PRINCESS MARGARET CANCER CENTRE
CLINICAL PRACTICE GUIDELINES

LUNG SITE

MESOTHELIOMA
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1. **INTRODUCTION**

Malignant pleural mesothelioma is a rare tumour arising from the mesothelial pleural surface of the lungs. It is related to asbestos exposure (associated in 80% of all MPM cases), with a 30-40 year latency period between exposure and cancer development. Despite the current awareness of the danger of asbestos, restrictions, and safety measures that have been widely implemented in the West (e.g. banning of asbestos in USA and Canada in the early 1980s), mesothelioma incidence continues to rise in the previously exposed population due to this long latency period of many decades; its incidence in Canada is expected to plateau in 2020s.

2. **PREVENTION**

The association between asbestos and mesothelioma is well established. Legislation currently exists to minimize the exposure of the Canadian population to this known carcinogen. Smoking is an additional synergistic factor to asbestos.

3. **SCREENING AND EARLY DETECTION**

There are no data yet to support routine screening for mesothelioma. Preliminary results of a screening research study exploring the effectiveness of low-dose CT scanning does not appear to justify the routine screening in this population.

4. **DIAGNOSIS**

Clinical Evaluation is similar to the one described under lung cancer. Issues specific to Mesothelioma:
- Occupational History of exposure to asbestos

Oncological Imaging:
- CXR, CT chest (with contrast) and CT abdomen/pelvis are part of routine investigations. PET may be utilized if aggressive management is contemplated

Other Investigations typically include the following:
- PFTs
- Biopsy – VATS
- Path review
- Lymph node assessment in selected cases (via a biopsy)
- Preop assessment: VQ scan, echocardiogram
5. **PATHOLOGY**

Malignant mesothelioma may be mistaken for adenocarcinoma or mesotheliosis. The subtypes of malignant mesothelioma are epithelioid (the most common), sarcomatoid, desmoplastic, and biphasic (mixed). Epithelioid is the most favorable histological subtype.

Staging is according to the AJCC/ITMIG staging classification, based on the extent of primary tumor, nodal disease and presence or absence of metastases; details are presented in Appendix I.

6. **MANAGEMENT**

The optimal management of mesothelioma remains controversial. Surgery is the main therapeutic modality for early stage, but an aggressive multimodality treatment may be of benefit for selected patients. Chemotherapy is a consideration for patients with advanced unresectable disease. Supportive care measures, including palliative radiotherapy and analgesia, are essential to palliate pain and other symptoms. Narcotic analgesics play a role in palliation of dyspnea as well as pain.

Considerations for patient treatment will include:
- Stage of disease
- ECOG PS
- Histological subtype
- Patient's symptoms

Although some patients have been reported to achieve long-term survival with multimodality therapy, such cases are highly selected. Due to the rare nature of this disease, cases should be managed within specialist multidisciplinary teams and specialist thoracic surgeons.

**Early stage potentially resectable mesothelioma:**
- Extrapleural pneumonectomy (EPP) +/- Consideration of neoadjuvant chemotherapy and postoperative hemithoracic radiotherapy
- If eligible for the neoadjuvant IMRT Radiotherapy study (cT1/T2 cN0 M0), short course neoadjuvant radiotherapy delivering 25 Gy in 5 fractions over one week with IMRT followed by extrapleural pneumonectomy. If found to be N2 at surgery will be for adjuvant chemotherapy within 6 months post op.
- Observation or chemotherapy for patients who are not suitable for surgery

**Locally advanced mesothelioma**
- Chemotherapy alone
- Neoadjuvant chemotherapy ± EPP (if downstaged) ± adjuvant hemithoracic RT
- Palliative Radiotherapy
- Best supportive care
6.1 Surgery

Combined modality approach
Patients with early stage resectable mesothelioma are considered for extrapleural pneumonectomy (EPP). Modern surgical series have shown EPPs to be safely tolerated. Mortality from extrapleural pneumonectomy ranges from 6% to 30% but in experienced centres is 6-8%. Adjuvant or neoadjuvant treatments (chemotherapy, radiation or both) may be utilized to reduce the risk of recurrence after surgery.

EPP, also called pleuropneumonectomy, is performed through a thoracotomy incision, and includes an en bloc resection of the entire lung, the pleurae including the parietal, visceral, mediastinal, and diaphragmatic portions, and at the surgeon’s discretion part or all of the ipsilateral hemidiaphragm and pericardium. If the patient had previous incisions or percutaneous interventions, the scar from this intervention as well as its tract all the way down to the pleural cavity will be excised en bloc with the specimen. The surgery will include a mediastinal lymphadenectomy, and the lymph nodes obtained will be labelled according to the mediastinal lymph node station mapping system used for non-small cell lung cancer. Any area of gross tumor invasion of the chest wall will be resected en bloc with the specimen. Reconstruction of resected diaphragm and/or pericardium may or may not be done, depending on the surgeon’s discretion. However, all efforts will be made to ensure that the level of the diaphragm at the end of the surgery will be such that abdominal contents will be excluded as much as possible from the hemithoracic radiation field. At the end of the resection, metallic surgical clips will be placed to mark any areas concerning for gross or microscopic residual disease, as well as to mark the level of the diaphragm. At the end of the resection, the surgeon must routinely assess and determine if there is macroscopic residual tumor (R2 resection) or not.

Palliative treatment approach
Surgical therapy for more advanced mesothelioma, which is not completely resectable, includes drainage of effusions, chest tube pleurodesis, or thoracoscopic pleurodesis. Effusion control may be difficult because of the restrictive nature of the tumour. Selected patients may be considered for palliative surgical resection and decortication. Such procedures may provide temporary relief from effusions but there is no established surgical role for palliation of pain associated with chest wall invasion. Operative mortality from pleurectomy/decortication is about 2%.

6.2 Radiotherapy

Combined modality approach
In the radical setting, radiotherapy is not used alone. It is part of a multimodality approach. Radiotherapy is usually delivered in the adjuvant (postoperative) setting. Hemithoracic RT dramatically reduces the risk of local recurrence. The role of radical radiotherapy is limited by the volume being treated, which is a large complex volume (the entire hemithorax), the surrounding structures (heart, liver, kidneys, contralateral
lung, spinal cord, and esophagus), and the requirement for delivery of a high dose. Hemithoracic intensity modulated radiotherapy (IMRT) improves accuracy, precision and reduces toxicity. The dose in this setting is 50 Gy in 25 fractions over 5 weeks to the entire hemithorax with concomitant 10 Gy boost to areas at high risk (i.e. positive margins).

A current PMH Phase I/II Feasibility study is looking at the delivery of hemithoracic RT neoadjuvantly with 25 Gy in 5 fractions over one week with a concurrent boost of 5 Gy to gross disease using IMRT. This is followed by surgery with EPP the following week. If patients have pathologically involved mediastinal nodes (ypN2), they will then receive adjuvant chemotherapy (usually cisplatin and anti-folate doublet).

The radiotherapy planning for a radical hemithoracic treatment approach is complex. The patient will be immobilized on the CT simulator in the supine position using standard techniques. Scars and drain sites are marked with radio-opaque wires and covered with 5 mm thick bolus. The bolus extends 4 cm around the wires. The treatment planning CT scan begins above the hyoid and continued to below the kidneys with a slice thickness of 5 mm. The clinical target volume (CTV), and critical organs at risk (OARs) are defined by the radiation oncologist and reviewed with the thoracic surgeon.

The CTV is defined as: the superior border is 5 mm superior to the most superior surgically violated space (usually this is the thoracic apex); the anterior, posterior, and lateral margins are 5 mm beyond to the inside of the thorax or skin if near a surgically violated space; the postero-medial margin is the ipsilateral mediastinum, including the medial diaphragmatic crus, and the subcarinal areas 5 mm medial to the pericardial fat; the anteromedial margin is 5 mm medial to the most medial surgical clips; and the inferior margin is 5 mm inferior to the diaphragmatic insertion into the thoracic outlet as defined by the lower ribs.

Planning target volumes (PTV) includes a three-dimensional uniform expansion of the CTV by 5 mm. The normal tissues outlined are the heart, liver, spinal cord, contralateral lung, right and left kidneys, and esophagus and are expanded by at least 5 mm to account for positioning uncertainties.

The isocenter is the geometric centre of mass of the combined target volumes. Planning will be done by multiple iterations on the treatment planning system until an acceptable plan is achieved. Five to ten non-opposed gantry angles will be used, depending on the patient geometry. The prescription point must be placed within the CTV and be representative of the dose it will receive (usually at the CTV’s geometric centre of mass). Only megavoltage photon beams (at least 6 MV energy) will be permitted. Dose will be calculated with tissue inhomogeneity corrections. The prescription includes 50 Gy in 25 daily fractions over 5 weeks to the CTV and at least 95% of the PTV. Planning constraints include mean lung dose to the contralateral lung of <9.5 Gy, <33% of the kidney volume to >22.5 Gy, <60% of the liver (for right sided tumors) volume getting >30 Gy, <60% of the heart volume (for left sided cases) getting >40 Gy and for esophagus, <30% volume to >55 Gy.
**Palliative treatment approach**

Palliative treatment of more localised symptomatic areas such as painful areas of the chest wall or involvement of the mediastinum may be feasible. Typical fractionation is 20 Gy in 5 fractions over 1 week.

It is known that disease may recur in sites of biopsy, chest drain insertion or VATS scars. A small RCT has shown reduction in port site (chest wall) recurrence with pre-emptive palliative RT. In this setting, we will consider a course of RT to prevent such a symptomatic recurrence; the dose used is 21 Gy in 3 fractions delivered daily using a direct photon or electron beam.

#### 6.3 Chemotherapy

**Combined modality**

Neoadjuvant chemotherapy is used as systemic treatment as well as a cytoreductive strategy in this setting. The agents of choice include cisplatin and an anti-folate agent (such as pemetrexed or raltitrexed). These have been shown to improve overall survival in MPM patients in phase 3 clinical trials. Response is sometimes difficult to assess given the pleural-based pattern of disease.

**Palliative treatment approach**

Patients may be considered for palliative chemotherapy with cisplatin and pemetrexed, if their ECOG PS and lack of significant co-morbidities will allow. It has been shown in a large Phase III RCT, that combination cisplatin/pemetrexed vs cisplatin alone, has a significant improvement in OS. The median survivals were 12.1 versus 9.3 months respectively.

However, as the rate of disease progression is highly variable, it is reasonable for patients who have few or no symptoms to be managed expectantly. A trial of systemic chemotherapy may be offered to fit patients with symptoms requiring palliation. The probability of benefit is greater in those with epithelioid tumours. Alternatives include gemcitabine in combination with a platinum analog, monotherapy with vinorelbine, or an investigational protocol.

**Cisplatin/Pemetrexed Regime:**

Patient must start Vitamin B12 injections and Folic acid at least 7 days before.
Folic Acid 1mg po, 1 tablet daily for 30 days; start 1 week prior to pemetrexed & continue X 3 weeks after last dose of pemetrexed.
Vit B12 1000mcg im every 9 weeks (63 DAYS), starting 7 days prior to first dose of pemetrexed & continuing until 21 days after last dose of pemetrexed.

Cisplatin 75mg/m2 Day1 & Pemetrexed 500 mg/m2 Day1 on a 21 day cycle
Anti-emetics will include ondansetron 24mg po and dexamethasone 20mg po pre chemo
Hydration with 1 litre of N Saline +KCL +Mg iv over 1 hr pre and post cisplatin & Mannitol 12g infused IV over 5-10 minutes post cisplatin
Pemetrexed 500 mg/m2 (max 1000mg) IV in 100ML normal saline over 10mins
Cisplatin 75 mg/M2 IV in 500ML normal saline infused IV over 1 hour.
Antiemetics: Dexamethasone 4mg BD & Ondansetron 16mg daily & Prochlorperazine 10mg TID (PRN) x 3 days post chemo

Carboplatin will replace cisplatin if contraindication to cisplatin. If carboplatin replaces cisplatin, the dose will be calculated at AUC5.

Cisplatin/Raltitrexed Regime:

Cisplatin 75mg/m2 Day1 & Raltitrexed 3 mg/m2 Day1 on a 21 day cycle
Anti-emetics will include ondansetron 24mg po and dexamethasone 20mg po pre chemo
Hydration with 1 litre of N Saline +KCL +Mg iv over 1 hr pre and post cisplatin & Mannitol 12g infused IV over 5-10 minutes post cisplatin
Raltitrexed 3 mg/m2 IV in 50ML normal saline over 15 mins
Cisplatin 75 mg/M2 IV in 500ML normal saline infused IV over 1 hour.
Antiemetics: Dexamethasone 4mg BD & Ondansetron 16mg daily & Prochlorperazine 10mg TID (PRN) x 3 days post chemo

Carboplatin will replace cisplatin if contraindication to cisplatin. If carboplatin replaces cisplatin, the dose will be calculated at AUC5.

6.3 Oncology Nursing Practice

Refer to general oncology nursing practices

7. SUPPORTIVE CARE

7.1 Patient Education

Patient education is an integral aspect of cancer management in the lung site group. In addition to one-on-one education specific to the patient situation, there are a multitude of written educational materials that we provide to patients. There are general pamphlets on specific cancers and the main treatments including the Lung Cancer Patient Guide, published by Lung Cancer Canada, 2010. Many from the Canadian Cancer Society, some of which are available in multiple languages, which is useful given the fact that many of our patients do not speak English), as well as specific PMH created brochures that describe specific treatments (eg thoracic radiation, specific chemotherapy regimen etc), specific tests (eg PET scan) and specific symptoms (eg how to manage pain, or fatigue). The specific educational content is provided depending on the patient's diagnosis and management options. In addition, there is a library with resources available to the patient,
including books, a Lung Cancer CD-ROM educational Resource and a librarian/patient educator who is available to search for specific information with the patient/family.

7.2 Psychosocial Care

Refer to general oncology psychosocial care guidelines

7.3 Symptom Management

Lung cancer patients have a multitude of physical and emotional symptoms related to their disease, treatment and co-morbid condition. The common symptoms include pain, dyspnea, fatigue, nausea, vomiting, constipation, anxiety, depression etc. DART and ESAS (Distress Assessment and Response Tool and Edmonton Symptom Assessment System) are the screening tools used to identify the symptoms of most concern to the patient. They add to the clinical assessment of the patient made by the clinician at an individual attendance, but are also recorded serially at each attendance, to observe outcomes of interventions used. Patients answers are reviewed by the nurse and oncologists, symptom management guides are used in response to this screening and patients with significant burden of symptoms can be referred to appropriate services (eg palliative care, social work etc).

7.4 Clinical Nutrition

There is a dedicated dietician for the lung site group. Nutritional advice and support may be required if there has been a substantial weight loss prior to diagnosis, difficulties maintaining oral intake during combined modality treatment (due to esophageal toxicity) or patients with esophageal compression from their malignancy. Occasionally patients experience dysphasia following surgical interventions which may require nutritional intervention. The goals of nutritional support are to maintain patient’s weight throughout treatment and improve any preexisting nutritional deficiencies.

7.5 Palliative Care

Refer to general oncology palliative care guidelines

7.6 Other

Patients with thoracic malignancies frequently develop deep venous thrombosis (DVT) and pulmonary emboli (PE). There is a Thrombosis clinic available at TGH for urgent referral and management of DVT & PE. Daily SQ injection of low molecular weight heparin is the therapy of choice in cancer patients with DVT/PE, for 6 months, or in the case of active incurable cancer, may be life-long. Inpatients who are not fully mobile are given prophylactic doses of subcutaneous heparin.

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APPENDIX I – MESOTHELIOMA STAGING – IMIG (International Mesothelioma Interest Group) Staging System

AJCC staging system for malignant pleural mesothelioma
Primary tumor (T)
Tx: Primary tumor cannot be assessed
T0: No evidence of primary tumor
T1: Tumor involves ipsilateral parietal pleura, with or without mediastinal pleura with or without diaphragmatic pleural involvement
T1a: No involvement of the visceral pleura
T1b: Tumor also involves the visceral pleura
T2: Tumor involves each of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following:
Involvement of the muscles of the diaphragm
Involvement of the lung tissue deeper to the pleura covering the lung
T3: Locally advanced but potentially resectable tumour. Tumor involves all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following:
Involvement of the endothoracic fascia
Involvement of the mediastinal fat
Single focus of tumor involving the soft tissue of the chest wall
Involvement of pericardium but nontransmural involvement (without penetration of pericardium)

T4: Locally advanced but technically unresectable tumour. Tumor involves all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following:
Diffuse or multi-focal involvement of the soft tissue of the chest wall +/- associated rib destruction
Invasion through the diaphragm to the peritoneal cavity
Direct extension to the contralateral pleura
Invasion into spine
Penetration of the pericardium
Pericardial effusion which is positive for cancer cells
Involvement of heart muscle
Direct extension of tumour to mediastinal organs

Lymph node involvement (N)
NX: Regional lymph nodes cannot be assessed
N0: No regional lymph node involvement
N1: Involvement of ipsilateral broncho-pulmonary and or hilar lymph nodes only
N2: Involvement of subcarinal lymph node(s), and or ipsilateral mediastinal lymph nodes including the ipsilateral internal mammary and peridiaphragmatic nodes.
N3: Involvement of contralateral mediastinal, contralateral internal mammary, or contralateral hilar lymph node(s) and or same side or opposite side supraclavicular or scalene lymph node(s)
Distant metastasis (M)
Mx: Distant metastasis cannot be assessed
M0: No distant metastasis
M1: Distant metastasis present

Stage Groupings: TNM Subsets
Stage 1  T1 N0 M0
Stage IA  • T1a N0 M0
Stage IB  • T1b N0 M0
Stage II  • T2, N0 M0
Stage III • T1, T2 N1 M0
  • T1, T2, N2, M0
  • T3, N0, N1, N2, M0
Stage IV  • T4 Any N M0
  • Any T N3 M0
  • Any T Any N, M1