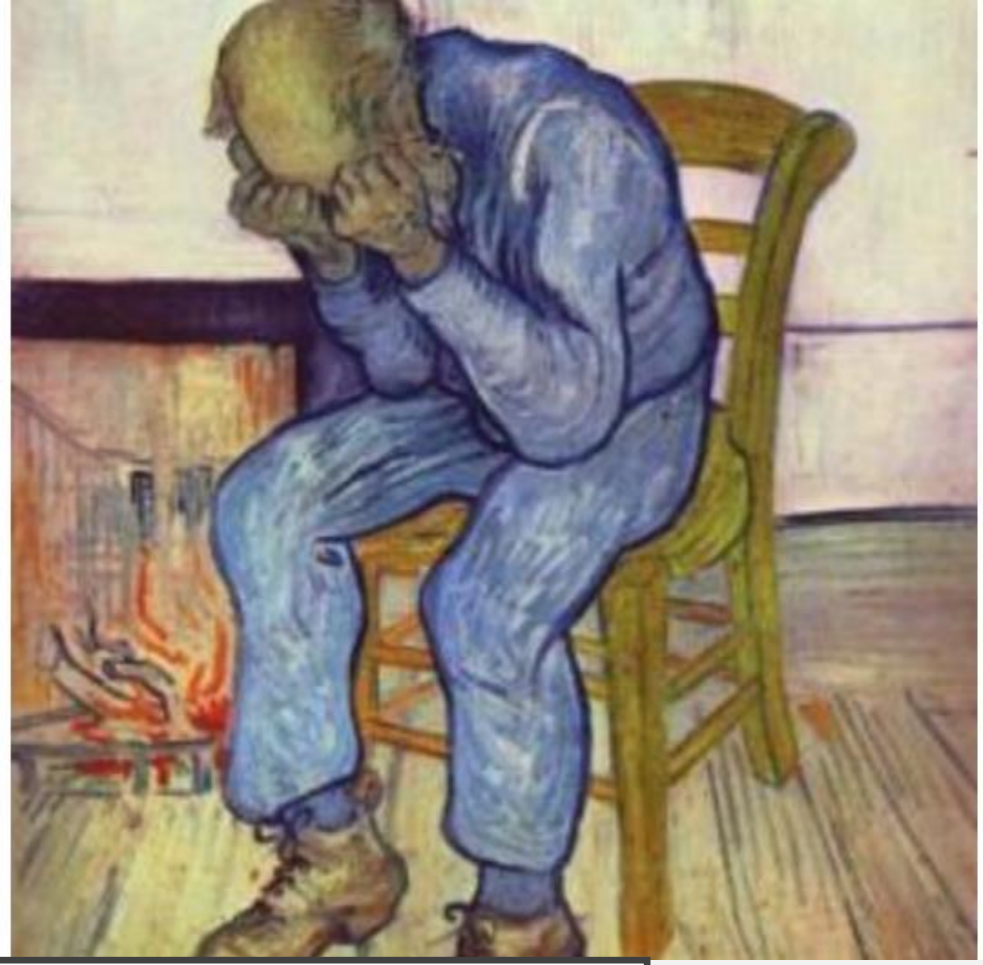
Mesothelioma Treatment in Toronto Moves from SMART to SMARTER

SMARTER Surgery for Mesothelioma After Radiation Therapy using **Extensive pleural Resection**

"We are currently enrolling patients on the next study iteration of oligofractionated radiotherapy followed by resection (SMARTER trial; NCT04028570) to address some of the challenges identified. Specifically, we modified radiotherapy fractionation doses to allow either extrapleural pneumonectomy or extended pleurectomy-decortication, at the discretion of the thoracic surgeon. Extended pleurectomy-decortication is easier to tolerate than extrapleural pneumonectomy; therefore, it might facilitate postoperative recovery and expand the cohort of patients who can receive the treatment.

SMART also appears to stimulate an immune response, which could be leveraged as a platform for immunotherapy in the future"





RT FOR SYMPTOM PALLIATION

PALLIATIVE RADIOTHERAPY FOR MESOTHELIOMA

	N	% pain control
Gordon 1982	29	62 %
Ball 1990	18	72%
Bissett 1991	22	59%
Davis 1994	71	> 50%
De Graff-Strukowska 1999	189	39-50 %
Stathopoulos 2005	7	71 %
El Hossieny 2010	26	57 %
Jenkins 2011	54	54

- All **retrospective** series, small numbers
- Wide **variation** of radiotherapy dose/technique
- **Limited** evidence to support the use of palliative RT to control pain

SYSTEMS-1

Dose? RT technique?

Is Radiotherapy Useful for Treating Pain in Mesothelioma?

A Phase II Trial

Nicholas MacLeod, FRCR,† Anthony Chalmers, PhD,†‡ Noelle O'Rourke, MD,† Karen Moore, BSc,† Jonathan Sheridan, FRCR,† Lynn McMahon, BSc,† Caroline Bray, MSc,† Jon Stobo, MSc,† Alan Price, FRCP,† Marie Fallon, MD,* and Barry J. Laird, MD*†§*

- ✓ 40 pts
- ✓ 20 Gy in 5 fractions
- ✓ Both 2-dimensional and 3-dimensional planning were used to plan treatment
- ✓ 14/40 (35 %) pts had improvement of pain at week 5

Journal of Thoracic Oncology, 2015

Contents lists available at ScienceDirect

Clinical and Translational Radiation Oncology

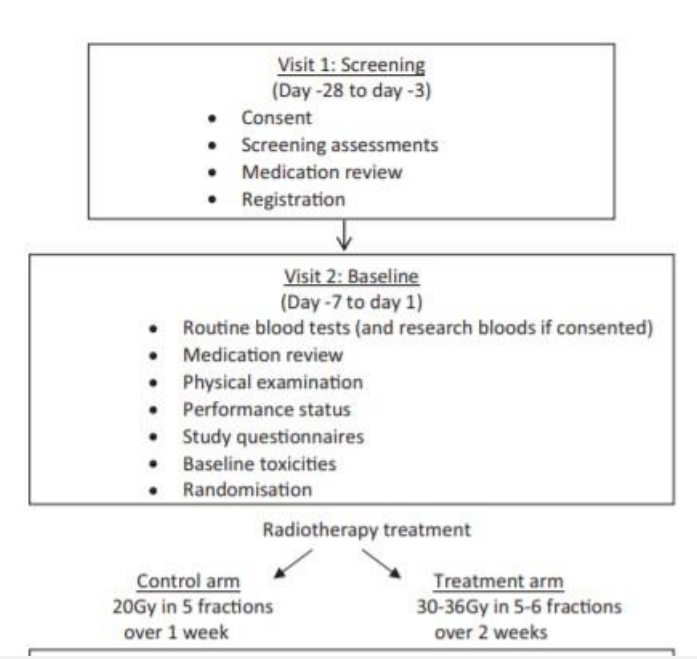
journal homepage: www.elsevier.com/locate/ctro

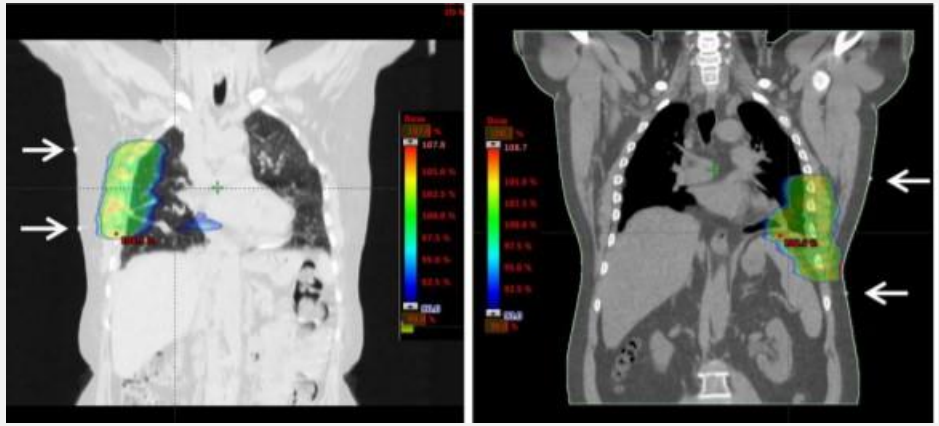
Short Communication

SYSTEMS-2: A randomised phase II study of radiotherapy dose escalation for pain control in malignant pleural mesothelioma

M. Ashton [a,b,*], N. O'Rourke [b], N. Macleod [b], B. Laird [c], J. Stobo [d], C. Kelly [d], L. Alexander [d], K. Franks [e], K. Moore [b], S. Currie [b], R. Valentine [b], A.J. Chalmers [a,b]

[a] Institute of Cancer Sciences, University of Glasgow, UK





- Multicentric, phase II, randomised dose escalation study of radiotherapy for pain control in MPM
- Multicentre UK study
- 36 GY in 6 fr vs 20 Gy in 5 fr
- IMRT or 3DCRT
- Recruitment target: 112 pts
- Ongoin

Review Article on Radiotherapy in Thoracic Malignancies

Controversies in the role of radiotherapy in pleural mesothelioma

Gerard G. Hanna[1,2]^, Thomas John[2,3], David L. Ball[1,2]

Given the insidiously invasive nature of mesothelioma, using radiotherapy to palliate local invasion is logical.

However, one challenge in delivering palliative radiotherapy in mesothelioma is identifying the appropriate target volume.

Commonly chest wall pain may be difficult to localise within diffuse disease throughout the pleural cavity, thus making precise targeting of the symptomatic site more an art than a science.

Transl Lung Cancer Res 2021

ERS/ESTS/EACTS/ESTRO GUIDELINES

Should radiotherapy be used for pain relief in patients with MPM?

Recommendation: we suggest that palliative radiotherapy for pain relief should be considered in cases of painful sites of disease caused by local infiltration of normal structures

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

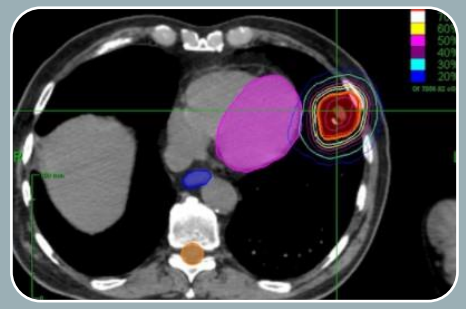
TAKE HOME

The use of prophylactic RT of tracts after diagnostic or therapeutic pleural procedures to prevent chest wall metastases is not recommended [I, D]

RT can be considered in an adjuvant setting after MCR to reduce the local failure rate; however, no evidence is available for its use as a standard treatment [II, D]

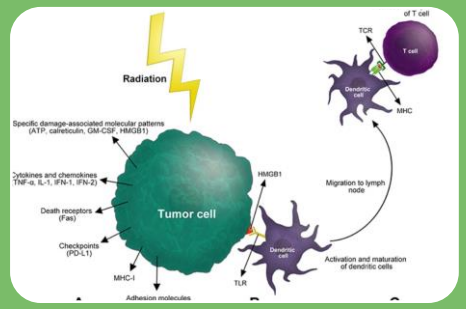
RT can be considered for palliation of pain related to local infiltration of thoracic structures [III, B]

FUTURE DIRECTION AND NEED OF EVIDENCE



Role of Hypofractionated RT/SBRT in patients with oligorecurrent MPM after multimodality treatment (limited data)

Schoder. Front Oncol 2019



Role of immunotherapy plus SBRT in unresectable MPM: when, how, etc…

Role of Proton Therapy

Clear dosimetric advantages

No robust comparative data

Consensus statement on PT in MM (2020) suggest that IMPT should be considered, when available….

«Tutti parlano di pace ma nessuno educa alla pace. A questo mondo si educa per la competizione, e la competizione è l'inizio di ogni guerra. Quando si educherà per la cooperazione e per offrirci l'un l'altro solidarietà, quel giorno si starà educando per la pace.»

Maria Montessori