Journal of
Nuclear Medicine & Radiation Therapy

Donato et al., J Nucl Med Radiat Ther 2013, S2
DOI: 10.4172/2155-9619.S2-011

Review Article Open Access

Malignant Pleural Mesothelioma: Management and Role of Radiation Therapy

Donato V[1], Dognini J[1]*, Arcangeli S[1], Melis E[2] and Facciolo F[2]

[1]Radiotherapy Department, S Camillo, Forlanini Hospital, Rome, Italy
[2]Thoracic Surgery Unit, Department of Surgical Oncology, Regina Elena National Cancer Institute of Rome, Italy

Abstract

Malignant pleural mesothelioma is a neoplasm derived from the mesothelial surfaces of the pleura. There are tree different mesothelioma types: Epithelioid Mesothelioma; Sarcomatoid; Biphasic /Mixed Mesothelioma. Patients with mesothelioma have a poor prognosis with a median survival ranging from 6 to 18 months depending on the stage of the disease at the time of diagnosis.

Standard Management: For patients with clinical stage I-III and Epithelial or Mixed histology who are considered medically fit, surgery is recommended with extrapleural pnemonectomy (EPP) or pleurectomy/decortication (P/D). Adjuvant radiation therapy is recommended for patients with good performance status: the goal of adjuvant radiotherapy is to improve local control and it is an effective palliative treatment for relief of chest pain associated with mesothelioma. Chemotherapy alone is recommended for those who are not operable, those with clinical stage IV MPM or those with sarcomatoid histology.

Radiotherapy: The target volumes delineation, defined by the radiation oncologist, is crucial because of large and irregularly shaped area at risk, high dose required for local control, the promixity of many structures as ipsilateral kidney, heart, spinal cord, esophagus, controlateral lung and the ipsilateral lung itself in inoperable cases. Actually sophisticated RT techniques such as IMRT, IGRT, and especially helical-slit IMRT (HT) might become appropriate alternatives for either definitive or palliative treatment for suitable patients based on compatible pulmonary toxicity criteria.

The actual MPM guidelines suggest that the dose of radiation should be based on the purpose of the treatment. So the dose of radiation for adjuvant therapy should be 50-54 Gy with negative margins and 54-60 Gy with microscopic-macroscopic positive margins, in 1.8-2.0 Gy/day. For prophylactic radiation to surgical sites, a total dose of 21 Gy (3 x 7 Gy) is recommended.

Keywords: Malignant pleural mesothelioma; Radiation therapy

Introduction

Malignant pleural mesothelioma (MPM) is a neoplasm derived from the mesothelial surfaces of the pleura. It typically spreads and invades locally but distant metastases to the controlateral lung, peritoneum, bone or liver can occur [1]. In 1960, the association between MPM and asbestos was first recognized and current patterns reflect a 20-40 years latency in disease development [2]. There are tree different MPM types: Epithelioid Mesothelioma, the most common type responsible for 50 to 70 percent of cases; Sarcomatoid that more often appears in other internal organs than the lungs; Biphasic / Mixed Mesothelioma that contains both the sarcomatoid and epithelioid mesothelioma cancer cells. Patients with MPM have a poor prognosis with a median survival ranging from 6 to 18 months depending on the stage of the disease at the time of diagnosis.

Pathogenesis

Mesothelioma is an insidious disease with long latency after asbestos exposure. New cases are continually diagnosed, although levels are declining with recognition of the asbestos risk and efforts to remove asbestos from the workplace. Researchers have examined the association between asbestos and respiratory ailments for decades. The majority of asbestos fibers are either amphibole (sharp, rod-like) or serpentine. The serpentine fibers make up 90% of the type seen in the US and are considered less carcinogenic than the amphibole type. These fibers are typically found in brake linings, ship building, cement, and ceiling and pool tiles. The Occupational Safety and Health Administration (OSHA) set acceptable levels of exposure at 0.2 fibers/mL^3 for fibers 5 microns or greater and up to 5 fibers/mL^3 for smaller fibers. Inhaled asbestos fibers are trapped in the lower third of the lung, where they initiate an inflammatory response. The fibers are phagocytosed into mesothelial cells and initiate an oncogenic cascade of events that includes activation of c-Myc and c-Jun oncogenes, binding with epidermal growth factor receptors (EGFRs), and promotion of antiapoptotic genes such as Bcl-xl [3].

Clinical Presentation

Signs and symptoms associated with mesothelioma are relatively nonspecific and can be seen with almost any intrathoracic disease process, benign or malignant. Most patients have a cough, usually nonproductive. Dyspnea is also common. Chest wall pain may be a relatively unique symptom, usually described as a focal ache. Pleural effusions are common and are right sided 60% of the time. Five percent may present with bilateral effusions. Pleural plaques are common, and 1 out of 5 patients develop bibasilar fibrosis, characteristic of

***Corresponding author:** Dognin J, Radiotherapy Department, S Camillo, Forlanini Hospital , Rome, Italy, E-mail: jessica.dognini@libero.it

Received June 26, 2013; **Accepted** August 20, 2013; **Published** August 26, 2013

Citation: Donato V, Dognini J, Arcangeli S, Melis E, Facciolo F (2013) Malignant Pleural Mesothelioma: Management and Role of Radiation Therapy. J Nucl Med Radiat Ther S2: 011. doi:10.4172/2155-9619.S2-011

chronic asbestosis. Computed tomography (CT) may show pleural-based nodularity. Magnetic resonance imaging can define invasion of the diaphragm or mediastinal structures, important in preoperative assessment. Positron emission tomography (PET) is useful because mesothelioma has hypermetabolic characteristics and PET can be used not only for staging but for posttreatment follow-up as well. Several paraneoplastic syndromes have been described with mesothelioma. These include hypercalcemia, hypoglycemia, autoimmune hemolytic anemia, hypercoagulable states, and disseminated intravascular coagulation. These syndromes are nonspecific and can be seen with a number of malignancies [4].

Diagnosis

Diagnosis of mesothelioma can be difficult. The disease is relatively uncommon and the amount of tissue obtained is often minimal and may not be adequate to perform the necessary battery of tests that can distinguish mesothelioma from other pleural-based malignancies. Histologic variability may make diagnosis challenging. The most common histologic type is epithelioid and is associated with the best prognosis. Sarcomatoid variants with characteristic spindle morphology are associated with a worse prognosis. Often, mixed epithelioid and sarcomatoid histologies can be seen. Tissue obtained by cytologic analysis of pleural fluid or blind pleural biopsy is limited and under classifies the correct histology up to 25% of the time. If pleural fluid is obtained, large volume collections should be performed and a cytospin analysis conducted to increase diagnostic accuracy. Thoracoscopic biopsies with direct visualization of pleural nodules provide the best yield. Immunohistochemical staining is important to distinguish mesothelioma from adenocarcinomas of lung origin or metastatic from other sites [5]. Calretinin is commonly positive in mesothelioma, with a reported sensitivity of 95% and specificity of 87%. Thrombomodulin has the best specificity at 92% but is less sensitive at 68%. Other useful antibodies directed against mesothelial-associated antigens include mesothelin, cytokeratin 5, Wilms' tumor-1 gene product, and HBME-1 and the nonmesothelial antigens Lewis-Y blood group (antibody BG8), MOC-31, BerEp4, CD15, and the carcinoembryonic antigen family [6].

Accurate diagnosis of mesothelioma depends on adequate tissue. Traditional diagnostic procedures have included pleural fluid cytology obtained through thoracentesis, needle biopsy of pleural tissue under CT guidance, video-assisted thoracoscopy surgery with direct visualization and biopsy of pleural nodules, and open thoracotomy. Pleural fluid is usually bloody and exudative with elevated protein, lactase dehydrogenase, and cell counts, but this finding is nonspecific and the sensitivity of pleural fluid cytology is low. Video-assisted thoracoscopy has a diagnostic accuracy of 98% in experienced hands and allows for the possibility of simultaneous pleurodesis [7,8].

Staging

Several staging systems for mesothelioma have been used over the years, almost exclusively dealing with primary pleural mesothelioma. Peritoneal mesothelioma does not have its own staging system [9]. Staging is done using the International Mesothelioma Interest Group (IMIG) INM staging system which was approved by the American Joint Committee on Cancer (AJCC) (Table 1).

Standard Management

Once a diagnosis of pleural mesothelioma is confirmed, a thorough staging work-up should be undertaken to determine if a patient is amenable to surgical resection [4-11]. Pretreatment evaluation for patients with MPM diagnosis includes chest and abdominal CT with contrast 2) FDG-positron emission tomography (PET-CT). If possible, PET-CT scans should be obtained before pleurodesis, because talc causes pleural inflammation, which can affect the FDG-avidity. [12,13]. The work-up includes not only imaging and surgical staging as mentioned above, but a complete assessment of comorbidities, cardiac status, and pulmonary function testing. For patients with clinical stage I-III and Epithelial or Mixed histology who are considered medically fit, surgery is recommended with extrapleural pnemonectomy (EPP) or pleurectomy/decortication (P/D). Extrapleural pneumonectomy (EPP) was historically considered a potentially radical surgery. It involves the en bloc resection of lung, pleura, pericardium and diaphragm [14]. This aggressive operation is fraught with significant morbidity and many patients are not candidates due to poor cardioplomonary reserve or extent of disease [15,16]. Pleurectomy/Decortication (P/D) involves resection of the parietal and visceral pleurae, pericardium and diaphragm (if needed) leaving the lung intact and, historically, was reserved for patients who were unable to undergo EPP [17,18]. The perioperative outcome of EPP has improved significantly in recent years because of better surgical techniques and perioperative care [19,20]. (However, the long-term survival is still unsatisfactory due to high incidence of recurrence. Distant recurrence remained a problem in up to 55% of patients so it prompted the inclusion of chemotherapy into the multimodality approach [19]. Local recurrence after EPP, occurs in up to 80% of patients [15,19,2-23]. Recent evidence suggests that radiation therapy to the chest cavity after EPP, decreases this risk.

Adjuvant radiation therapy is recommended for patients with good performance status: the goal of adjuvant radiotherapy is to improve local control and it is an effective palliative treatment for relief of chest pain associated with mesothelioma. When there is no resection of disease delivery of high dose RT to the entire hemothorax in the setting of an intact lung has not been shown to be associated with significant survival benefit and the toxicity is significant. Chemotherapy alone is recommended for those who are not operable, those with clinical stage IV MPM or those with sarcomatoid histology.

Surgical Therapy of MPM

The role of surgery in the management of mesothelioma has been largely confined, for many years, to obtain tissue samples for pathological diagnosis or to achieve symptom's control by pleurodesis; nevertheless, in the last decades the increased incidence of the disease, together with first reports of long-term survivors has resulted in a more aggressive surgical approach (Figures 1 and 2).

Three surgical operations are currently available for the treatment of mesothelioma: extrapleural pneumonectomy, better known as pleuropneumonectomy (EPP), pleurectomy-decortication, and palliative pleurectomy.

Extrapleural pneumonectomy is the only one radical surgical option for the treatment of mesothelioma. It provides the best cytoreduction and allows postoperative higher radiation doses to be delivered to the ipsilateral hemithorax, after the lung has been removed; it is also the only feasible procedure when a thick tumor rind obliterates the pleural space.

Careful selection and preoperative assessment are mandatory in candidates for extrapleural pneumonectomy.

All patients need histological proven diagnosis of stage I to III pleural mesothelioma (T1/T3 disease, without cardiac involvement, N0/N2 disease and M0).

T1	T1a	Tumor limited to the ipsilateral parietal pleura, including mediastinal and diaphragramatic pleura No involvement of the visceral pleura
	T1b	Tumor involving the ipsilateral parietal pleura, including mediastinal and diaphragramatic pleura Scattered foci of tumor also involve in the visceral pleura
T2		Tumor involving each of the ipsilateral pleura surfaces (parietal, mediastinal and diaphragramatic and visceral pleura) with at least one of the following features:
	✓	Involvement of diaphragmatic muscle
	✓	Confluent visceral pleural tumor (including the fissures) or extensions of tumor from visceral pleura into the underlying pulmonary parenchyma
	T3	Describes locally advanced but potentially resectable tumor Tumor involving all of the ipsilateral pleura surfaces (parietal, mediastinal and diaphragramatic and visceral pleura) with at least one of the following features:
	✓	Involvement of the endotharacic facia
	✓	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	Describes locally advanced technically unresectable tumor Tumor involving all of the ipsilateral pleura surfaces (parietal, mediastinal and diaphragramatic and visceral pleura) with at least one of the following features:
	✓	Diffuse extension or multifocal masses of tumor in the chest wall, with or without associated rib destruction
	✓	Diffuse transdiaphragramatic extension of tumor to the peritoneum
	✓	Direct extension of tumor to the contralateral pleura
	✓	Direct extension of tumor to one or more mediastinal organs
	✓	Direct extension of tumor into the spine
	✓	Tumor extending through to the internal surface of pericardium, with or without a pericardial effusion; or tumor involving the myocardium N-lymph nodes
	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 theipsilateral mediastinal lymph nodes, including the ipsilaternal mammary nodes
	N3	Metastases in the contralateral mediastinal, contralateral internal mammary, contralateral supraclavicular lymph nodes
	M-	metastases
	Mx	Presence of distant metastasis cannot assessed
	M0	No distant metastasis
	M1	Distant metastasis present

Stage	Description
Ia	$T_{1x}N_0M_0$
Ib	$T1_bN_0M_0$
II	$T_2N_0M_0$
III	$AnyT_3M_0$
	$AnyN_1M_0$
	$AnyN_2M_0$
IV	$AnyT_4$
	$AnyN_3$
	$AnyM_1$

Table 1: The International Mesothelioma Interest Group (IMIG) staging system.

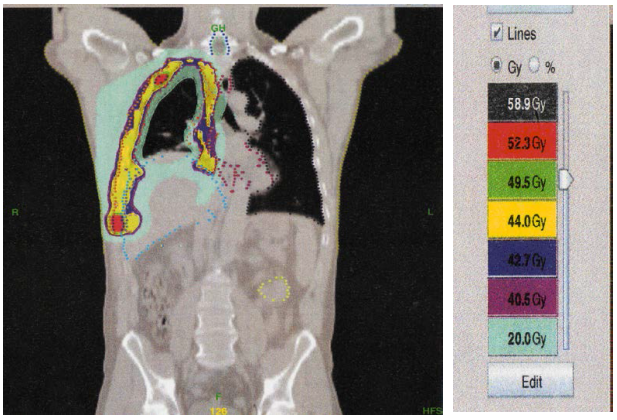

Figure 1: A coronal view of the dose distribution in a representative case.

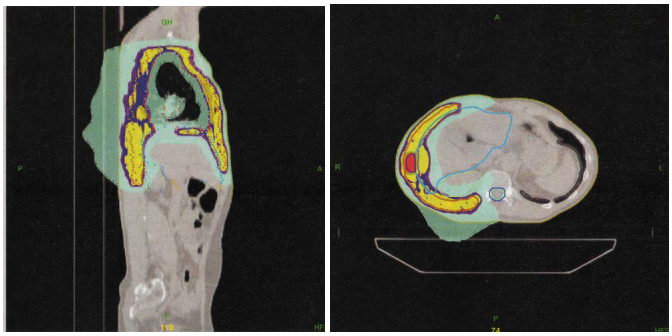

Figure 2: A sagittal and axial view of the dose distribution in a representative case.

Cardio-pulmonary assessment is mandatory in all patients candidate to extrapleural pneumonectomy; to be eligible for EPP patients need a Karnofsky performance status higher than 70, normal liver and kidney function tests.

VATS indications are staging, diagnosis and palliative treatment of malignant pleural mesothelioma. Thoracoscopic exploration allows examination of parietal, visceral, diaphragmatic and mediastinal pleura; it also allows inspection of pericardium and yields high quality bioptic samples.

Talc poudrage results in a highly effective control of pleural

effusion and provides excellent palliation for patients whose general medical condition prevents a more aggressive treatment. Nevertheless thoracoscopy and talc pleurodesis facilitates subsequent extrapleural dissection and prevent intraoperative spillage of malignant cells during extrapleural pneumonectomy; it should be performed 30 to 40 days before EPP.

Mortality rate of extrapleural pneumonectomy is comparable, at present, to a standard pneumonectomy, ranging about 3.8%; accurate patient selection, advances in preoperative and intraoperative management and postoperative care are very important to achieve such low mortality.

Palliative pleurectomy is based on the partial or total resection of the parietal pleura, to control pleural effusion by creating a durable pleruodesis; pleurectomy-decortication (P/D) is instead an attempt to remove all grossly evident pleural disease, without removing the underlying lung. If the tumor has not spread to the underlying lung, P/D is performed to remove the entire tumor; P/D is associated with few complications, low mortality rates and has the best results in early stage patients. Blood loss and air leaks are the most common complications.

Decortication is performed to remove any tumor on the visceral lining; the technical goal of this procedure is the macroscopic oncological radicality and the good re-expansion of the lung.

Radiation Therapy

The role of radiotherapy in MPM is defined by symptomatic relief and palliation, prevention of neoplastic cell seeding and adjuvant therapy following surgery for early stage disease [24]. The effect of radiation monotherapy on prolonging survival is minimal so the multimodality approach has a strong locoregional treatment rationale. The target volumes delineation, defined by the radiation oncologist, is crucial because of large and irregularly shaped area at risk, high dose required for local control, the promixity of many structures as ipsilateral kidney, heart, spinal cord, esophagus, controlateral lung and the ipsilateral lung itself in inoperable cases.

The first question is on surgery's technique before RT: pleurectomy/decortication (P/D) or extrapleural pneumonectomy (EPP)? Yan et al. reported an observational study on a cohort of 70 patients with MPM to evaluate perioperative and long term outcomes associated with EPP. Of these 70 patients, 63 (90%) had a complete cytoreduction and the remaining 7 (10%) had residual macroscopic disease. Postoperatively, 28 patients received adjuvant ipsilateral radiotherapy and 16 patients received pemetrexed combined with cisplatin or carboplatin. Eleven patients received more than 1 adjuvant therapy and 4 received neoadjuvant chemotherapy. The follow-up was complete. The median survival was 20 months (range 0-104 months) with 1-2-3-4 and 5 years survivals of 62%, 41%, 30% and 15 % respectively. Twenty-six patients (37%) remained alive at the last follow-up. The present study demonstrayed a perioperative mortality of 5.7% and an overall morbidity of 37% supporting the use of EPP in carefully selected patients with MPM [25]. Adjuvant radiotherapy seems improve locoregional control of MPM. Rusch et al. performed a phase II trial of surgical resection and adjuvant high-dose henithoracic radiation for MPM. From 1995 to 1998, 88 patients were entered into the study. The operations performed included 62 EPP and 5 P/D; procedures for exploration only were performed in 21 patients. Seven patients died postoperatively. Adjuvant radiation was administered to 57 patients with a median dose of 54 Gy (range 20-64 Gy). In general radiation was well tolerated with most toxicities being of grades 1 and 2. Grade toxicities included fatigue, esophagitis, nausea and vomiting. The most serious grade 4 toxicity was an esophagopleural fistula which developed several months after the completion of radiation and required surgical intervention. Survival was estimated for the patients who underwent EPP. The median survival was 17 months and the overall survival at 3 years was 27% with a longer median survival for stage I and II tumors [23]. In another study 35 patients were treated with EPP followed by hemithoracic radiation therapy using combined photon and electron technique (median dose 54 Gy: range 45-54 Gy and 180 cGy/die). The radiation therapy target volume was the entire hemithorax, including the pleural folds and the thoracotomy and chest tube incision sites. The most common toxicities were RTOG grades 1 and 2 nausea and vomiting as well as lung, esophageal and skin toxicities resulting in a feasible and well tolerated treatment regimen with adequate dose distributions [22]. However, radiotherapy for patients with MPM and an attempt to treat the entire involved pleural surface at a potentially curative dose (60 Gy), is limited because of the large target volume, the high risk of radiation pneumonitis and the radiosenitivity of heart, mediastinum, liver and spinal cord. In this setting, more sophisticated RT techniques such as IMRT, IGRT, and especially helical-slit IMRT (HT) might become appropriate alternatives for either definitive or palliative treatment for suitable patients based on compatible pulmonary toxicity criteria. A report of 2003 studied 28 patients with MPM who underwent EPP surgery with no evidence of extrathoracic disease and were treated with postoperative radiotherapy using IMRT. They were irradiated between 2000 and 2002. Treatment was delivered once daily in five fractions/week using 6 MV photons. CTV doses were 45-50 Gy to hemithorax with boost taken to 60 Gy. The commonest side effects were nausea, anorexia, and vomiting occurring in 89% of patients and fatigue occurring in 80% of patients. Dysphagia caused by radiation esophagitis was mild or absent. At a median follow-up of 9 months (range 5-27 months) the overall survival at 1 and 2 years was 65% and 49% respectively. The disease specific survival at 1 and 2 years was 88% and 58% respectively with in-field local control of 100%. IMRT is praticable with minimal target motion; IMRT plans can irradiate the hemithorax without spreading the dose to the remaining lung [22]. This Radiothearpy technique has allowed for an increase in dose to the pleural cavity and a reduction in radiation doses to organs at risk. Kristensen et al. reports and analyses the incidence of fatal pulmonary toxicity in patients treated at Rigs hospital, Copenhagen. Twenty-six patients were treated with induction chemotherapy followed by extrapleural pneumonectomy and IMRT between April 2003 and April 2006. The entire preoperative pleural surface area was treated to 50 Gy and areas with residual disease or close surgical margins were treated to 60 Gy in 30 fractions. The main toxicities were nausea, vomiting, esophagitis, dyspnea, and thrombocytopenia. Four patients (15%) experienced grade 5 lung toxicity, i.e. pneumonitis 19–40 days after the completion of radiotherapy. Patients with pneumonitis had a significantly larger lung volume fraction receiving 10 Gy or more (V10) (median: 60.3%, range 56.4-3.2%) compared to patients without pneumonitis (median: 52.6%, range: 25.6–80.3%) (p=0.02). Mean lung dose (MLD) was also significantly higher in patients who developed pneumonitis (median 13.9 Gy, range: 13.6–14.2 Gy) than in patients who did not (median=12.4 Gy, range: 8.4–15.4 Gy) (p=0.04) [26]. Helical tomotherapy is a promising method, and achieves a better dose conformity. Sterzing et al. in 2008 evaluated the potential of Helical Tomotherapy in the adjuvant radiotherapy of MPM comparing target homogeneity, conformity and normal tissue dose with step-and-shoot IMRT. Ten patients with MPM were treated in our department with 54 Gy to the hemithorax delivered by step-and-shoot IMRT. A planning comparison was performed by creating radiation plans for helical

tomotherapy. Both modalities achieved excellent dose distributions while sparing organs at risk. Target coverage and homogeneity could be increased significantly with helical tomotherapy compared with step-and-shoot IMRT so could be an excellent option for adjuvant intensity-modulated radiotherapy of MPM [27].

The actual MPM guidelines suggest that the dose of radiation should be based on the purpose of the treatment. So the dose of radiation for adjuvant therapy should be 50-54 Gy with negative margins and 54-60 Gy with microscopic-macroscopic positive margins, in 1.8-2.0 Gy/day. For prophylactic radiation to surgical sites, a total dose of 21 Gy (3x 7 Gy) is recommended. Computed Tomography (CT) is used in RT planning: each patient is simulated and treated in supine position with both arms raised above their heads positioning. The Clinical Tumor Volume (CTV) should encompass the entire pleural surface (for partial resection cases) or the entire hemithorax, surgical clips and any potential sites with residual disease. The Planning Target Volume (PTV) should consider the target motion and daily set-up errors. IMRT is a promising treatment technique that allows a more conformal high-dose RT improving coverage to the hemithorax. Especially IMRT with Helical tomoterapy technique achieves a better dose conformity [28-35].

Radiation Technique after Radical Pleurectomy/ Decortication: Volumes, Prescription and Delivery

The clinical target volume (CTV) should encompass the entire pleural surface, from the lung apex down to the insertion of the diaphragm - often in the vicinity of the L2 vertebral body - including ipsilateral mediastinal lymph nodes in case of pathological N1–2 disease. Extensive elective nodal irradiation is not recommended. Thoracotomy scars should also be included in the CTV. Medially, the CTV includes the ipsilateral pericardium. Any potential sites of residual disease (positive margins, or areas of PET FDG uptake at postoperative restaging) should receive a radiation boost. IGRT should be used to minimize target motion and daily set-up errors. If it is indeed the case, an isotropic expansion of 5 mm around the CTV can be considered for planning target volume (PTV). Organs at risk should include the ipsilateral and contralateral lung, heart, esophagus, liver, kidneys, gastrointestinal tract, and spinal cord [36-41].

Dose prescription to the median dose point of the entire PTV is 50 Gy delivered in 25 fractions (2 Gy/fraction), and a simultaneous boost to any fluorodeoxyglucose-avid areas or regions of particular concern for residual disease up to 60 Gy (2.4 Gy/fraction) [42].

Specific dosimetric guidelines for OARs (organ at risks) in accordance to the Quantec dose-volume model are the following: lung: V5 less than 60%, V20 less than 4-10%, mean lung dose less than 8 Gy; spinal cord: maximum dose less than 50 Gy; esophagus: mean volume less than 34Gy, V35 less than 50%, V50 less than 40%; heart: mean volume less than 26Gy, V30 less than 46%, V25 less than 10%; gastrointestinal tract: V15 less than 120 cc, V45 less than 195 cc; kidneys: mean kidney dose less than 18 Gy, V28 less than 20%, V20 less than 32%; liver V30 less than 40%.

Dose computation and treatment delivery are performed on the Tomo-Therapy HiArt II system (TomoTherapy Inc., Madison, WI). Image Guided Radiotherapy (IGRT) is performed by means of a Megavolt Computed Tomography (MVCT) before each daily session and positioning done using the integrated registration with the planning CT to account for set-up uncertainties [43-48].

The use of radiation therapy as adjuvant treatment is practicable. Intensity-Modulated Radiotherapy (IMRT) especially using helical tomotherapy allows the safe delivery of high dose of radiation. It can provide a highly conformal dose to irregularly shaped target and a steep dose gradient near the critical structures. Surgery and radiotherapy could be the future for MPM treatment [49-56].

References

1. Zellos L, Christiani DC (2004) Epidemiology, biologic behavior, and natural history of mesothelioma. Thorac Surg Clin 14: 469-477, viii.
2. WAGNER JC, SLEGGS CA, MARCHAND P (1960) Diffuse pleural mesothelioma and asbestos exposure in the North Western Cape Province. Br J Ind Med 17: 260-271.
3. Heintz NH, Janssen-Heininger YM, Mossman BT (2010) Asbestos, lung cancers, and mesotheliomas: from molecular approaches to targeting tumor survival pathways. Am J Respir Cell Mol Biol 42: 133-139.
4. Flores RM, Akhurst T, Gonen M, Larson SM, Rusch VW (2003) Positron emission tomography defines metastatic disease but not locoregional disease in patients with malignant pleural mesothelioma. J Thorac Cardiovasc Surg 126: 11-16.
5. Yaziji H, Battifora H, Barry TS, Hwang HC, Bacchi CE, et al. (2006) Evaluation of 12 antibodies for distinguishing epithelioid mesothelioma from adenocarcinoma: identification of a three-antibody immunohistochemical panel with maximal sensitivity and specificity. Mod Pathol 19: 514-523.
6. Husain AN, Colby TV, Ordóñez NG, Krausz T, Borczuk A, et al. (2009) Guidelines for pathologic diagnosis of malignant mesothelioma: a consensus statement from the International Mesothelioma Interest Group. Arch Pathol Lab Med 133: 1317-1331.
7. Bölükbas S, Manegold C, Eberlein M, Bergmann T, Fisseler-Eckhoff A, et al. (2009) Survival after trimodality therapy for malignant pleural mesothelioma: Radical Pleurectomy, chemotherapy with Cisplatin/Permetrexed and radiotherapy. Lung Cancer 71: 75-81.
8. Heffner JE, Klein JS (2008) Recent advances in the diagnosis and management of malignant pleural effusions. Mayo Clin Proc 83: 235-250.
9. Boutin C, Rey F, Gouvernet J, Viallat JR, Astoul P, et al. (1993) Thoracoscopy in pleural malignant mesothelioma: a prospective study of 188 consecutive patients. Part 2: Prognosis and staging. Cancer 72: 394-404.
10. Edge S, Byrd DR, Compton CC, Fritz AG, Greene FL, et al. (2010) AJCC Cancer Staging Manual. 7th ed. Springer Publications, New York, USA
11. Arapis K, Caliandro R, Stern JB, Girard P, Debrosse D, et al. (2006) Thoracoscopic palliative treatment of malignant pleural effusions: results in 273 patients. Surg Endosc 20: 919-923.
12. Schulze M, Boehle AS, Kurdow R, Dohrmann P, Henne-Bruns D (2001) Effective treatment of malignant pleural effusion by minimal invasive thoracic surgery: thoracoscopic talc pleurodesis and pleuroperitoneal shunts in 101 patients. Ann Thorac Surg. 71: 1809-1812.
13. Sugarbaker DJ, Norberto JJ (1998) Multimodality management of malignant pleural mesothelioma. Chest 113: 61S-65S.
14. Ahmadzadehfar H, Palmedo H, Strunk H, Biersack HJ, Habibi E, et al. (2007) False positive 18F-FDG-PET/CT in a patient after talc pleurodesis. Lung Cancer 58: 418-421.
15. Rusch VW, Piantadosi S, Holmes EC (1991) The role of extrapleural pneumonectomy in malignant pleural mesothelioma. A Lung Cancer Study Group trial. J Thorac Cardiovasc Surg 102: 1-9.
16. Grondin SC, Sugarbaker DJ (1999) Pleuropneumonectomy in the treatment of malignant pleural mesothelioma. Chest 116: 450S-454S.
17. van Ruth S, Baas P, Zoetmulder FA (2003) Surgical treatment of malignant pleural mesothelioma: a review. Chest 123: 551-561.
18. Rusch VW (1997) Pleurectomy/decortication in the setting of multimodality treatment for diffuse malignant pleural mesothelioma. Semin Thorac Cardiovasc Surg 9: 367-372.
19. Sugarbaker DJ, Jaklitsch MT, Bueno R, Richards W, Lukanich J, et al. (2004) Prevention, early detection, and management of complications after 328 consecutive extrapleural pneumonectomies. J Thorac Cardiovasc Surg 128: 138-146.

20. de Perrot M, McRae K, Anraku M, Karkouti K, Waddell TK, et al. (2008) Risk factors for major complications after extrapleural pneumonectomy for malignant pleural mesothelioma. Ann Thorac Surg 85: 1206-1210.

21. Yajnik S, Rosenzweig KE, Mychalczak B, Krug L, Flores R, et al. (2003) Hemithoracic radiation after extrapleural pneumonectomy for malignant pleural mesothelioma. Int J Radiat Oncol Biol Phys 56: 1319-1326.

22. Rusch VW, Rosenzweig K, Venkatraman E, Leon L, Raben A, et al. (2001) A phase II trial of surgical resection and adjuvant high-dose hemithoracic radiation for malignant pleural mesothelioma. J Thorac Cardiovasc Surg 122: 788-795.

23. Yan TD, Boyer M, Tin MM, Wong D, Kennedy C, et al. (2009) Extrapleural pneumonectomy for malignant pleural mesothelioma: outcomes of treatment and prognostic factors. J Thorac Cardiovasc Surg 138: 619-624.

24. Kristensen CA, Nøttrup TJ, Berthelsen AK, Kjaer-Kristoffersen F, Ravn J, et al. (2009) Pulmonary toxicity following IMRT after extrapleural pneumonectomy for malignant pleural mesothelioma. Radiother Oncol 92: 96-99.

25. Ahamad A, Stevens CW, Smythe WR, Liao Z, Vaporciyan AA, et al. (2003) Promising early local control of malignant pleural mesothelioma following postoperative intensity modulated radiotherapy (IMRT) to the chest. Cancer J 9: 476-484.

26. Sterzing F, Sroka-Perez G, Schubert K, Münter MW, Thieke C (2008) Evaluating target coverage and normal tissue sparing in the adjuvant radiotherapy of malignant pleural mesothelioma helical tomotherapy compared with step-and-shoot IMRT. Radiother Oncol 86: 251-257.

27. de Graaf-Strukowska L, van der Zee J, van Putten W, Senan S (1999) Factors influencing the outcome of radiotherapy in malignant mesothelioma of the pleura--a single-institution experience with 189 patients. Int J Radiat Oncol Biol Phys 43: 511-516.

28. Rice DC, Smythe WR, Liao Z, Guerrero T, Chang JY, et al. (2007) Dose-dependent pulmonary toxicity after postoperative intensity-modulated radiotherapy for malignant pleural mesothelioma. Int J Radiat Oncol Biol Phys 69: 350-357.

29. Rice DC, Stevens CW, Correa AM, Vaporciyan AA, Tsao A, et al. (2007) Outcomes after extrapleural pneumonectomy and intensity-modulated radiation therapy for malignant pleural mesothelioma. Ann Thorac Surg 84: 1685-1692.

30. Tsao AS, Wistuba I, Roth JA, Kindler HL (2009) Malignant pleural mesothelioma. J Clin Oncol 27: 2081-2090.

31. Pilling J, Dartnell JA, Lang-Lazdunski L (2010) Integrated Positron emission tomography-computed tomography does not accurately stage intrathoracic disease of patients undergoing trimodality theapy for malignant pleural mesothelioma. Thorac Cardiovasc Surg 58: 215-219.

32. Van Schil PE (2013) Treatment of mesothelioma: still a long way to go! Chin J Cancer Res 25: 132-133.

33. Shersher DD, Liptay MJ (2013) Multimodality treatment of pleural mesothelioma. Surg Oncol Clin N Am 22: 345-355.

34. Rusch V, Baldini EH, Bueno R, De Perrot M, Flores R, et al. (2013) The role of surgical cytoreduction in the treatment of malignant pleural mesothelioma: meeting summary of the International Mesothelioma Interest Group Congress, September 11-14, 2012, Boston, Mass. J Thorac Cardiovasc Surg 145: 909-910.

35. Yanagawa J, Rusch V (2013) Surgical management of malignant pleural mesothelioma. Thorac Surg Clin 23: 73-87, vi.

36. Chen SE, Pace MB (2012) Malignant pleural mesothelioma. Am J Health Syst Pharm 69: 377-385.

37. Raja S, Murthy SC, Mason DP (2011) Malignant pleural mesothelioma. Curr Oncol Rep 13: 259-264.

38. Cao CQ, Yan TD, Bannon PG, McCaughan BC (2010) A systematic review of extrapleural pneumonectomy for malignant pleural mesothelioma. J Thorac Oncol 5: 1692-1703.

39. Sugarbaker DJ, Wolf AS (2010) Surgery for malignant pleural mesothelioma. Expert Rev Respir Med 4: 363-372.

40. Richards WG, Godleski JJ, Yeap BY, Corson JM, Chirieac LR, et al. (2010) Proposed adjustments to pathologic staging of epithelial malignant pleural mesothelioma based on analysis of 354 cases. Cancer 116: 1510-1517.

41. Hasegawa S (2009) [Therapeutic strategies for resectable malignant pleural mesothelioma]. Nihon Geka Gakkai Zasshi 110: 338-342.

42. Okubo K, Sonobe M, Fujinaga T, Shoji T, Sakai H, et al. (2009) Survival and relapse pattern after trimodality therapy for malignant pleural mesothelioma. Gen Thorac Cardiovasc Surg 57: 585-590.

43. Flores RM (2009) Surgical options in malignant pleural mesothelioma: extrapleural pneumonectomy or pleurectomy/decortication. Semin Thorac Cardiovasc Surg 21: 149-153.

44. Buduhan G, Menon S, Aye R, Louie B, Mehta V, et al. (2009) Trimodality therapy for malignant pleural mesothelioma. Ann Thorac Surg 88: 870-875.

45. Wolf AS, Daniel J, Sugarbaker DJ (2009) Surgical techniques for multimodality treatment of malignant pleural mesothelioma: extrapleural pneumonectomy and pleurectomy/decortication. Semin Thorac Cardiovasc Surg 21: 132-148.

46. Batirel HF, Metintas M, Caglar HB, Yildizeli B, Lacin T, et al. (2008) Trimodality treatment of malignant pleural mesothelioma. J Thorac Oncol 3: 499-504.

47. Flores RM, Pass HI, Seshan VE, Dycoco J, Zakowski M, et al. (2008) Extrapleural pneumonectomy versus pleurectomy/decortication in the surgical management of malignant pleural mesothelioma: results in 663 patients. J Thorac Cardiovasc Surg 135: 620-626.

48. Schipper PH, Nichols FC, Thomse KM, Deschamps C, Cassivi SD, et al. (2008) Malignant pleural mesothelioma: surgical management in 285 patients. Ann Thorac Surg 85: 257-264.

49. Flores RM, Krug LM, Rosenzweig KE, Venkatraman E, Vincent A, et al. (2006) Induction chemotherapy, extrapleural pneumonectomy, and postoperative high-dose radiotherapy for locally advanced malignant pleural mesothelioma: a phase II trial. J Thorac Oncol 1: 289-295.

50. Neragi-Miandoab S (2006) Multimodality approach in management of malignant pleural mesothelioma. Eur J Cardiothorac Surg 29: 14-19.

51. Stahel R, Weder W (2005) Neoadjuvant chemotherapy in malignant pleural mesothelioma. Lung Cancer 49 Suppl 1: S69-70.

52. Erasmus JJ, Truong MT, Smythe WR, Munden RF, Marom EM, et al. (2005) Integrated computed tomography-positron emission tomography in patients with potentially resectable malignant pleural mesothelioma: Staging implications. J Thorac Cardiovasc Surg 129: 1364-1370.

53. Sugarbaker DJ, Flores RM, Jaklitsch MT, Richards WG, Strauss GM (1999) Resection margins, extrapleural nodal status and cell type determine postoperative long-term survival in trimodality therapy of malignant pleural mesothelioma: results in 183 patients. J Thorac Cardiovasc Surg117: 54-65.

54. Grondin SC, Sugarbaker DJ (1999) Pleuropneumonectomy in the treatment of malignant pleural mesothelioma. Chest 116: 450S-454S.

55. Curran D, Sahmoud T, Therasse P, van Meerbeeck J, Postmus PE, et al. (1998) Prognostic factors in patients with pleural mesothelioma: the European Organization for Research and Treatment of Cancer experience. J Clin Oncol 16: 145-152.

56. Sugarbaker DJ, Norberto JJ, Swanson SJ (1997) Extrapleural pneumonectomy in the setting of multimodality therapy for diffuse malignant pleural mesothelioma. Semin Thorac Cardiovasc Surg 9: 373-382.

This article was originally published in a special issue, **Surgical Oncology: Clinical Importance** handled by Editor(s). Dr. Liqiang Zhang, Arizona State University, USA; Dr. Salomone Di Saverio, Surgery and Trauma Surgery Unit, Italy