Mesothelioma

Bailey Nelson, MD - PGY-3

Faculty Advisor: Emily C. Daugherty, MD - Assistant Professor

Department of Radiation Oncology
University of Cincinnati Cancer Center
Cincinnati, Ohio
Outline

- Case Presentation
  - Workup
  - Management
    - Adjuvant radiotherapy
      - Target delineation
      - Constraints
      - Plan Evaluation
      - Follow-up
  - Adjuvant radiotherapy
  - Target delineation
  - Constraints
  - Plan Evaluation
  - Follow-up

- Background
- Workup
- Staging
- Management
  - Chemotherapy
  - Surgery
  - Radiation
    - RT after EPP
    - RT after P/D
    - Pre-operative RT
    - Palliative RT
Case: Clinical Presentation

- 67-year-old man presents to ED from pulmonologist’s office with a large right-sided hydropneumothorax on CXR. He reports that 1 year prior, he was incidentally found to have a right-sided pneumothorax on CXR. Complains of new dyspnea and cough.

- **PMH/PSH:** HTN, HLD. Prior back and R shoulder surgery
- **FH:** Father (deceased) had mesothelioma – known asbestos exposure at his work at a paper mill.
- **SH:** Retired welder, known exposure to chromium in electroplating; Former smoker (15 pack-year smoking history, quit over 30 years ago).
- **Medications/Allergies:** non-contributory
- **Physical Examination:** Well-appearing, no palpable lymphadenopathy in cervical or supraclavicular lymph nodes. Lung sounds clear, but decreased at bases. Normal respiratory effort. No audible friction rub. No pain reported on deep inhalation.
Case: Diagnostic Workup

• **IR** consulted for chest tube

• **Imaging** ordered
  - Repeat CXR: worsening right-sided pneumothorax with an ipsilateral pleural effusion/ hydropneumothorax
  - CT Chest: right pleural effusion, approximately 15% right pneumothorax

• **Thoracentesis**: 800cc of bloody, exudative fluid
  - Pleural fluid cytology negative x 2

• **Thoracoscopy and right pleural biopsy** performed:
  - Invasive tumor, consistent with malignant mesothelioma, epithelioid type
    - Immunostains for pankeratin (positive), CK5/6 (positive), calretinin (positive), podoplanin (positive), TTF-1(negative), and p40 (negative)
Case: Diagnostic Workup

• CT Chest/Abdomen with contrast: No distant metastases or regional lymphadenopathy; calcified pleural plaques bilaterally

• PET/CT: FDG uptake is seen in chest wall, mediastinal, and diaphragmatic pleura

• PFTs: FEV1 64%, FVC 58%, FEV1/FVC 81%, DLCO 74%

• Thoracic Surgery consultation:
  • Performed cervical mediastinoscopy with diagnostic laparoscopy: Station 7 and 4R, negative for malignancy
  • Per thoracic surgeon, staged as cT3 due to intra-op findings
Case: Imaging

FDG avid right pleural nodularity. No extrapleural disease.

Large hydropneumothorax, increased in size from PET/CT. Pleural plaques unchanged.
Case: Diagnostic Workup

• Multidisciplinary tumor board evaluation
  • Team recommended induction chemotherapy with pemetrexed + cisplatin followed by restaging and potential resection
  • Decision based on:
    • ECOG Performance Status of 0
    • Epithelioid histology
    • Potentially resectable cT3N0 disease
  • Per NCCN, malignant mesothelioma **should be treated/referred to centers that have experience treating the disease**
Case: Management

• **Induction chemotherapy:** Patient completed 3 cycles of cisplatin and pemetrexed

• **Surgical Resection:**
  - Right thoracotomy, extended pleurectomy and total decortication (P/D), diaphragm resection with reconstruction, mediastinal lymph node resection and latissimus muscle flap transfer, gross total resection

• **Surgical Pathology:**
  - **Histology:** epithelioid malignant mesothelioma
  - **Extension:** limited to parietal pleura with focal involvement of ipsilateral visceral, mediastinal and diaphragmatic pleura, involves diaphragmatic muscle; solitary focus extending into soft tissues of chest wall
  - **Pathologic AJCC 8th edition stage:** ypT3N0cM0 (Stage IB)

• Post-operative course was uneventful
Case: Adjuvant Therapy

• After multidisciplinary discussion post-operatively, adjuvant radiotherapy was recommended given the patient’s good performance status and extension into the diaphragm and soft tissues of the chest wall
  • NCCN recommends consideration of adjuvant hemithoracic IMRT after P/D
  • Goal of PORT is to improve local control

• Consult with Radiation Oncology:
  • Hemithoracic IMRT 50.4 Gy recommended
Adjuvant Radiotherapy

• CT Simulation and Image Guidance:
  • Position: supine, arms over head, customized mold, vac-lock bag
    • Place a wire marker over scars and drain sites, consider bolus to increase surface dose if clinically indicated
    • If bolus used, typically 0.5 cm thick and 3-3.5 cm in diameter
  • 4D CT scan and/or free-breathing CT recommended
  • Borders: include entire thorax
    • Extend from above lung apex to at least L3 (lowest insertion point of the diaphragm with margin inferiorly)

• Co-register PET-CT and MRI scans if available
• All patients should have daily image guidance with kV images or Cone Beam CT scans (CBCT)
Target Delineation

• Target Volumes:
  • **GTV**: gross disease (if applicable)
  • **iGTV**: expansion of GTV to account for respiratory motion (if applicable)
  • **CTV_Inner**: lung/chest wall interface, with 3 mm *internal* margin surrounding slices with GTV
  • **CTV_Outer**: lung/chest wall interface, with 3 mm *external* margin surrounding slices with GTV
  • **ITV_Inner**: internal expansion of CTV_Inner to account for heart and respiratory motion
  • **ITV_Outer**: external expansion of CTV_Outer to account for heart and respiratory motion
  • **PTV_Inner**: 6mm *internal* expansion of ITV_Inner
  • **PTV_Outer**: 1 cm *external* expansion of ITV_Outer
    • Adjust to cover the entire thickness of the chest wall. Expand PTV_Outer to the lateral edge of the sternum anteriorly, costovertebral joint and lateral edge of the vertebral body, costodiaphragmatic and costomediastinal recess and crus of the diaphragm
  • **PTV**: the rind between the PTV_Outer and PTV_Inner constitutes the final PTV
Target Delineation

• Contouring Resources:
    • https://pubmed.ncbi.nlm.nih.gov/31125736/
  • NRG LU-006 Contouring Atlas Reference
    • https://www.nrgoncology.org/ciro-lung
Case: Contours

ITV_5040

PTV_5040
<table>
<thead>
<tr>
<th>Target/OAR</th>
<th>Dosimetric Guideline</th>
</tr>
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<tbody>
<tr>
<td>GTV</td>
<td>D95% ≥ 95%</td>
</tr>
<tr>
<td>PTV</td>
<td>D95% ≥ 94%&lt;br&gt;D5% &lt; 115%&lt;br&gt;Dmax ≤ 130% (all hotspots &gt;115% must be in PTV)</td>
</tr>
<tr>
<td>Spinal Cord</td>
<td>D0.03 cc ≤ 50 Gy</td>
</tr>
<tr>
<td>Contralateral Lung</td>
<td>Mean ≤ 8 Gy (≤ 10 Gy acceptable)&lt;br&gt;V20 ≤ 5% (≤ 7% acceptable)&lt;br&gt;V5 ≤ 50% (≤ 80% acceptable)</td>
</tr>
<tr>
<td>Ipsilateral Lung</td>
<td>V40 ≤ 67% (≤ 90% acceptable)</td>
</tr>
<tr>
<td>Esophagus</td>
<td>Mean ≤ 34 Gy</td>
</tr>
<tr>
<td>Brachial Plexus</td>
<td>Dmax &lt; 65 Gy</td>
</tr>
<tr>
<td>Heart</td>
<td>Right-sided disease: V40 ≤ 25%&lt;br&gt;Left-sided disease: V40 ≤ 35%</td>
</tr>
<tr>
<td>Kidneys</td>
<td>V18 ≤ 33%</td>
</tr>
<tr>
<td>Liver-GTV</td>
<td>Mean ≤ 30 Gy&lt;br&gt;V30 ≤ 50%</td>
</tr>
<tr>
<td>Sp_Bowel</td>
<td>D0.03cc ≤ 55%&lt;br&gt;D5cc &lt; 50 Gy</td>
</tr>
<tr>
<td>Stomach-PTV</td>
<td>Mean ≤ 30 Gy</td>
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</table>
# Case: Plan Evaluation

<table>
<thead>
<tr>
<th>Tissue</th>
<th>D95%</th>
<th>V40%</th>
<th>Gent</th>
<th>Max</th>
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<tbody>
<tr>
<td>PTV</td>
<td>96%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart</td>
<td></td>
<td>26%</td>
<td>Mean: 20.4 Gy</td>
<td></td>
</tr>
<tr>
<td>Esophagus</td>
<td></td>
<td></td>
<td>Mean: 31.6 Gy</td>
<td></td>
</tr>
<tr>
<td>Contralateral Lung</td>
<td>Mean: 5 Gy</td>
<td>V20: 0.03%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ipsilateral Lung</td>
<td></td>
<td>V40: 67%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spinal Cord</td>
<td></td>
<td></td>
<td>Max 44.6 Gy</td>
<td></td>
</tr>
<tr>
<td>Liver-GTV</td>
<td></td>
<td>Mean: 27 Gy</td>
<td>V30: 35%</td>
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Case: Follow-Up

• **Treatment Course**
  - Grade 1 esophagitis
  - Grade 1 lung toxicity (mild cough)

• **Post-RT Follow-Up**
  - Patient required steroids ~ 1 year following RT for presumptive grade 2 radiation pneumonitis
  - Post-treatment PFTs showed restrictive defect (~1 year following RT)
    - Referred to Pulmonology

• Currently with no evidence of disease ~1.5 years following completion of RT
  - Not on oxygen
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      - RT after P/D
      - Pre-operative RT
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Background

- Malignant mesotheliomas account for <2% of all cancers; 81% mesotheliomas are pleural - could also arise from peritoneum, pericardium, tunica vaginalis

- The most common risk factor: **known asbestos exposure**
  - **Long latency period** from exposure, ≥ 20-40 years
  - Exposure accounts for at least 80-90% of all cases
  - Occupations with high risk of exposure:
    - Auto mechanics, construction workers, firefighters, insulation installers, machinists, miners, power plant workers, railroad workers, shipyard workers
    - Secondhand exposure commonly occurs when asbestos fibers are brought home on workers’ hair, skin and clothing

- Other risk factors: smoking (tobacco use is synergistic), BAP1 mutation, DNA tumor simian virus SV40 (acts as co-carcinogen with asbestos), prior RT

- Patients most commonly present with recurrent pleural effusion and/or pleural thickening found incidentally on CXR, dyspnea and chest pain
Workup Pearls

- Thorascopic biopsy preferred (VATS) in order to minimize number of ports due to concern for needle track seeding; FNA not recommended for diagnosis

- Mesothelioma may be confused with metastatic adenocarcinoma, other mets to pleura, such as thymoma metastatic to pleura
  - **Mesothelioma:** (-) for TTF-1, PAS, CEA but (+) for calretinin, vimentin, WT1, and cytokeratin 5/6.

- **Understaging common with PET/CT** but PET useful to determine presence of distant metastatic disease and thus, is highly recommended

- **MRI is not routinely recommended** but can be useful to delineate tumor extension into diaphragm, endotheracic fascia, chest wall or iatrogenic tumor seeding

- **If surgical resection is being considered,** perform mediastinoscopy or endobronchial ultrasound (EBUS) FNA of mediastinal lymph nodes and obtain PFTs

- Pleurodesis status should be known when interpreting CT or PET imaging; talc produces pleural inflammation which can lead to false-positive result
Genetic Testing: BAP1

• BRCA1-Associated Protein (BAP1) is a gene which can increase susceptibility to mesothelioma

• BAP1 is a tumor suppressor and metastasis suppressor gene
  • Associated with uveal melanoma, malignant mesothelioma, renal cell carcinoma, and cutaneous melanoma
  • Median age of mesothelioma diagnosis significantly younger among BAP1 mutation carriers as compared to non-carriers (58y v 68y, respectively)
  • Overrepresentation of peritoneal malignant mesotheliomas in mutation carriers
  • Tendency for epithelioid mesothelioma in mutation carriers

• Consider genetic testing for these patients.
| **T category** | TX: Primary tumor cannot be assessed  
T0: No evidence of primary tumor  
T1: Tumor limited to the ipsilateral parietal with or without involvement of visceral pleural, mediastinal pleura or diaphragmatic pleura  
T2: Involvement of the diaphragmatic muscle or extension of tumor into pulmonary parenchyma  
T3: Locally advanced but potentially resectable (involvement of endothoracic fascia, extension into mediastinal fat, solitary completely resectable focus of tumor extending into soft tissues of the chest wall, nontransmural involvement of pericardium)  
T4: Locally advanced technically unresectable (extension to peritoneum, rib destruction, contralateral pleural involvement, extension to mediastinal organs, extension to spine, involving myocardium, etc) |
| **N category** | NX: Regional lymph nodes cannot be assessed  
N0: No regional lymph node metastases  
N1: Metastases in the ipsilateral bronchopulmonary, hilar, or mediastinal lymph nodes  
N2: Metastases in the contralateral mediastinal, ipsilateral, or contralateral |
| **M category** | M0: No distant metastases  
M1: Distant metastases present |
| **Group Stage** | IA: T1N0  
IB: T2-3N0  
II: T1-2N1  
IIIA: T3N1  
IIIB: T4N0-1, T1-4N2  
IV: M1 |
NCCN Guidelines v1. 2021

**Clinical Stage**

- **Primary Treatment**
  - Induction chemotherapy\(^g\) with pemetrexed and cisplatin (or carboplatin)
  - Chest CT with contrast and PET/CT for mediastinal assessment based on CT or other evidence of advanced disease
  - Surgical exploration\(^i\)
  - Unresectable

**Adjuvant Treatment**

- Consider hemithoracic pleural IMRT\(^k\)
- Progression\(^g,h\)

**Clinical stage I-IIIA and Epithelioid or Biphasic histology\(^b,c\)**

- Hemithoracic RT\(^k\)
- Chemotherapy\(^g\) and consider sequential hemithoracic pleural IMRT\(^k\)
- Sequential chemotherapy\(^g\) + Hemithoracic RT\(^k\)
- Systemic therapy\(^g\)
Chemotherapy

- **Pemetrexed/cisplatin preferred over cisplatin alone** → phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma (Vogelzang, *et al.* 2003)
  - Chemo-naïve patients unable to have curative surgery randomized to either pemetrexed/cisplatin v cisplatin
  - Median survival time in the pemetrexed/cisplatin arm was 12.1 months versus 9.3 months in the control arm \((P = .020)\)
  - Median time to progression was significantly longer in the pemetrexed/cisplatin arm (5.7 months versus 3.9 months \((P = .001)\))
  - Response rate was 41.3% in pemetrexed/cisplatin arm vs 16.7% in cisplatin arm
Surgery

- Only epithelioid and biphasic histologies should be considered for potential resection
  - Generally avoided in sarcomatoid MPM due to its aggressive nature
- The goal of surgery is complete gross cytoreduction of tumor
- Mediastinal node sampling should occur and obtain at least 3 nodal stations

<table>
<thead>
<tr>
<th>Pleurectomy and Decortication (P/D)</th>
<th>Extrapleural Pneumonectomy (EPP)</th>
</tr>
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<tbody>
<tr>
<td>Complete removal of the pleura and gross tumor +/- <em>en bloc</em> resection of pericardium and/or diaphragm with reconstruction with mediastinal lymph node sampling</td>
<td><em>En bloc</em> resection of the pleura, <strong>lung</strong>, ipsilateral diaphragm, and often pericardium with mediastinal lymph node sampling</td>
</tr>
<tr>
<td>For earlier stage disease (confined to pleural envelope, no N2) with epithelioid histology, P/D may be safer than EPP</td>
<td>Associated with a higher mortality rate</td>
</tr>
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Radiotherapy in Mesothelioma

- RT after EPP
  - SAKK 17/04
- RT after P/D
  - IMPRINT
  - Current trial: NRG LU-006
- Pre-operative RT
  - SMART Protocol

- Proton Therapy
- RT for prophylaxis of procedure tract metastases
  - SMART Trial
- Unresectable
  - Hemithoracic vs Palliative RT
  - STELLAR Trial
  - Checkmate 743
Adjuvant Hemithoracic RT after EPP

• SAKK 17/04 study
  • 3C neoadjuvant chemotherapy \(\rightarrow\) EPP
    • R0 or R1 resection, randomized to hemithoracic RT versus no hemithoracic RT
  • Primary endpoint = locoregional control
    • Overall, no significant difference between adjuvant RT v no adjuvant RT
  • One grade 5 pneumonitis event in the RT group
  • **Conclusion**: hemithoracic RT not supported for malignant mesothelioma after neoadjuvant chemotherapy and EPP
  • **Limitations**: poor accrual, patient dropout, lack of radiotherapy guidelines, lack of central review of target and normal structures
Hemithoracic RT after P/D

• **IMPRINT**: Phase II Study of Hemithoracic Intensity-Modulated Pleural Radiation Therapy As Part of Lung-Sparing Multimodality Therapy in Patients with MPM
  
  • *Eligibility criteria*: MPM (any histology), no metastatic disease, no prior chemo or RT, KPS 70 or greater
  
  • Patients received pemetrexed and platinum for 4 or fewer cycles
  
  • Patients with resectable tumors underwent surgery 4-6 weeks after chemotherapy with P/D
  
  • Hemithoracic IMRT began 4-6 weeks after chemotherapy or 8 or fewer weeks postoperatively
IMPRINT Results

• 27 patients underwent hemithoracic RT
  • Median dose of 46.8 Gy (28.8 - 50.4 Gy)

• Toxicity
  • 30% of patients developed ≥ grade 2 radiation pneumonitis; all resolved
  • No grade 4 or 5 radiation pneumonitis observed
  • Most common acute toxicity was grade 3 fatigue

• Survival
  • Median PFS 12.4 months
  • Median OS 29.1 months in patient who completed trimodality treatment, including RT to a dose of 54 Gy; 2y OS 59% in resectable patients

• Conclusion: Hemithoracic IMRT is safe and its incorporation within chemotherapy and P/D forms a new lung-sparing treatment paradigm
Current Clinical Trial: **NRG LU-006**

- **Phase III Study** Assessing the Addition of Radiation Therapy to Surgery and Chemotherapy to Treat Malignant Pleural Mesothelioma

- **Eligibility**
  - Stage I-IIIA malignant pleural mesothelioma amenable to resection by P/D
  - Epithelioid or biphasic histology

- **Arm 1**: chemotherapy, P/D (sequencing at discretion of treating physician); no radiotherapy

- **Arm 2**: chemotherapy, P/D → IMRT or Proton Therapy

- **Primary Outcome**: overall survival

- **Secondary Outcomes**: Local-failure-free survival, DMFS, PFS, toxicity, QoL
Another Approach: SMART Protocol

- **S**urgery for **M**esothelioma **A**fter **R**adiation **T**herapy (published by Princess Margaret group)
  - All resectable cT1-3N0M0 histologically proven, previously untreated MPMs were eligible
  - Patients received 25 Gy in 5 fractions to the entire ipsilateral hemithorax with a concomitant 5 Gy boost to areas at risk (*EPP within 1 week of completing RT*)
  - Adjuvant chemo offered to ypN2 patients
  - Estimated study completion date: July 1, 2030

- **R**esults
  - 96 patients accrued from 2008-2019
  - 49% of patients had 30-day perioperative grade 3-4 events and 1 patient had a grade 5 event (pneumonia)
  - EPP performed 5 (range 2-12) days after completing IMRT
  - 5-year cumulative incidence of distant recurrent was 63.3%
  - Most common first sites of recurrence were contralateral chest and peritoneal cavity
Proton Therapy in Mesothelioma

• Consensus Statement on Proton Therapy in Mesothelioma (Zeng et al, 2020)
  • Compared with photons, there are dramatic reductions in dose to the contralateral lung, heart, liver, kidneys and stomach using proton therapy in both the post-pneumonectomy and lung-intact settings

• Challenges with proton therapy
  • Tissue heterogeneity
  • Organ motion
  • Changing anatomy during treatment course
  • Long treatment time (per fraction)
Radiation for Prophylaxis of Procedure Tract Metastases

• SMART Trial
  • Phase III trial of patients with mesothelioma who had undergone large-bore pleural interventions
  • Patients randomized 1:1 to immediate RT (within 35 days of intervention) versus deferred RT (given after pleural tract metastases diagnosed)
    • 21 Gy in 3 fractions in both groups
  • No significant difference seen in tract metastasis incidence between the groups
• Prophylaxis of procedure tract not recommended
Unresectable MPM: NCCN v1.2021

Clinical stage, IIIb or IV, Sarcomatoid, or Medically inoperable

PS 0–2 → Consider observation → Progression → Systemic therapy
or Systemic therapy

PS 3–4 → Best supportive care

March 2, 2021
Radical Hemithoracic RT versus Palliative RT

• Patients with non-metastatic malignant pleural mesothelioma who underwent non-radical lung-sparing surgery + chemotherapy (Trovo, et al. 2020)
  • Randomized 1:1 to radical hemithoracic RT (RHRT) v palliative RT (PRT)
    • RHRT: 50 Gy in 25 fractions; gross residual disease received SIB to 60 Gy
• Primary endpoint was overall survival
  • 2-year OS 58% in RHRT arm vs 28% in PRT arm (SS)
• Toxicity in the RHR arm
  • 20% experienced grade ≥ 3 acute toxicity
    • 31% with grade 3-4 late toxicity
  • 16% with grade ≥ 2 pneumonitis
    • Including 1 grade 5 toxicity
Palliative RT

• Utilized for hemoptysis, spinal cord compromise, pain

• Factors influencing the outcome of radiotherapy in malignant mesothelioma of the pleura - a single-institution experience with 189 patients (de Graff-Strukowska, *et al.* 1999)
  • A higher local response rate was seen for patients treated with a 4 Gy per fraction scheme versus fractions < 4 Gy
  • RT provided local palliation in at least 50% of patients using a 4 Gy per fraction scheme to a median dose of 36 Gy
Unresectable MPM

- **STELLAR trial**
  - **Tumor Treating Fields (TTFs)** combined with pemetrexed and cisplatin or carboplatin as first-line treatment for unresectable MPM
  - Phase II trial
  - Median overall survival was 18.2 months
  - Skin reaction was the only adverse event associated with TTFs
Unresectable MPM

• **CheckMate 743**: First-line nivolumab plus ipilimumab in unresectable MPM
  – Eligible patients: 18 years or older with unresectable MPM (previously untreated), ECOG score 0 or 1
  – Randomly assigned 1:1 to nivolumab + ipilimumab for up to 2 years or platinum (cisplatin or carboplatin) + pemetrexed for up to 6 cycles
  – Findings
    • Nivolumab + ipilimumab significantly extended OS vs chemotherapy (18.1 mo vs 14.1 mo, p=0.002)
    • Grade 3-4 treatment toxicity reported in 30% of immunotherapy group and 32% of chemotherapy group
Recommended Follow-Up

- H&P and CT Chest with IV contrast q 3 months x 2 years → q 6 months x 3 years → annually thereafter
- PET CT if suspicious findings on CT Chest
- Biopsy if suspicious findings on CT Chest and/or PET CT
Conclusions

• Mesothelioma is a rare malignancy
  • Only ~2600 cases in the US per year

• Safe delivery of RT with two intact lungs is technically challenging and sparing of these critical, radiosensitive organs is vital to avoid excess toxicity

• Development of highly conformal radiotherapy techniques (IMRT) has enabled safe delivery of high-dose RT to the hemithorax and strict lung constraints must be respected to avoid grade 3+ RP

• Hemithoracic IMRT after P/D should be considered in centers with robust experience and expertise in managing MPM
References


References


March 2, 2021
References


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