

# Mesothelioma

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# Outline

- Case Presentation

- Workup

- Management

- 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.

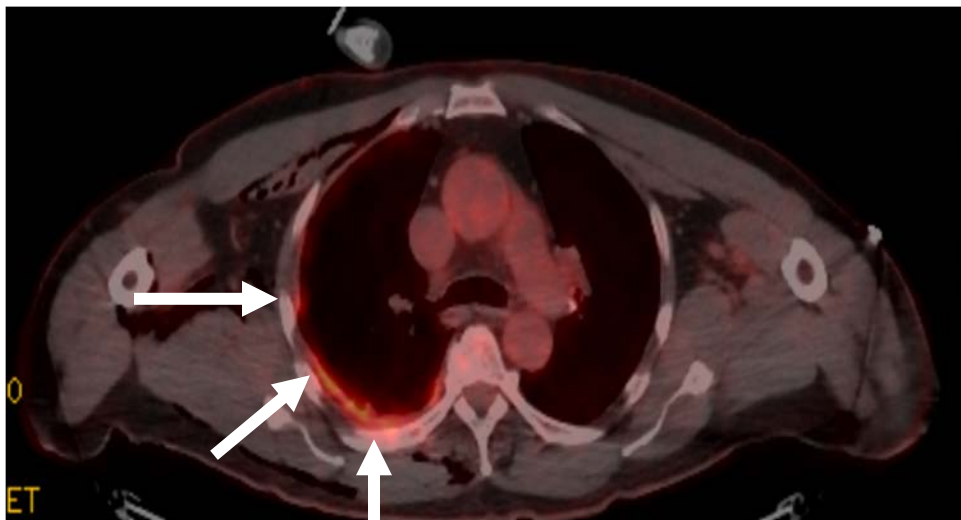
# Case: Diagnostic Workup

- **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)

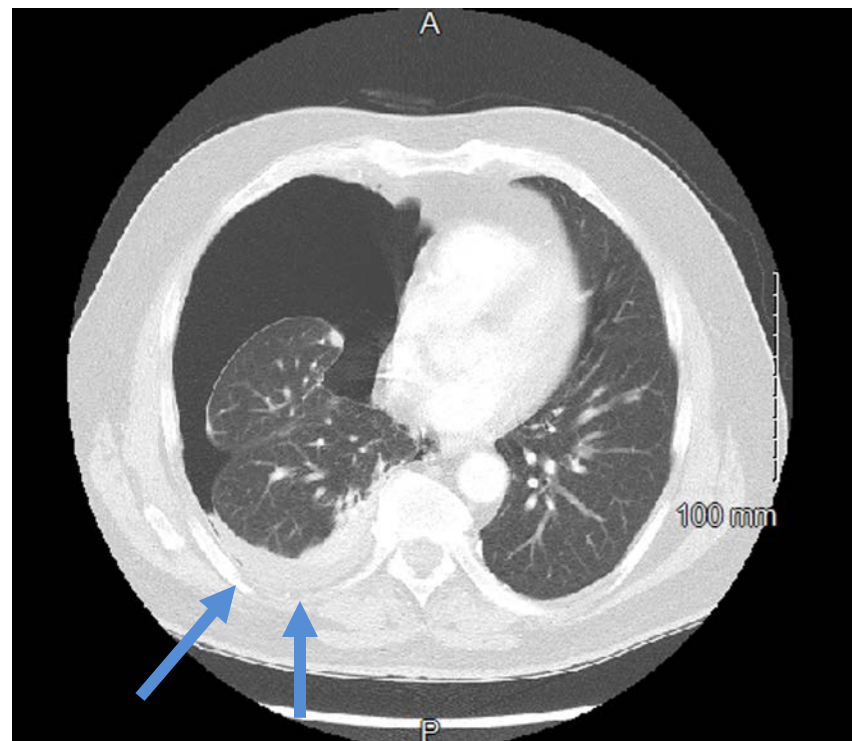
# Case: Diagnostic Workup

- **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 8<sup>th</sup> 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 3-3.5cm 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 costomedistinal recess and crus of the diaphragm*
  - **PTV:** the rind between the PTV\_Outer and PTV\_Inner constitutes the final PTV

# Target Delineation

- **Contouring Resources:**

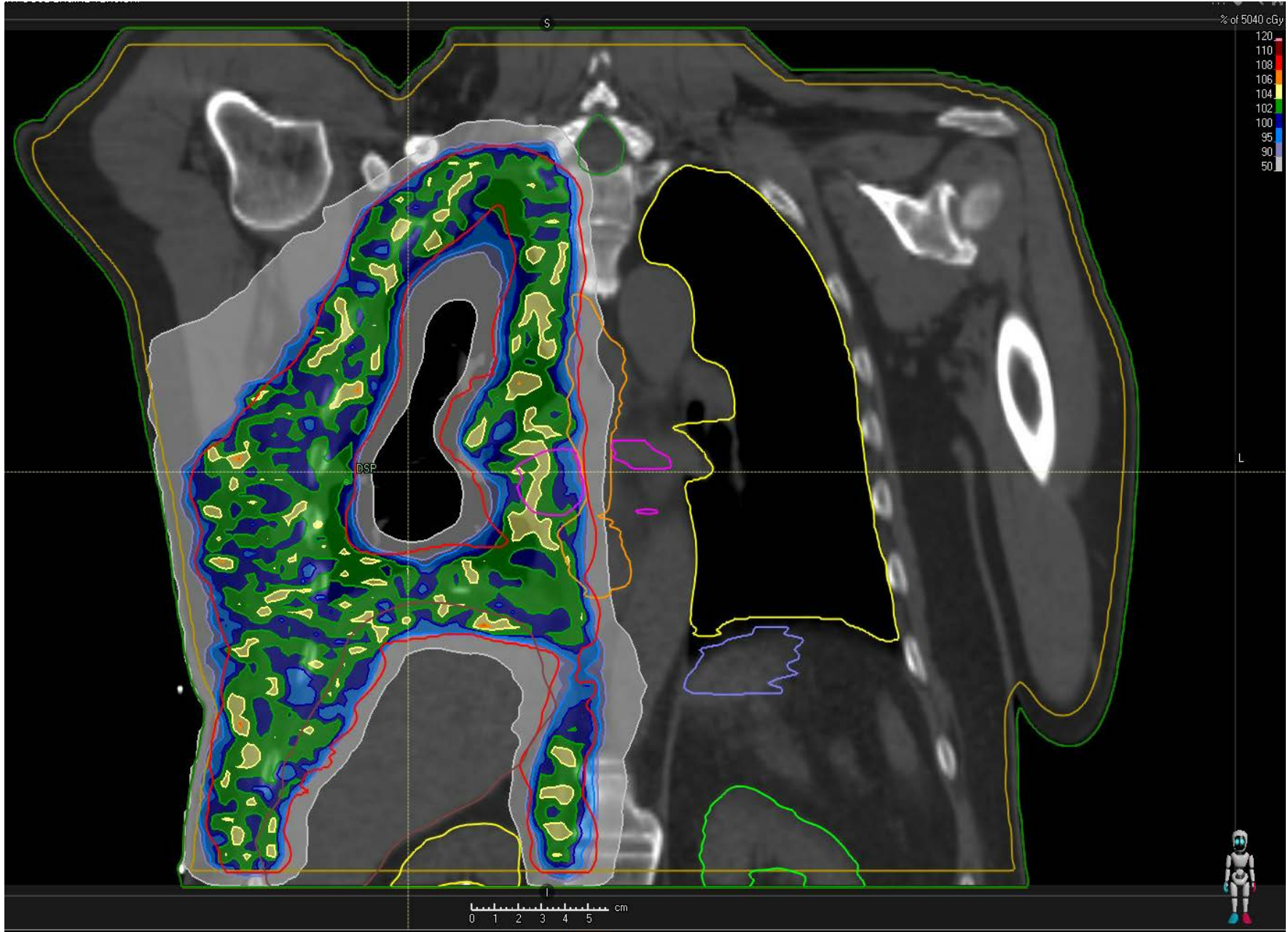
- Gomez, *et al.* “The Use of Radiation Therapy for the Treatment of Malignant Pleural Mesothelioma: Expert Opinion from the National Cancer Institute Thoracic Malignancy Steering Committee, International Association for the Study of Lung Cancer, and Mesothelioma Applied Research Foundation.” *J Thorac Oncol.* 2019 Jul;14(7):1172-1183. doi: 10.1016/j.jtho.2019.03.030
  - <https://pubmed.ncbi.nlm.nih.gov/31125736/>
- NRG LU-006 Contouring Atlas Reference
  - <https://www.nrgoncology.org/ciro-lung>

# Case: Contours

ITV\_5040

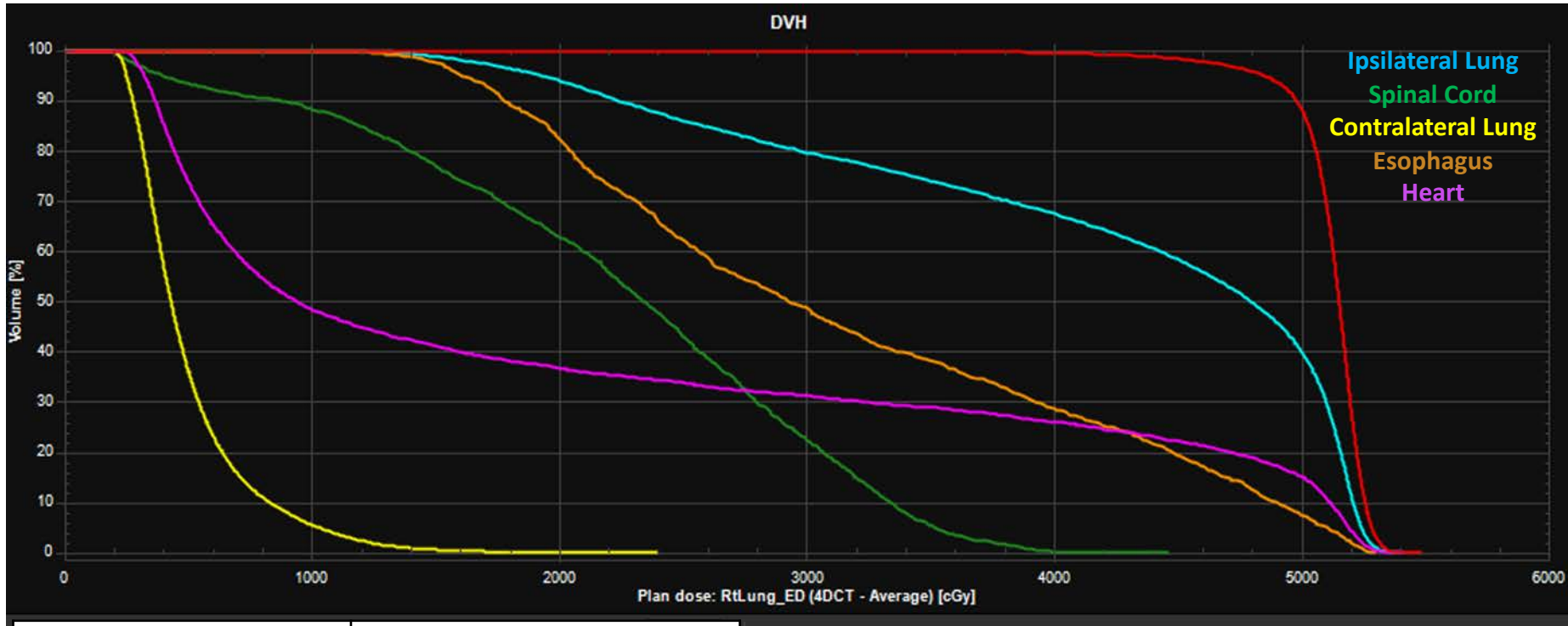
PTV\_5040





Target/OAR	Dosimetric Guideline
GTV	D95% $\geq$ 95%
PTV	D95% $\geq$ 94% D5% $<$ 115% Dmax $\leq$ 130% (all hotspots $>$ 115% must be in PTV)
Spinal Cord	D0.03 cc $\leq$ 50 Gy
Contralateral Lung	Mean $\leq$ 8 Gy ( $\leq$ 10 Gy acceptable) V20 $\leq$ 5% ( $\leq$ 7% acceptable) V5 $\leq$ 50% ( $\leq$ 80% acceptable)
Ipsilateral Lung	V40 $\leq$ 67% ( $\leq$ 90% acceptable)
Esophagus	Mean $\leq$ 34 Gy
Brachial Plexus	Dmax $<$ 65 Gy
Heart	Right-sided disease: V40 $\leq$ 25% Left-sided disease: V40 $\leq$ 35%
Kidneys	V18 $\leq$ 33%
Liver-GTV	Mean $\leq$ 30 Gy V30 $\leq$ 50%
Sp_Bowel (Space occupied by Small and Large Bowel)	D0.03cc $\leq$ 55% D5cc $<$ 50 Gy
Stomach-PTV	Mean $\leq$ 30 Gy

# Case: Plan Evaluation



<b>PTV</b>	D95%: 96%
<b>Heart</b>	V40: 26% Mean: 20.4 Gy
<b>Esophagus</b>	Mean: 31.6 Gy
<b>Contralateral Lung</b>	Mean: 5 Gy V20: 0.03%

<b>Ipsilateral Lung</b>	V40: 67%
<b>Spinal Cord</b>	Max 44.6 Gy
<b>Liver-GTV</b>	Mean: 27 Gy V30: 35%



# 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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- Chemotherapy

- Surgery

- Radiation

- RT after EPP

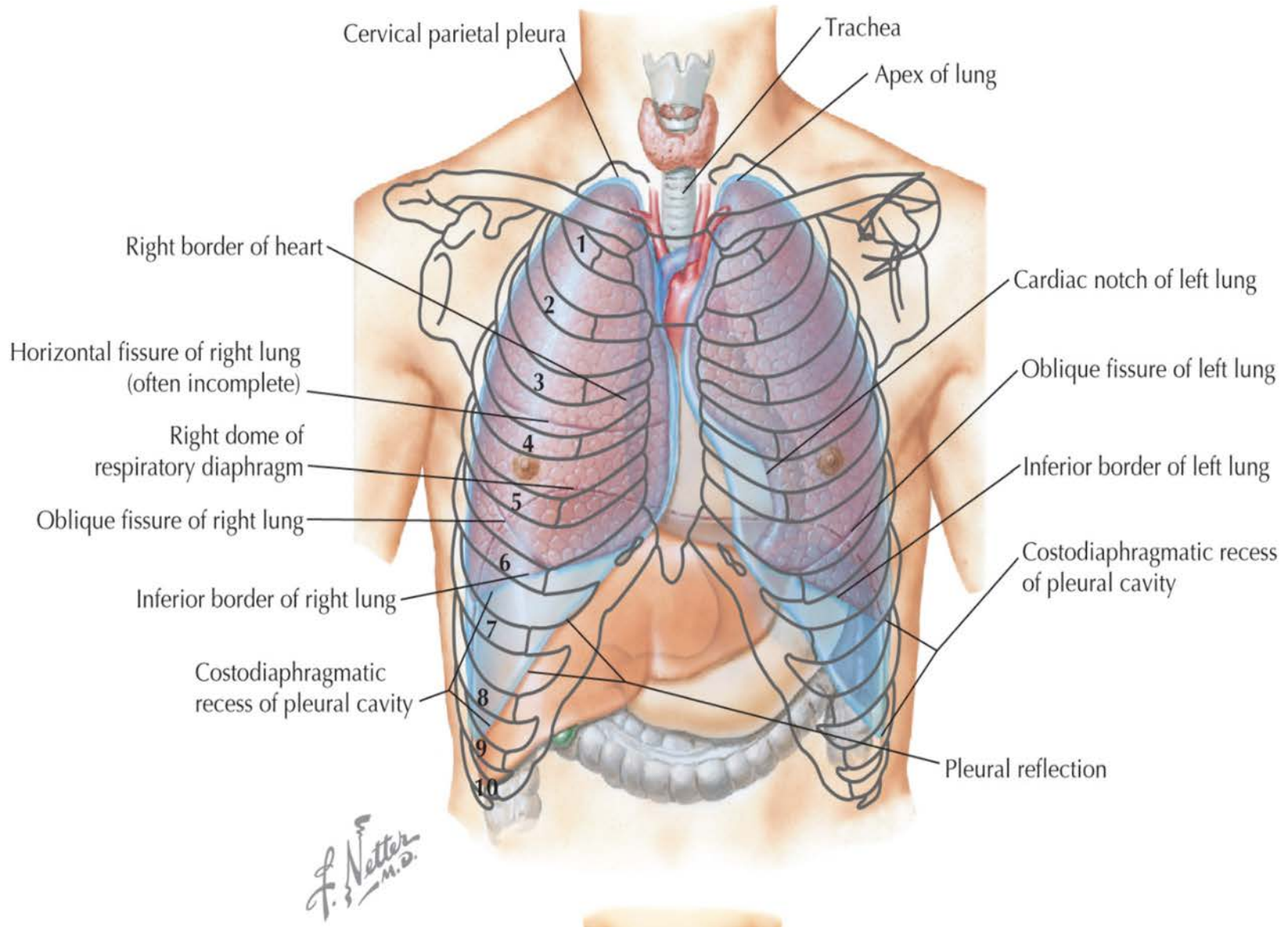
- RT after P/D

- Pre-operative RT

- Palliative RT

# 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,  $\geq 20$ -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<sup>1</sup>
- 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

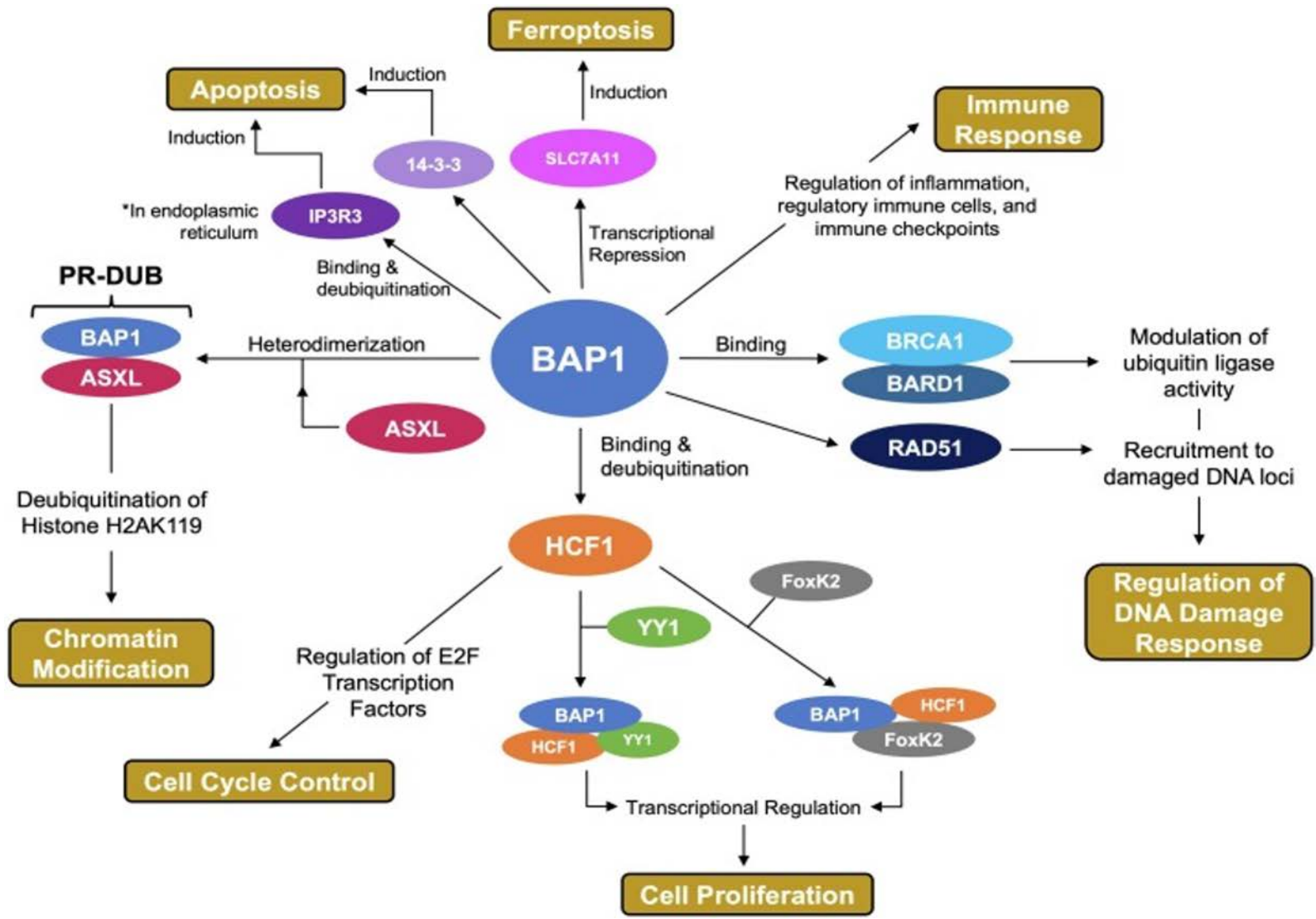


# Workup Pearls

- 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, endothoracic 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.**



# AJCC 8<sup>th</sup> Edition Staging

## 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

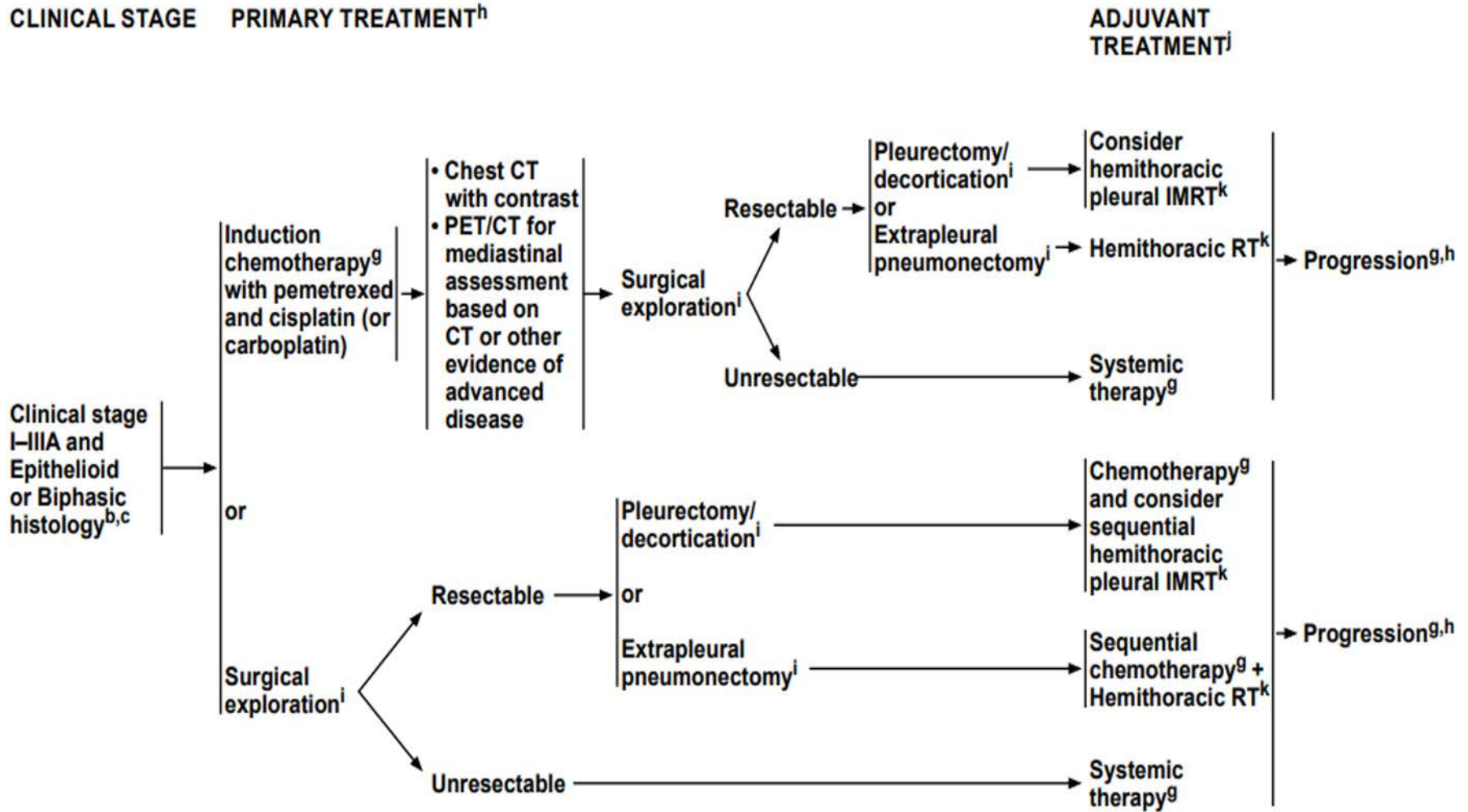
**M0:** No distant metastases  
**M1:** Distant metastases present

## Group Stage

**IA:** T1N0  
**IB:** T2-3N0  
**II:** T1-2N1  
**IIIA:** T3N1  
**IIIB:** T4N0-1, T1-4N2  
**IV:** M1



# NCCN Guidelines v1. 2021



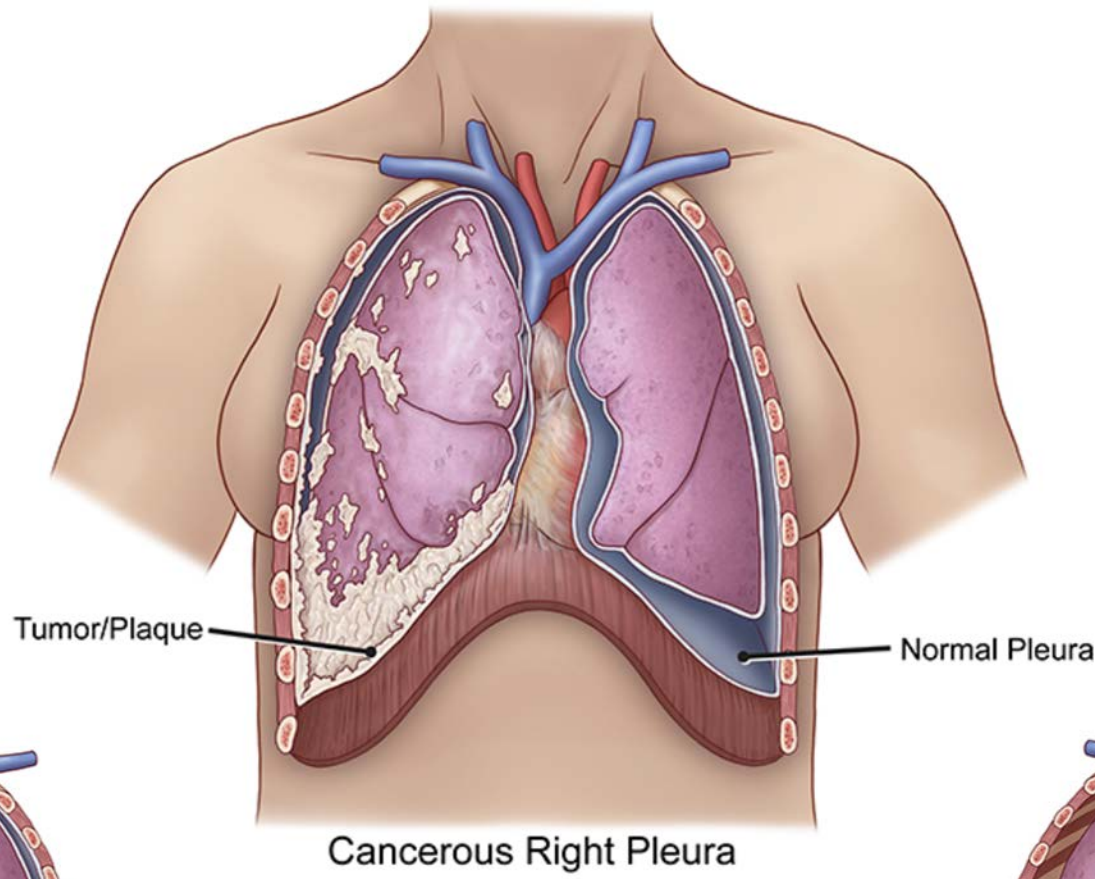
# Chemotherapy

- **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

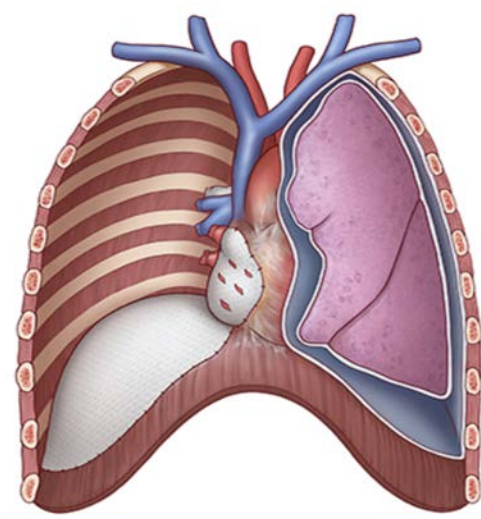
# Surgery

- 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

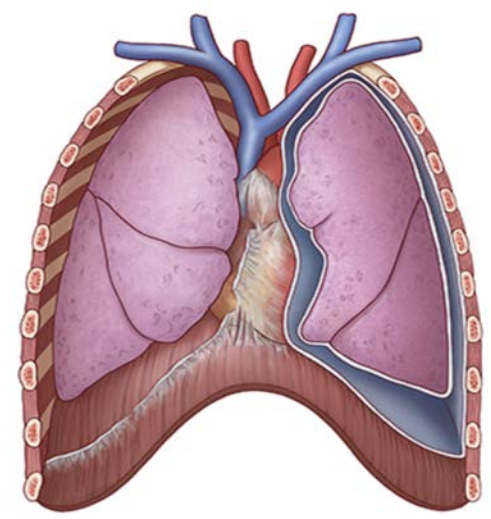
Pleurectomy and Decortication (P/D)	Extrapleural Pneumonectomy (EPP)
Complete removal of the pleura and gross tumor +/- <i>en bloc</i> resection of pericardium and/or diaphragm with reconstruction with mediastinal lymph node sampling	<i>En bloc</i> resection of the pleura, <b>lung</b> , ipsilateral diaphragm,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



Cancerous Right Pleura



Extrapleural Pneumonectomy



Pleurectomy/Decortication

# 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 → 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  $\geq$  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

- **Surgery for Mesothelioma After Radiation Therapy** (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
- Results
  - 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

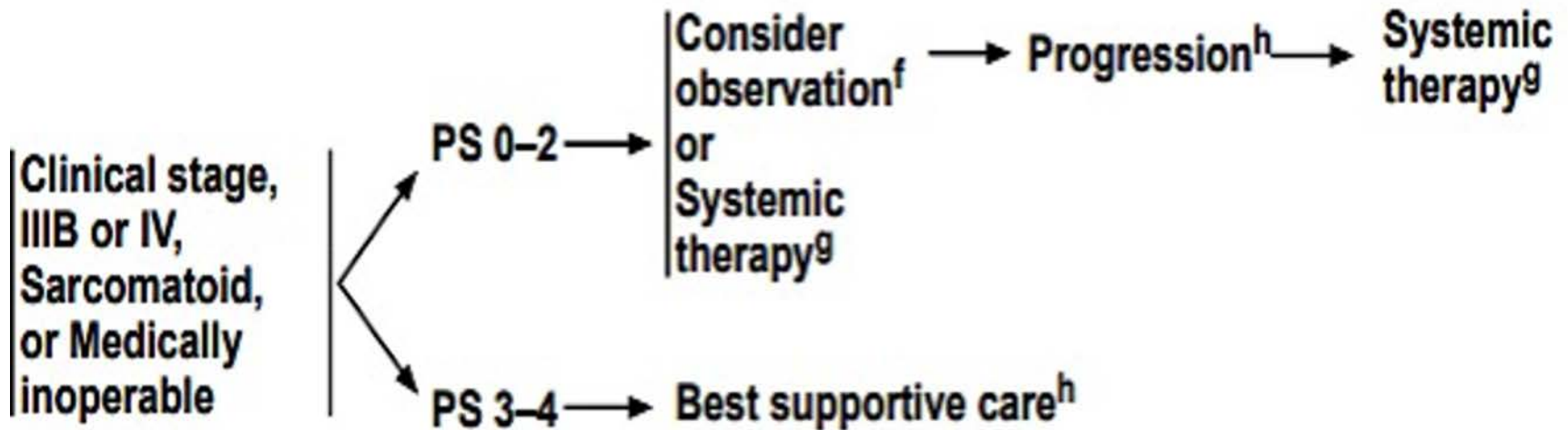
- Consensus Statement on Proton Therapy in Mesothelioma (Zeng *et al*, 2020)
  - Compared with photons, there are dramatic reductions in dose to the contralateral lung, heart, liver, kidneys and stomach using proton therapy in both the post-pneumonectomy and lung-intact settings
  - Challenges with proton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



# 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  $\geq 3$  acute toxicity
    - 31% with grade 3-4 late toxicity
  - 16% with grade  $\geq 2$  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

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