Pleural Mesothelioma

Dr Vineeta Goel
Director and Head
Department of Radiation Oncology
Fortis H, Delhi

- Malignant pleural mesothelioma (MPM) is an aggressive and incurable malignancy that originates from the mesothelial cells that form the serosal lining of the pleural cavity.
- The median age at diagnosis is 75 years, and overall survival is 38% at 1 year and 7% at 3 years, reflecting the poor prognosis
- Onset of disease is often insidious and the diagnosis difficult to make.
- Patients predominantly present with dyspnoea, chest pain or both
- Many patients receive treatment for other benign conditions prior to the diagnosis being made

Malignant Pleural Mesothelioma - Epidemiology

- Mesothelioma tumours develop in mesothelial or sub-mesothelial cells of different tissues
- The large majority of mesothelioma cases are caused by exposure to asbestos

Pleural	> 90 % of cases
Peritoneal	4-7 % of cases
Pericardial	< 1% of cases
Testicular or other unspecified	< 1% of cases

Patterns of Pleural Mesothelioma incidence

- Incidence is difficult to accurately access
  - variable reporting rates worldwide
  - absence of mesothelioma from global databases
- In most European countries, and Japan, incidence of MPM is increasing, but it has peaked in US and Sweden
- Once a country introduces asbestos control measures, the number of mesothelioma cases is expected to plateau and then fall
- In many developing countries, which continue to use asbestos – it is predicted that mesothelioma prevalence will increase for many years in those countries.

Risk Factors

- Occupational or indirect exposure to asbestos
- 80% cases are caused by exposure to asbestos
  - Builders and construction workers
  - Engineering workers
  - Insulators
  - Families of workers exposed to asbestos
- Long latency period (30-50 years) between asbestos exposure and development of symptoms
- Other risk factors
  - Ionising radiation exposure
  - Erionite exposure
  - Exposure to zeolites
  - Genetic factors – Germline mutation to BAP1 gene
  - Infection with SV40

Clinical Features

- Dyspnoea due to
  - Pleural effusion (in early stages)
  - Lung encasement by pleural thickening (in later stages)
- Chest pain due to
  - Parietal pleural irritation or compression
  - Invasion of intercostal nerves
- Other S/S
  - Weight loss
  - Fatigue
  - Cough
  - Insomnia

Sub-types

1. Epithelioid
   - Most common (~60 %)
   - Associated with better outcomes than other subtypes
2. Sarcomatoid
   - 10-20%
   - Two additional rare subtypes under sarcomatoid MPM
     - Desmoplastic
     - Lymphohistiocytic
     - account for 5% of all MPM
   - Low response to systemic therapy
3. Biphasic/mixed – (~30%)
   - Classification requires >10% epithelioid and >10% sarcomatoid areas

Differentiating MPM from benign conditions & other malignancies is a frequent diagnostic problem

IHC Markers

- Definitive primary diagnosis usually requires IHC assessment of tissue biopsies
- Atleast two mesothelial markers and two adenocarcinoma markers
- The sacromatoid subtype may not exhibit typical mesothelial markers

- Malignant Mesothelioma
  - Calretinin
  - CK 5/6
  - Wilm’s tumor 1 (WT-1)
  - D2 40
- Adenocarcinoma
  - CEA
  - TTF-1
  - Leu M1

Prognostic Factors

- Poor prognostic factors
  - Thrombocytosis, leukocytosis, low Hb, PUO, sacromatoid or mixed histology
  - Age > 65 years
  - Male gender, poor performance status, associated smoking

- Good prognostic factors
  - Epithelial histology (stage 1)
  - Age < 65 years
  - Performance status of 0 to 1
  - Absence of chest pain

Table 3 EORTC prognostic groups

	Poor prognostic factors	Prognostic groups	Median survival	One-year OS (95% CI)	Two-year OS (95% CI)
EORTC index (1998)	ECOG performance status 1–2 White blood cell count $>8.3\times10^9$/L Male sex Probable/possible histologic diagnosis Sarcomatoid subtype	Low risk[a] (0–2 poor PF)	10.8 months	40% (30%–50%)	14% (6%–22%)
		High risk[b] ($\geq$3 poor PF)	5.5 months	12% (4%–20%)	0%

Notes: [a]Low risk equivalent to EPS $<$1.27. [b]High risk equivalent to EPS $>$1.27. Curran D, Shamoud T, Therasse P, et al, Prognostic factors in patients with pleural mesothelioma: the European Organization for Research and Treatment of Cancer experience, *J Clin Oncol*, 16, 1, 145–152. Adapted with permission. © (1998) American Society of Clinical Oncology.[33]

Malignant Pleural Mesothelioma – Treatment Options

There is no single treatment which has proven effective

- Surgery
- Radiation
- Chemotherapy
- Immunotherapy
- Gene Therapy

Tissue Diagnosis

- Positive pleural fluid cytology or histological confirmation via pleural biopsy
  - Existing guidelines recommend thoracocentesis as the initial pleural procedure, sensitivities as high as 73%
  - Recent prospective studies have demonstrated diagnostic yield of pleural fluid cytology 0–6% only

- Pleural biopsies with appropriate immunohistochemistry are required for the vast majority of cases
  - Percutaneously under radiological guidance or
  - Under direct vision at thoracoscopy

- Thoracoscopic biopsies from multiple sites remain the preferred approach
  - Larger biopsy size generally increases diagnostic confidence
  - Allows for histological subtyping
  - Deeper biopsies allow for the assessment of tumour invasion by including fat and/or skeletal muscle

Imaging

- CT chest and abdomen
  - Primary cross-sectional imaging modality and mainstay of radiological staging
  - Widely used and easily accessible
  - Performs poorly when assessing locoregional soft tissue disease or nodal metastases
- Contrast-enhanced magnetic resonance imaging (MRI)
  - Better to evaluate chest wall and diaphragmatic invasion
  - Accuracy in assessing nodal disease is low - sensitivity 66% for assessing N2 disease
- CT-PET
  - Superior to CT for extra-thoracic disease and identifying nodal disease
  - Assessment of response to therapy

Additional Evaluation

- Candidates for surgical resection – evaluate for
  - Contralateral pleural disease
  - Extra thoracic spread, or
  - Peritoneal involvement
- Mediastinoscopy or EBUS /FNAC of mediastinal lymph nodes
- VATS to exclude extension into the contralateral lung
- Laparoscopy to exclude transdiaphragmatic extension into peritoneal cavity

  -

Surgery

- Role of Surgery is controversial and limited to amall number of patients with early-stage disease
- The optimal outcome of MPM surgery is macroscopic complete resection, with either lung-sparing or lung-sacrificing surgery
- As complete surgical resection (R0 resection) remains elusive in most patients with MPM, local recurrence represents the most common form of disease relapse
- Multimodality therapy with neoadjuvant or adjuvant chemotherapy and radiation is practiced despite the lack of evidence-based data from randomized trials

- Palliative Surgery Occasionally performed in carefully selected patients with the intent to resect all visible tumor resulting in macroscopic complete resection, eliminate pleural effusion, improve local symptoms, and to increase the efficacy of adjuvant therapy

Extrapleural pneumonectomy	*En bloc* resection of the parietal and visceral pleura with the ipsilateral lung, +/– pericardium and diaphragm
Extended pleurectomy decortication	Parietal and visceral pleurectomy to remove all gross tumour with resection of the diaphragm and/or pericardium
Pleurectomy decortication	Parietal and visceral pleurectomy to remove all gross tumour without diaphragm or pericardial resection
Partial pleurectomy	Partial removal of parietal and/or visceral pleura for diagnostic or palliative purposes, but leaving gross tumour behind

- EPP involves en bloc resection of the parietal and visceral pleura along with the ipsilateral lung, pericardium and hemidiaphragm if necessary.
- EPD is lung-preserving, but attempts to remove all gross tumour with resection of the parietal and visceral pleura and diaphragm and/or pericardium
- Although many guidelines recommend maximal macroscopic resection for patients with early-stage mesothelioma, there is a paucity of high-quality evidence to support this.
- Both of these procedures are associated with significant post-operative mortality and morbidity, with some studies reporting morality rates as high as 15% when delivered as part of multimodal therapy

- The multicentre Mesothelioma and Radical Surgery (MARS) feasibility trial, by TREASURE et al
- First, and, to date, only RCT to evaluate the efficacy of EPP in addition to chemotherapy alone
- Induction platinum-based chemotherapy with subsequent randomisation to either EPP with subsequent radiotherapy or no EPP
- It suggested that EPP, as part of a trimodality approach, shortened survival compared to chemotherapy alone and had no effect on quality of life.
- High rate of adverse events in the interventional arm, with a post-operative mortality rate of 19%

Lancet Oncol 2011; 12: 763–772

- Meta-analyses in the past decade have suggested
  - Higher short-term perioperative mortality with EPP compared to EPD
  - Better long-term survival with EPD
- Consequently, EPP has largely been abandoned with practice shifting towards less aggressive EPD
- There is little high-quality evidence to support use of EPD
  - Studies evaluating EPD have been observational, single-centre and limited to highly selected patients with early-stage epithelioid disease
- The MARS 2 trial (clinicaltrials.gov identifier NCT02040272), is currently recruiting across the UK, seeks to address this significant gap in the literature by randomizing patients to EPD or pleurectomy decortication, at the surgeon's discretion, after chemotherapy induction compared to chemotherapy alone.

Ann Thorac Surgery 2015; 99: 472–480

Lung Cancer 2014; 83: 240–245

Future Oncol 2015; 11: 7–10.

- Pleurectomy decortication and partial pleurectomy, unlike EPP and EPD, do not attempt macroscopic complete resection and are debulking procedures.
- Neither has been shown to improve survival compared to no surgery, but they may improve quality of life
- The MesoVATS trial by RINTOUL et al. randomized patients to either VATS Partial Pleurectomy or talc pleurodesis via chest drain
  - VATS-PP did not confer a survival benefit compared to standard talc pleurodesis
  - Analysis of secondary outcomes suggested significantly better QoL at 6 and 12 months

Lancet 2014; 384: 1118–1127.

- Lack of robust data backing surgery in MPM
- British Thoracic Society guidelines do not recommend surgery outside clinical trials
- American Society of Clinical Oncology guidelines recommend maximal surgical cytoreduction in selected patients with early-stage non sarcomatoid MPM, as part of multimodality treatment, but should not be considered for sarcomatoid mesothelioma

Intraoperative Cytoreductive Treatment

- Intraoperative cytoreductive treatment can decrease local recurrence rates
- Various intraoperative treatments under investigation include
- Hyperthermic chemotherapy (HITOC)
- Hyperthermic povidone iodine lavage
- Fibrin associated cisplatin (applied as a spray), and
- Photodynamic therapy.

HITHOC

- HITHOC is part of surgery-based multimodality therapy proposed for primary or secondary serous surfaces malignancies to improve tumor local control and, consequently, prognosis
- It combines the advantages of antitumoral effects together with those of high temperature on the exposed tissues
- Underlying rationale - locally administered chemotherapy may enhance efficacy of chemotherapeutic agents by achieving high levels of drugs with limited systemic toxicity, while hyperthermia improves efficacy & penetration of chemotherapy
- It may be considered safe, feasible & effective local treatment to improve local effect of surgery
- Systematic review & meta-analysis of selected 21 papers by Zhao et al. – significantly prolonged median survival with Surgery + HITHOC
- Techniques used to perform HITHOC are extremely heterogeneous including surgical aspects and differences of antitumoral drugs perfused, their dosage, perfusion machine, temperature and time of the perfusion solution

*Zhao et al, Oncotarget **2017**, 8, 100640–100647*

Advantages of HITHOC	Multimodal treatment within a single procedure (surgery + chemotherapy + hyperthermia) Possibility to avoid demolitive surgery by enhancing cytoreduction with other treatments Good tolerability of the procedure by patients with a low morbidity-rate and a rapid post-operative recovery Lower systemic toxicity compared to traditional chemotherapy Compatibility with all the other adjuvant therapies
Limits of HITHOC	Limited indications related to patient performance status, the histology and stage of MPM Dedicated equipment and qualified and experienced staff Possibility of adverse events such as cardio- and nephrotoxicity, according to the regimens of chemotherapy used Prolonged timing of surgical and anesthesiological procedure

Preoperative Chemotherapy → EPP → Adjuvant Hemi thoracic RT

Trial	N	Epithelioid	Stage	Regimen	EPP	PORT	EPP mortality	Median survival, ITT (months)
Weder et al[73]	19	14 (74%)	T1–3, N0–2, M0	Cis Gem	16 (84%)	13 (68%)	1 (6%)	23
Flores et al[74]	19	14 (74%)	T3–4, N0–2, M0	Cis Gem	8 (42%)	7 (37%)	0	19
Rea et al[75]	21	20 (95%)	T1–3, N0–2, M0	Car Gem	17 (81%)	15 (71%)	0	25.5
Weder et al[76]	61	42 (69%)	T1–3, N0–2, M0	Cis Gem	45 (74%)	36 (59%)	1 (2%)	19.8
de Perrot et al[77]	60	44 (73%)	T1–3, N0–2, M0	Cis based	45 (75%)	30 (50%)	3 (7%)	14
Krug et al[78]	77	62 (81%)	T1–3, N0–2, M0	Cis Pem	54 (70%)	44 (57%)	2 (4%)	16.8
Van Schil et al[79]	58	NS	T1–3, N1, M0	Cis Pem	46 (79%)	38 (66%)	3 (7%)	18.4

Note: Cis based, cisplatin/vinorelbine (n=26), cisplatin/pemetrexed (n=24), cisplatin/raltitrexed (n=6), and cisplatin/gemcitabine (n=4).
Abbreviations: N, number of patients enrolled; EPP, extrapleural pneumonectomy; PORT, postoperative radiation therapy; ITT, intention-to-treat population; Cis Gem, cisplatin and gemcitabine; Car Gem, carboplatin and gemcitabine; Cis Pem, cisplatin and pemetrexed; NS, not stated; Cis, cisplatin.

37%–71% of patients successfully completed all therapy, and in the intent-to-treat analyses, median survivals ranged from 14 to 25.5 months

Multimodality Management - Rationale

- High local and distant recurrence following either EPP or Pleurectomy /Decortication

- Adjuvant RT
- Rusch et al single-institution experience in 57 patients who received postoperative hemithoracic radiation to 54 G following EPP
- This approach was feasible and decreased local recurrence rates in comparison to historical controls

- Neoadjuvant RT
- Neoadjuvant intensity-modulated RT to 25 G followed by a 5 G boost to “areas of risk” delivered prior to EPP was shown to be safe and feasible in 25 patients with MPM

Indications for Radiation Therapy

Radiation therapy has had an evolving role with regard to its role in the multidisciplinary treatment for MPM

(1) Hemithoracic radiation to be used before or after extrapleural pneumonectomy (EPP)

(2) Procedure tract radiation therapy

(3) Hemithoracic radiation as an adjuvant treatment after lung-sparing procedures, such as pleurectomy/decortication (P/D)

(4) Palliative radiation for focal symptoms caused by the disease.

Indications for Radiation Therapy

- Radiotherapy has been used both for focal palliation and as part of multimodality regimens after cytoreductive surgery to limit disease relapse in the ipsilateral hemithorax
- There are limited data to support the effectiveness of this approach or its impact on survival
- A number of centers have reported extremely encouraging overall survival with adjuvant intensity-modulated radiotherapy following EPP or EPD
- However, these case series findings have not been replicated in larger multicentre trials and the authors of these studies have subsequently concluded that the routine use of hemithoracic radiotherapy cannot be justified

Lung Cancer 2015; 89: 175–180.

Int J Clin Oncol 2016; 21: 523–530

Lancet Oncol 2015; 16: 1651–1658

Palliative Radiotherapy

- Radiotherapy is also used with palliative intent to reduce chest wall masses or alleviate pain associated with rib invasion or infiltration of intercostal nerves
- Evidence is limited to retrospective case series or single-arm prospective studies
- Responses are often not durable, with pain recurrence within the previous RT field within 3 months
- SYSTEMS study, recruited 40 patients from three UK centres; reported significant improvement in pain at 12 weeks in 1/3rd patients and complete response in 12.5% patients

Lung Cancer 2014; 83: 133–138

J Thorac Oncol 2015; 10: 944–950

Adjuvant Hemithoracic Radiation Therapy after EPP

- The efficacy of EPP followed by hemithoracic radiation therapy has been promising, with in-field failure rates of approximately 15% to 35%
- Efforts should be made to minimize the dose to the heart, particularly for left-sided tumors

Neoadjuvant Radiation Therapy Followed by EPP (the SMART Approach)

- No randomized or multi-institutional prospective data supporting this approach
- Should be performed only in highly experienced centers & within the context of a clinical trial
- The hypothesis for the SMART study - giving radiation as neoadjuvant therapy, before EPP, would impair the ability of tumor clonogens to reimplant and recur at distant sites in the coelomic cavity
- Accelerated fractionation regimen of 25 to 30 Gy in five daily fractions over 1 week
- After completion of radiation therapy (usually 10 days after the initial dose), patients then proceed to undergo a planned EPP to remove the irradiated lung, thereby avoiding the risk of severe radiation pneumonitis.
- The intent is to deliver a neoadjuvant dose to the entire ipsilateral hemithorax, from the thoracic inlet down to the thoracic outlet, including diaphragmatic attachments, as well as the ipsilateral mediastinal nodal stations, upper retroperitoneal nodes, and any biopsy/chest tube tract sites.

Adjuvant Radiation Therapy with Two Intact Lungs

Proton Beam Therapy