Chapter 16
Mesothelioma and Thymic Tumors

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MESOTHELIOMA

PEARLS

- Rare: only 2,000–3,000 cases per year in the US.
- Eighty percent cases involve asbestos exposure.
- Strong causal relationship exists with cigarette smoking.
- Can affect visceral pleura, parietal pleura, and peritoneum.
- May mimic adenocarcinoma on pathologic examination; immunohistochemical staining required for definitive diagnosis.

WORKUP

- H&P, CXR, CT/MRI chest, PET/CT, pulmonary function tests.
- On CT, look for pleural thickening, effusions, contraction of ipsilateral hemithorax.
- Functional imaging important because prior talc pleurodesis results in pleural thickening, which may be indistinguishable from disease-related plaques.
- Circumferential pleural thickening, mediastinal/chest wall/diaphragm involvement, and/or irregular pleural contour are most likely malignant.

STAGING (AJCC 7TH ED., 2010): MESOTHELIOMA

Editors' note: All TNM stage and stage groups referred to elsewhere in this chapter reflect the 2002 AJCC staging nomenclature unless otherwise noted as the new system below was published after this chapter was written.

Primary tumor (T)

TX: Primary tumor cannot be assessed
T0: No evidence of primary tumor
T1: Tumor limited to the ipsilateral parietal pleura with or without mediastinal pleura and with or without diaphragmatic pleural involvement
  T1a: No involvement of the visceral pleura
  T1b: Tumor also involving the visceral pleura
T2: Tumor involving each of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following:
  Involvement of diaphragmatic muscle
  Extension of tumor from visceral pleura into the underlying pulmonary parenchyma
T3: Locally advanced but potentially resectable tumor. Tumor involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following:
  Involvement of the endothoracic fascia
  Extension into the mediastinal fat
  Solitary, completely resectable focus of tumor
  Extending into the soft tissues of the chest wall
  Nontransmural involvement of the pericardium
T4: Locally advanced technically unresectable tumor. Tumor involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following:
  Diffuse extension or multifocal masses of tumor in the chest wall, with or without associated rib destruction
  Direct transdiaphragmatic extension of tumor to the peritoneum
  Direct extension of tumor to the contralateral pleura
  Direct extension of tumor to mediastinal organs
  Direct extension of tumor into the spine
  Tumor extending through to the internal surface of the pericardium with or without a pericardial effusion or tumor involving the myocardium

Regional lymph nodes (N)

NX: Regional lymph nodes cannot be assessed
N0: No regional lymph node metastases
N1: Metastases in the ipsilateral bronchopulmonary or hilar lymph nodes
N2: Metastases in the subcarinal or the ipsilateral mediastinal lymph nodes including the ipsilateral internal mammary and peridiaphragmatic nodes
N3: Metastases in the contralateral mediastinal, contralateral internal mammary, ipsilateral or contralateral supraclavicular lymph nodes

Distant metastasis (M)

M0: No distant metastasis
M1: Distant metastasis present

Anatomic stage/prognostic groups

I: T1 N0 M0
IA: T1a N0 M0
IB: T1b N0 M0
II: T2 N0 M0
III: T1, T2 N1 M0
  T1, T2 N2 M0
  T3 N0, N1, N2 M0
IV: T4 Any N M0
  Any T N3 M0
  Any T Any N M1

continued

TREATMENT RECOMMENDATIONS

2002 Stage	Recommended treatment	~MS
I–II	■ If resectable/N0: extrapleural pneumonectomy (EPP) → 4–6 week break → RT 1.8/54 Gy ■ If resectable/N + or medically unsuitable for EPP consider pleurectomy/decortication → 4–6 week break → RT 1.8/54 Gy ■ If surgically inoperable → neo-adjuvant chemo and reevaluate for resection; if remains unresectable, continue chemo	Stage I: 35 months Stage II: 16 months
III–IV	■ Primary EPP followed by adjuvant RT ± chemo vs. Neo-adjuvant chemo → resection → RT 1.8/54 Gy ± adjuvant CT	Stage III: 12 months Stage IV: 6 months

STUDIES

- Rusch (2001): phase II trial of 88 patients treated with EPP and adjuvant hemithoracic RT (54 Gy). MS 34 months for Stage I–II and 10 months for late stage. Toxicity included fatigue and esophagitis.
- Vogelzang et al. (2003): phase III single-blinded study of pemetrexed and cisplatin vs. cisplatin alone in chemo naïve patients with malignant pleural mesothelioma. Addition of pemetrexed improved response rate (17→41%) and MS (9→12 months).
- Flores et al. (2006): phase II trial of stage III or IV patients treated with induction chemo (gemcitabine/cisplatin), EPP, and adjuvant radiotherapy (54 Gy). MS: resectable patients 33.5 months, unresectable patients 9 months, all patients 19 months.
- Lucchi et al. (2008): phase II study of stage II–III patients treated with intrapleural pre-op IL-2, pleurectomy/decortication, adjuvant intrapleural epidoxorubicin/IL-2, adjuvant radiotherapy (30 Gy), systemic chemotherapy (cisplatin/gemcitabine), and long-term IL-2. MS is 26 months, 2- and 5-year OS 60.2 and 23.3%, respectively.
- Allen et al. (2007a): retrospective review of outcomes associated with moderate dose hemithoracic RT (MDRT) vs. high dose

hemithoracic RT (HDRT) in 39 patients after EPP. (MDRT = 30 Gy to hemithorax, 40 Gy to mediastinum, and boost to positive margins or nodes to 54 Gy with concurrent CT; HDRT = 54 Gy with sequential CT). Median OS 19 months. HDRT yield lower LF rate (27%) vs. MDRT (50%; p = ns). RT technique was not predictive of local failure, distant failure, or OS.

- Perrot et al. (2009): retrospective review of 60 patients treated with trimodality therapy with induction chemo followed by EPP and adjuvant hemithoracic RT (≥50 Gy). Type of induction chemo did not impact survival. For N0 patients, MS 59 months, 5-year DFS 53%. Pathologic nodal status is a good predictor of survival.
- Rice et al. (2007): review of 100 consecutive patients treated with EPP. Sixty-three patients received IMRT (median dose 45 Gy). Chemo not routinely administered. Overall MS 10 months. For IMRT patients, MS 14 months (28 months if pN0), 3-year OS 20% (41% if pN0). Only 5% recurrence within irradiated field. Fifty-four percent developed distant recurrences.
- Krayenbuehl (2007): retrospective planning comparison of 17 patients treated with adjuvant 3D-CRT ($n = 8$) or IMRT ($n = 9$) following EPP. IMRT improved coverage and homogeneity vs. 3D-CRT ($p < 0.01$) through an increase in mean lung dose to ipsilateral and contralateral lung.
- Miles et al. (2008): retrospective review of 13 patients treated with IMRT to entire ipsilateral hemithorax and nodes (median dose 45 Gy) after EPP. With 9.5 months median follow-up, 23% had grade 2 or greater pulmonary toxicity; 46% developed LR and/or DM, and 46% were alive and NED. Authors describe dosimetric parameters for pulmonary toxicity.
- Sterzing et al. (2008): retrospective planning comparison of step and shoot IMRT and helical tomotherapy for 10 patients treated with adjuvant RT (54 Gy) following neoadjuvant chemo and EPP. Tomotherapy had improved coverage and homogeneity and decreased mean lung dose.
- Boutin (Chest 1995): randomized study of 40 patients treated with 7 Gy × 3 fx with electrons to drain sites vs. observation. RT to drain sites decreased LF 40–0%.
- O'Rourke (Radiother Oncol 2007). Randomized study of 61 patients after chest drain or pleural biopsy treated with 21 Gy in 3 fx to drain site vs. best supportive care. No difference in the risk of tract metastases between arms (<10%).
- Plathow et al. (2008): computed tomography, positron emission tomography, positron emission tomography/computed tomography, and magnetic resonance imaging for staging of limited pleural mesothelioma: initial results. Accuracy for detecting

stage II: CT 77%, PET 86%, MRI 80%, PET/CT 100%. Stage III: CT 75%, PET 83%, MRI 90%, and PET/CT 100%.

RADIATION TECHNIQUES

SIMULATION AND FIELD DESIGN

- Hemithoracic RT 4–8 weeks post resection.
- Simulate and CT pt supine, arms overhead, immobilization.
- Favor image-based (e.g., CT) planning.
- Earlier study by Allen et al. suggested IMRT may be associated with increased complications and/or deaths (Allen et al. 2006). However, later studies by the same group (Allen et al., 2007a, b) and others (Krayenbuhl, 2007) have shown decreased toxicity with careful planning.
- Conventional AP/PA borders: superior = top of T1; inferior = bottom L2; medial = contralateral edge of vertebral body (if mediastinum negative) or 1.5 cm beyond contralateral edge of vertebral body (if mediastinum involved), lateral = flash.
- Blocks: liver and stomach (covers diaphragm/abdomen interface), humerus, heart (after 20 Gy), spinal cord (after 41.4 Gy, shift medial border to ipsilateral edge of vertebral body).
- Scar: include in field, bolus, or boost to scar may be needed.
- Electron boost to areas of chest wall blocked for abdominal or cardiac protection.

DOSE PRESCRIPTIONS

- 1.8 Gy/fx to 54 Gy (off-cord after 41.4 Gy)
- Electrons: give concurrent with photon treatment, 1.53 Gy/fx (15% scatter under blocks from photon fields). Choose energy so that chest wall is covered by 90% IDL

DOSE LIMITATIONS

- Spinal cord: ≤45 Gy
- Lung: mean lung dose ≤8–10 Gy; V20 ≤4–10 Gy; V5 ≤75%
- Heart: limit 50% <25–40 Gy
- Esophagus: limit 1/3 to <60 Gy; 2/3 to <55 Gy; 3/3 to <45 Gy

COMPLICATIONS

- Acute: may include skin reactions, fatigue, nausea, vomiting, dysphagia, odynophagia, cough, dyspnea, L'hermitte's syndrome (radiationmyelitis), acute pneumonitis, pneumonia.

- Late: may include pericarditis, restrictive cardimyopathy, myocardial infarction, CHF, radiation myelopathy, radiation pneumonitis, pulmonary fibrosis.

THYMIC TUMORS

PEARLS

- Thymoma has an indolent, predominantly locally invasive growth pattern, but can metastasize.
- Thymoma accounts for 20% of mediastinal tumors and 50% of anterior mediastinal masses in adults; most common age at diagnosis = 40–60 years.
- Most common presentation is as an anterior mediastinal mass on CXR performed for other reasons; 40–50% are asymptomatic.
- Thymomas are often associated with immune and nonimmune mediated paraneoplastic syndromes: myasthenia gravis (MG; ~30%), pure red cell aplasia (PRCA; 5–10%), and hypogammaglobulinemia (Good's syndrome, 3–6%).
- Only 10–15% of patients with MG have a thymoma; 50% of patients with PRCA have a thymoma.
- Common presenting symptoms include fatigue, chest pain, cough, dyspnea, hoarseness, symptoms of superior vena cava syndrome, and/or paraneoplastic symptoms (i.e., MG: muscle weakness, dysphagia, blurred vision).
- Prognosis is related to stage and completeness of resection; on multivariate analysis, treatment dose ≥50 Gy is a prognostic factor (Zhu et al. 2004).
- Thymomas are chemosensitive tumors; complete and partial response rates = 1/3 and 2/3, respectively.
- Other histologies.
  - Thymic carcinoma: more locally-aggressive with ~30% LN and DM.
  - Thymic carcinoid: more locally-aggressive with 30% LN and 30–40% DM, associated with MEN, Cushing's, Eaton–Lambert, SIADH, and hypercalcemia paraneoplastic syndromes.

WORKUP

- H&P, CXR, and preoperative chest imaging, mainly CT chest with contrast; MRI and PET–CT have been used.

- Be careful to note entire pre-op tumor volume including anterior extension to sternum or anterior chest wall or posterior extension into the mediastinum.
- Serum studies to rule-out germ cell tumor (β-HCG, LDH, AFP, ACH receptor assay).
- Anterior mediastinoscopy with biopsy.

STAGING

Stage grouping (Masaoka system)		~5-Year survival
I:	Macroscopically completely encapsulated and microscopically no capsular invasion	I: 93%
II:	(1) Macroscopic invasion into surrounding fatty tissue or mediastinal pleura, or (2) microscopic invasion into capsule	II: 86%
III:	Macroscopic invasion into neighboring structures, i.e., mediastinum, pericardium, great vessels, or lung	III: 70%
IVa:	Pleural or pericardial dissemination	IV: 50%
IVb:	Lymphatic or hematogenous metastasis	

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TREATMENT RECOMMENDATIONS

- The role for radiotherapy in the management of malignant thymoma remains somewhat controversial; no randomized studies exist comparing treatment; retrospective data suffer from heterogeneity in treatment techniques
- Complete surgical resection (R0) is the mainstay of treatment
- Forty percent of completely resected thymomas recur; median time to local recurrence (LR) ~4 years

Recommended treatment

Stage	Recommended treatment
I	Complete (R0) resection
II	Complete (R0) resection ± post-op RT (depending on the risk of LR based on pathology). Favor post-op RT for close or involved margins, thymic carcinoma, and thymic carcinoid
III	Complete resection (if possible) → post-op RT If marginally resectable: pre-op RT ± chemo (cisplatin based) → resection if feasible If not a surgical candidate or unresectable: chemo-RT or definitive RT

IV	Induction combination chemo → RT and/or surgery depending on response
Chemo	Common first-line: cisplatin, doxorubicin, cyclophosphamide ± prednisone (CAPP). Other options available for first and second line (see NCCN guidelines)

STUDIES

RADIOTHERAPY

- Multiple retrospective reviews suggest that RT reduces recurrence rates and improves outcomes for incompletely resected stage II–IV thymoma. The role of post-op RT for completely resected stage II–III thymoma is controversial.
- Forquer et al. (2009): review of 901 patients with surgically resected thymoma or thymic carcinoma in SEER database. Post-op RT improved 5-year OS for patients with Stage II–III disease (66 76%), but not CSS (91 vs. 86%). No benefit of post-op RT Stage I patients.
- Kondo and Monden (2003): review of 1,320 patients with thymic epithelial tumors. Stage I treated with surgery alone. Stage II–III thymoma and thymic carcinoid treated with surgery and RT. Stage IV thymoma and thymic carcinoma treated with RT and chemo. Masaoka clinical stage is an excellent predictor of prognosis for thymoma and thymic carcinoma, but not thymic carcinoid. Complete resection is the most important prognostic factor. Post-op RT did not significantly reduce recurrence rate for patients with completely resected stage II–III thymoma.
- Zhu et al. (2004): retrospective review of 47 patients with noninvasive thymoma and 128 patients with invasive thymoma. Ninty-seven percent received post-op RT. Masaoka stage and extent of resection were the most important prognostic factors. Five-year LC rates: stage II 96%, stage III 56%, stage IVA 43%, stage IVB 22%, tumor bed only RT 68%, extended field RT 67%.
- Curran et al. (1988): retrospective study of 103 patients with thymoma. No recurrences among stage I patients after total resection without RT. Fifty-three percent with stage II/III thymoma had mediastinal recurrence without RT vs. 0% after total resection with RT, and 21% after subtotal resection or biopsy with RT.

- Monden et al. (1985): 127 patients treated with surgery ± RT. RT reduced recurrence from 30 to 15%.

COMBINED MODALITY

- Mornex (1995): retrospective review of 90 patients treated with surgery and RT (30–70 Gy) ± chemo (cisplatin based). Five out of ten-year OS was 51/39%. Extent of surgery impacted 10-year OS (43% for partial resection vs. 31% for biopsy only). Stage, histology, and chemo were not prognostic.
- Kim et al. (2004): phase II study of a multidisciplinary approach with induction chemotherapy, followed by surgical resection, radiation therapy, and consolidation chemotherapy for unresectable malignant thymomas. Induction chemo 77% response rate. OS rates 95% (5-year) and 79% (7-year). PFS rates 77% (5-year) and 77% (7-year).
- Wright et al. (2008): 10 patients with stage III–IVA thymoma tread with 2 cycles of cisplatin and etoposide with concurrent RT followed by surgery. Four patients had >90% necrosis in resected specimen. Eight patients had R0 resection. Seven patients received 2 more cycles of chemo. Five-year OS 69%.

RADIATION TECHNIQUES

SIMULATION AND FIELD DESIGN

- Simulate patient supine with arms overhead and adequate immobilization.
- Conformal, image-based planning techniques are preferred (IMRT, 3D-CRT, tomotherapy) to minimize dose to surrounding normal structures.
- Surgical clips denoting the extent of surgical resection and/or regions of residual disease are important for design of post-op fields.
- Volumes.
  - PTV = GTV/tumor bed and clips +1.5–2.0 cm margin.
- No need for SCV field(s) unless involved.
- Heterogeneity corrections are likely necessary.

DOSE PRESCRIPTIONS

- Pre-op RT: 1.8 Gy/fx to 45 Gy
- Stage II post-op: 1.8 Gy/fx to 45–50 Gy
- Stage III post-op: 1.8 Gy/fx to 50–54 Gy
- Gross residual disease: 1.8 Gy/fx to 54–60 Gy

DOSE LIMITATIONS

- Spinal cord: ≤45 Gy
- Lung: limit the volume receiving >20 Gy (V20) to <20–30%
- Heart: limit 50% <25–40 Gy
- Esophagus: limit 1/3 to <60 Gy; 2/3 to <55 Gy; 3/3 to <45 Gy

COMPLICATIONS

- Acute: may include skin reactions,fatigue, dysphagia, odynophagia, cough, dyspnea, L'hermitte's syndrome (radiationmyelitis), acute pneumonitis, pneumonia.
- Late: may include pericarditis, restrictive cardimyopathy, myocardial infarction, CHF, radiation myelopathy, radiation pneumonitis, pulmonary fibrosis.

FOLLOW-UP

- Late recurrences are not uncommon; long-term follow-up is indicated.
- Post-op RT has no impact on the incidence of subsequent pleural spread (outside of one RT field).

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