ARROCase: Thymoma

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Clinical Presentation

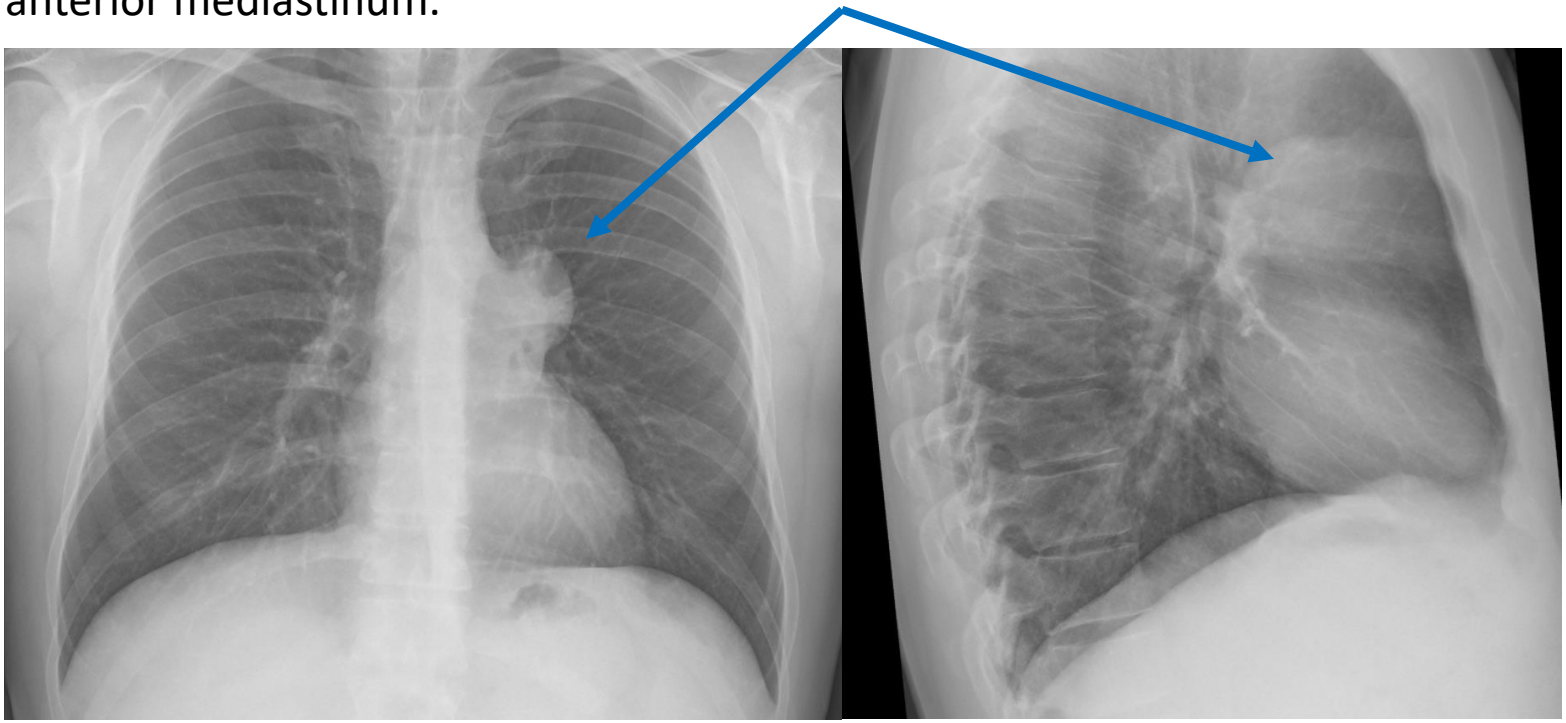
- 58 year-old woman presents to an ophthalmologist with ptosis, diplopia, malaise, and muscle weakness with chewing.
  - **PMH/PSH**: None.
  - **FH:** No family history of malignancy or neuromuscular disease.
  - **SH:** Married, works as insurance agent. Never smoker, no alcohol/drug use.
  - **Medications/allergies:** Non-contributory.
  - **Physical Examination:** +Diplopia, bilateral ptosis. Mild proximal muscle weakness.
  - Suspecting myasthenia gravis, she is referred to a neurologist.

Workup

- Neurology consultation
  - AChR modulating, blocking, and binding antibodies were each elevated.
  - A clinical diagnosis of myasthenia gravis was made, and she was started on prednisone and pyridostigmine with symptomatic improvement.
  - Prednisone was later tapered and mycophenolate was started.
- Imaging was ordered to rule out thymoma
  - **Chest x-ray** demonstrated a left anterior mediastinal mass.
  - **Chest CT+C** demonstrated an anterior mediastinal mass measuring 6.6x5.3x2.4cm without gross invasion of the lung or heart and without nodal, pleural, or intrathoracic metastases.

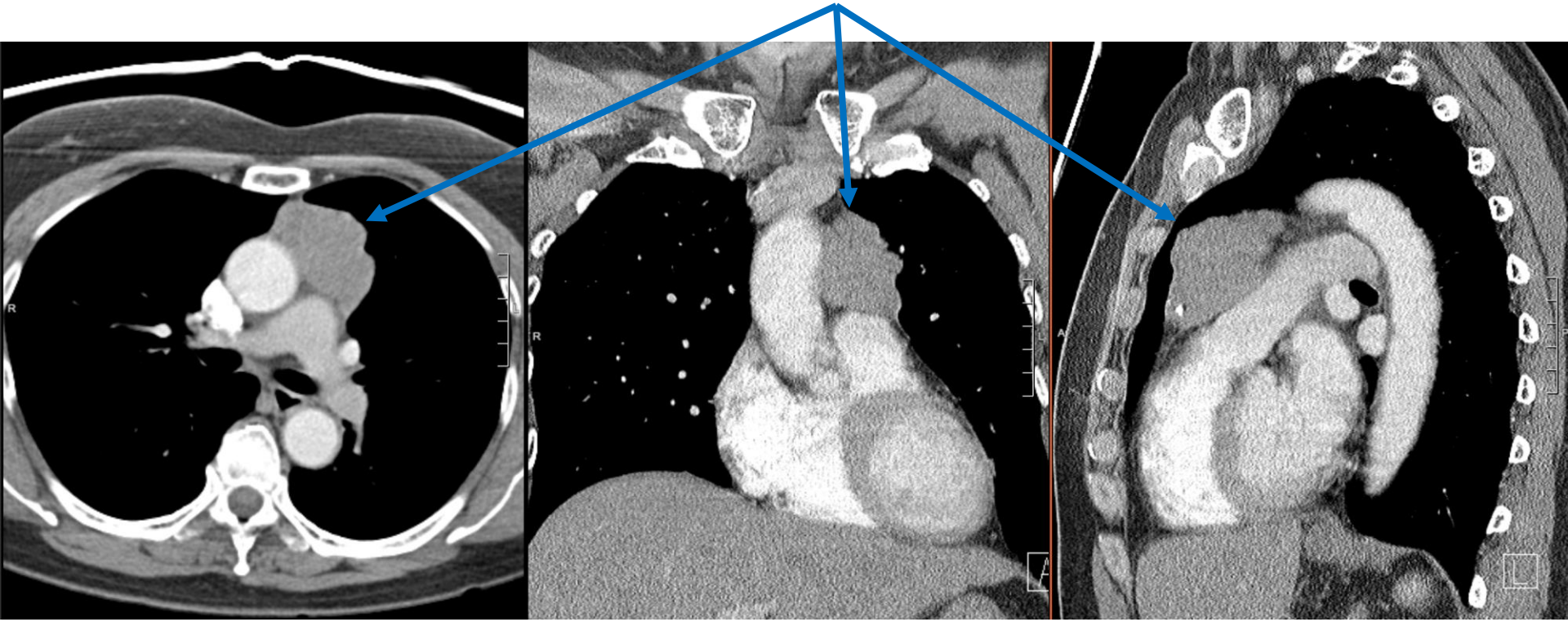
Workup

- **Chest X-Ray** demonstrated a left-sided mass obscuring the aortic contour in the anterior mediastinum.



Workup

- **Chest CT** demonstrated a left-sided anterior mediastinal mass measuring 6.6x5.3x2.4cm without gross invasion of the lung, pleura, or heart, and without nodal, pleural, or intrathroracic metastases.



Workup

- **Further workup:**
  - **CBC/CMP** unremarkable
  - **Pulmonary function testing** demonstrated FVC 3.56L (85% predicted), FEV1 2.68 (81% predicted), suggesting possible restrictive process.
  - **AFP, beta-HCG** were not elevated.
- **Consultation with thoracic surgery:**
  - Myasthenic symptoms had resolved with pyridostigmine/prednisone.
  - The anterior mediastinal tumor was clinically consistent with a resectable thymoma, and initial biopsy was not indicated.
  - Recommendation was for a median sternotomy and total thymectomy.
- **Differential diagnosis (anterior mediastinal mass)**
  - Thymoma, thymic carcinoma, thymic cyst, carcinoid, thymic lipoma, seminoma, germ cell tumor, teratoma, lymphoma, enlarged/ectopic thyroid

Resection

- **Resection:**
  - After median sternotomy, the mass encased the left phrenic nerve and was adherent to the left upper lobe and anterolateral (left) pericardium
  - Total thymectomy, *en bloc* resection of the left phrenic nerve, partial pericardiectomy, and *en bloc* left upper lobe wedge resection were performed for gross total resection.
  - Uncomplicated postoperative course
- **Surgical Pathology:**
  - **Histology:** thymoma, WHO Type B2, 5.5cm. Lymphocytes admixed with lesional cells. **[1]**
  - **Extent:** transcapsular invasion with involvement of the visceral pleura, parietal pleura, and pericardium
  - **Margins:** microscopic positive posterior margin (R1), 0.1cm to right+left lateral margins
  - **Modified Masaoka stage:** stage IIIA (+pericardial/pleural invasion, no great vessel invasion) **[2]**
  - **AJCC 8th edition stage:** pT2 cN0M0 (II)
- **Post-discharge follow-up:** no dyspnea despite left phrenic nerve sacrifice.

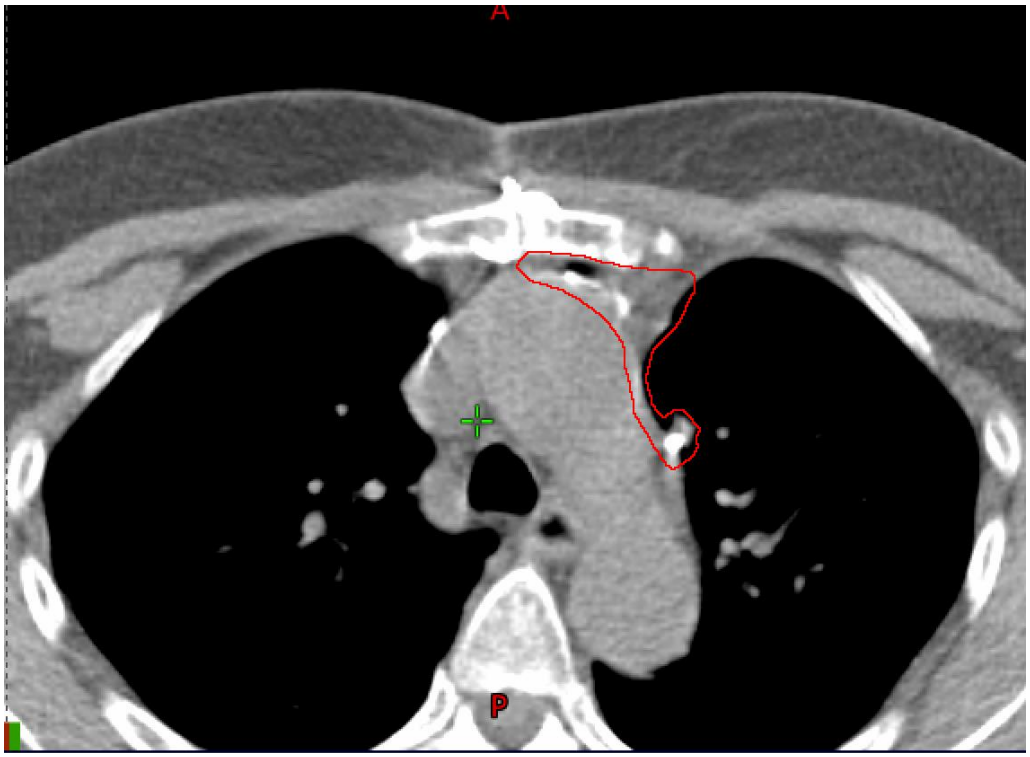
Adjuvant Therapy

- **Radiotherapy: [2,3]**
  - Given extent (Masaoka stage IIIA) and microscopic positive margin, adjuvant radiotherapy was recommended.
  - **Simulation:**
    - Supine, arms over head, vac bag, IV contrast
    - 4DCT, inspiration breath hold, expiration breath hold CT with 2mm slice thickness
  - **Technique:** volumetric-modulated arc radiotherapy

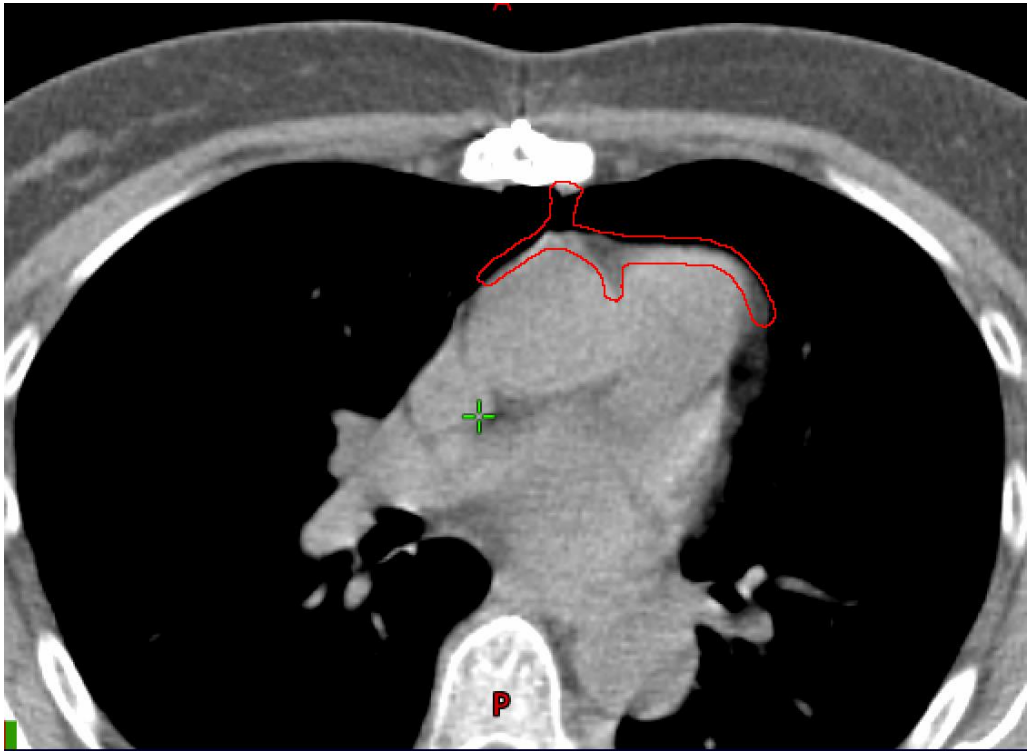
Adjuvant Therapy

- **Radiotherapy: [2,3]**
  - **Target volumes:**
    - Fuse pre-resection imaging and contour **pre-resection GTV**
    - Postoperative **CTV** encompasses entire surgical bed, clips, anterior mediastinum, and areas of pericardial/pleural contact with the preoperative GTV at risk for microscopic disease. Discussion with surgeon encouraged.
    - Motion-inclusive **ITV** vs. inspiration breath hold
    - Elective nodal irradiation not indicated
    - **CTV-to-PTV** margin dictated by image-guidance and LINAC tolerance (5mm)
  - **Prescription dose:**
    - 54 Gy in 30 fractions prescribed to cover 95% of PTV
    - Motion management/IGRT: daily CBCT with respiratory gating during treatment to exclude extreme breaths vs. inspiration breath hold
- **Chemotherapy:** not indicated

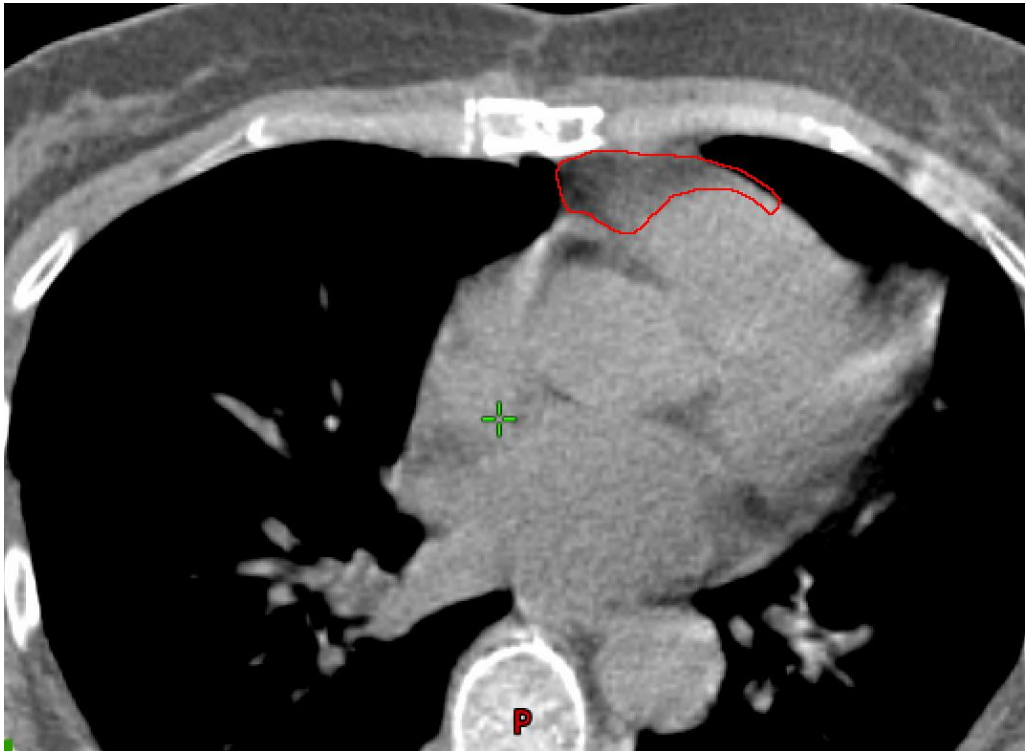
Postoperative Radiotherapy: CTV



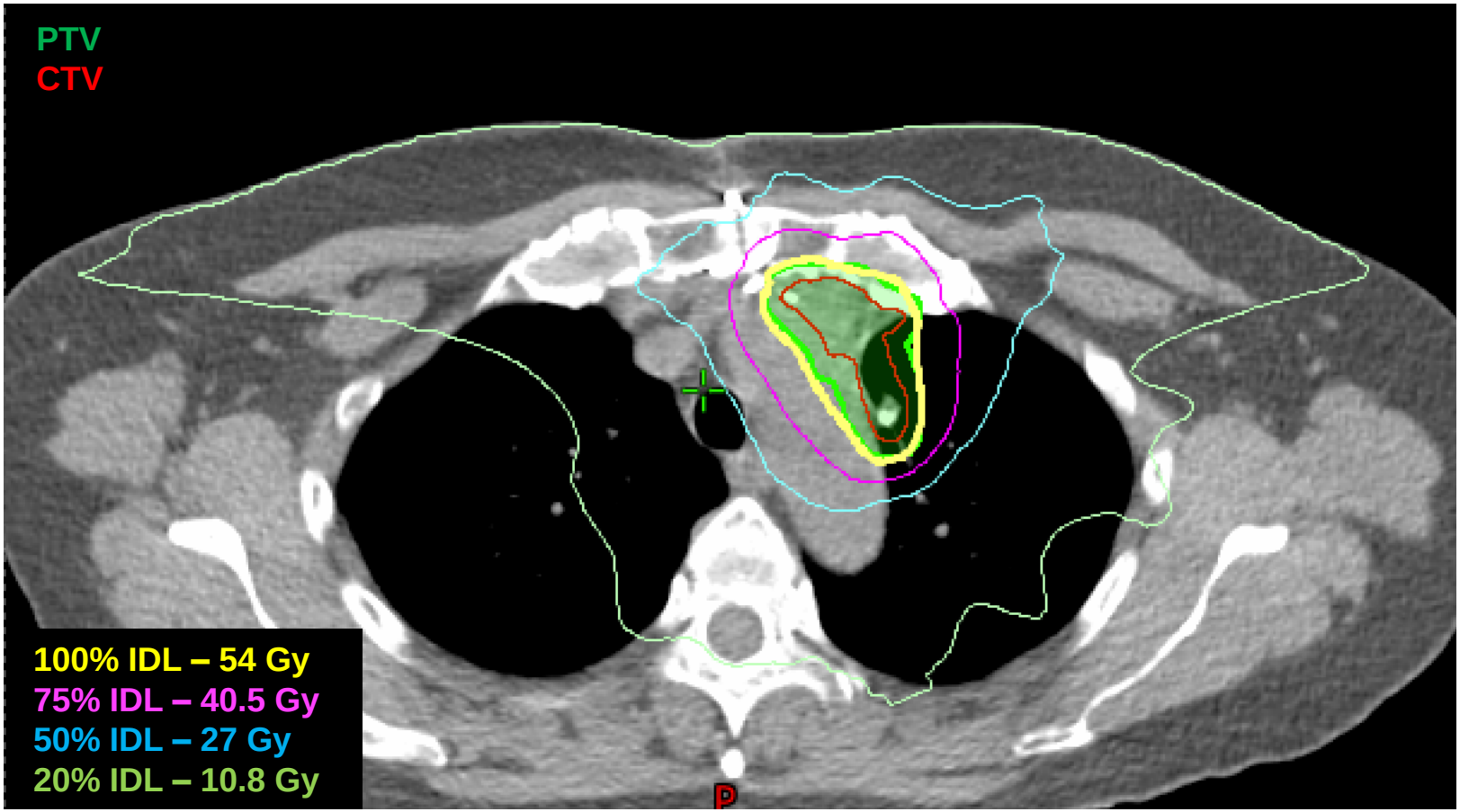
Postoperative Radiotherapy: CTV



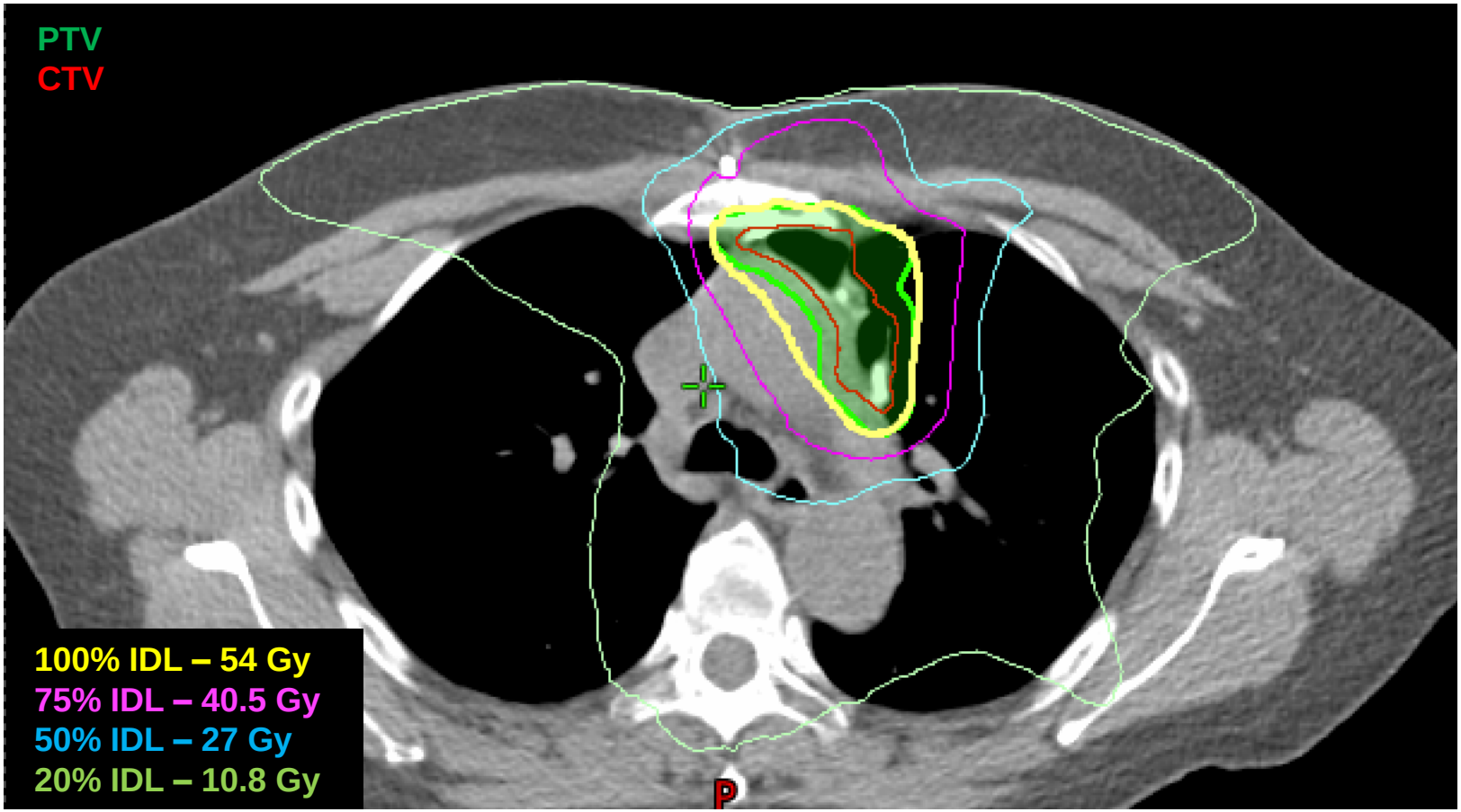
Postoperative Radiotherapy: CTV



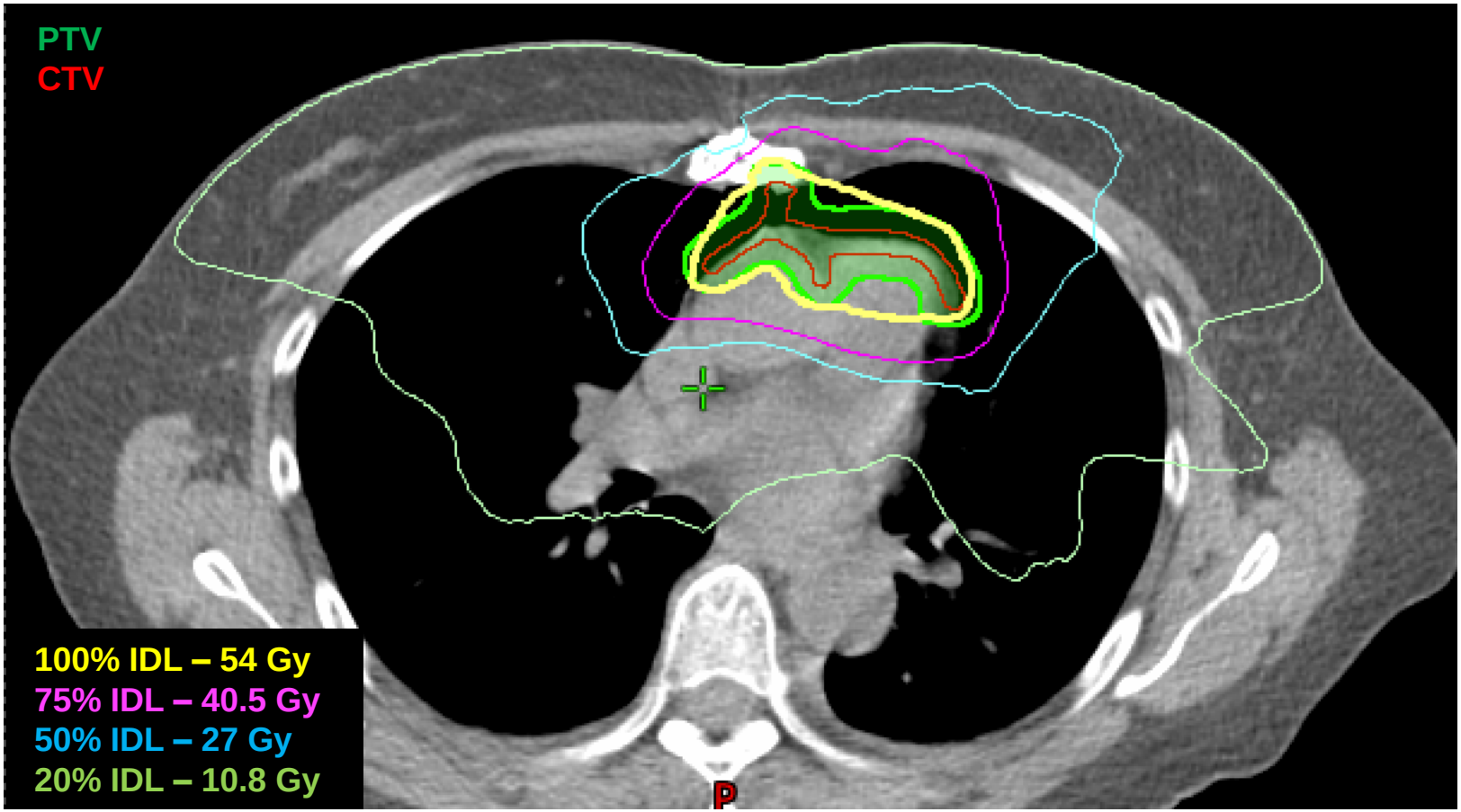
Postoperative Radiotherapy: Plan



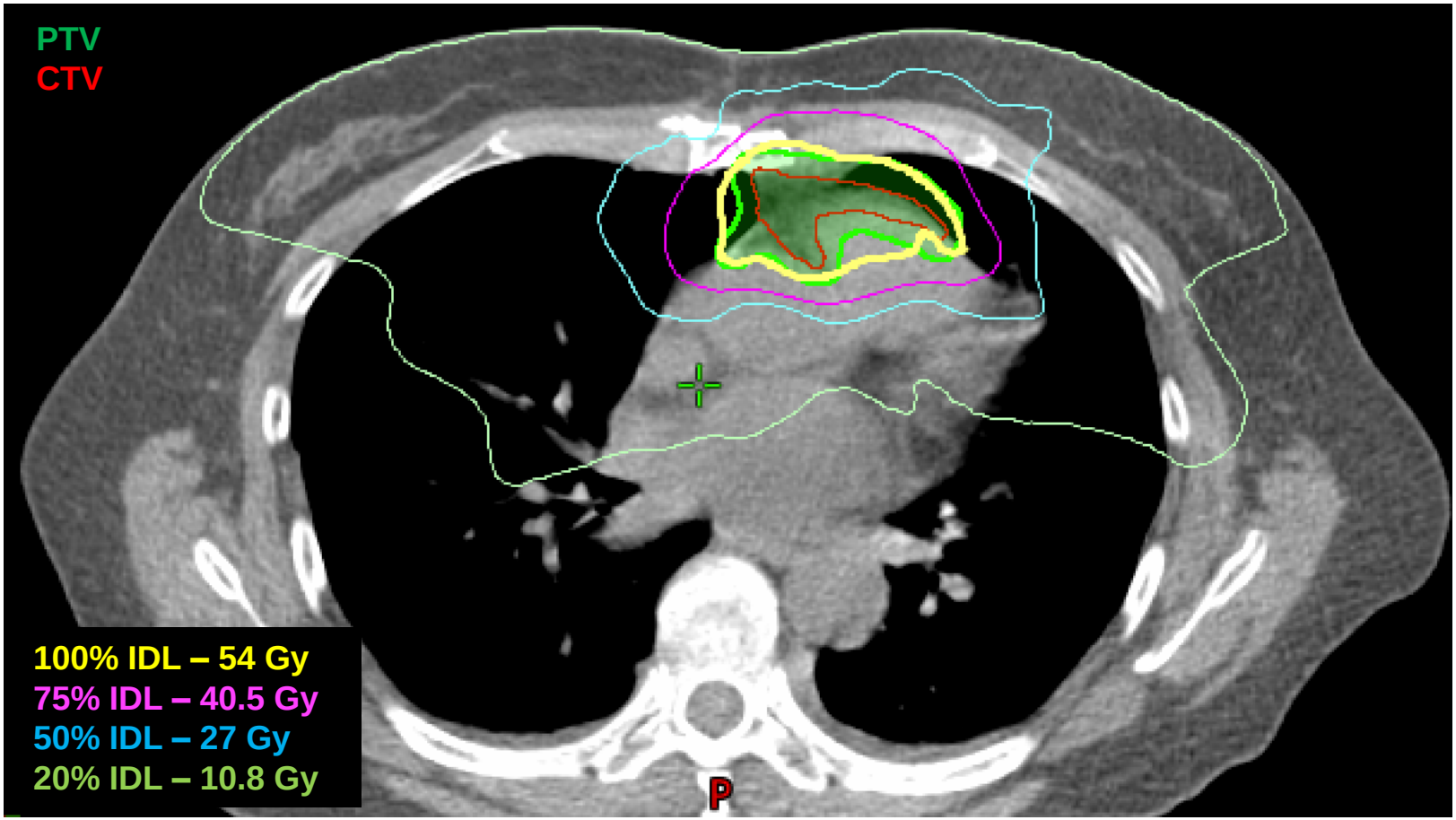
Postoperative Radiotherapy: Plan



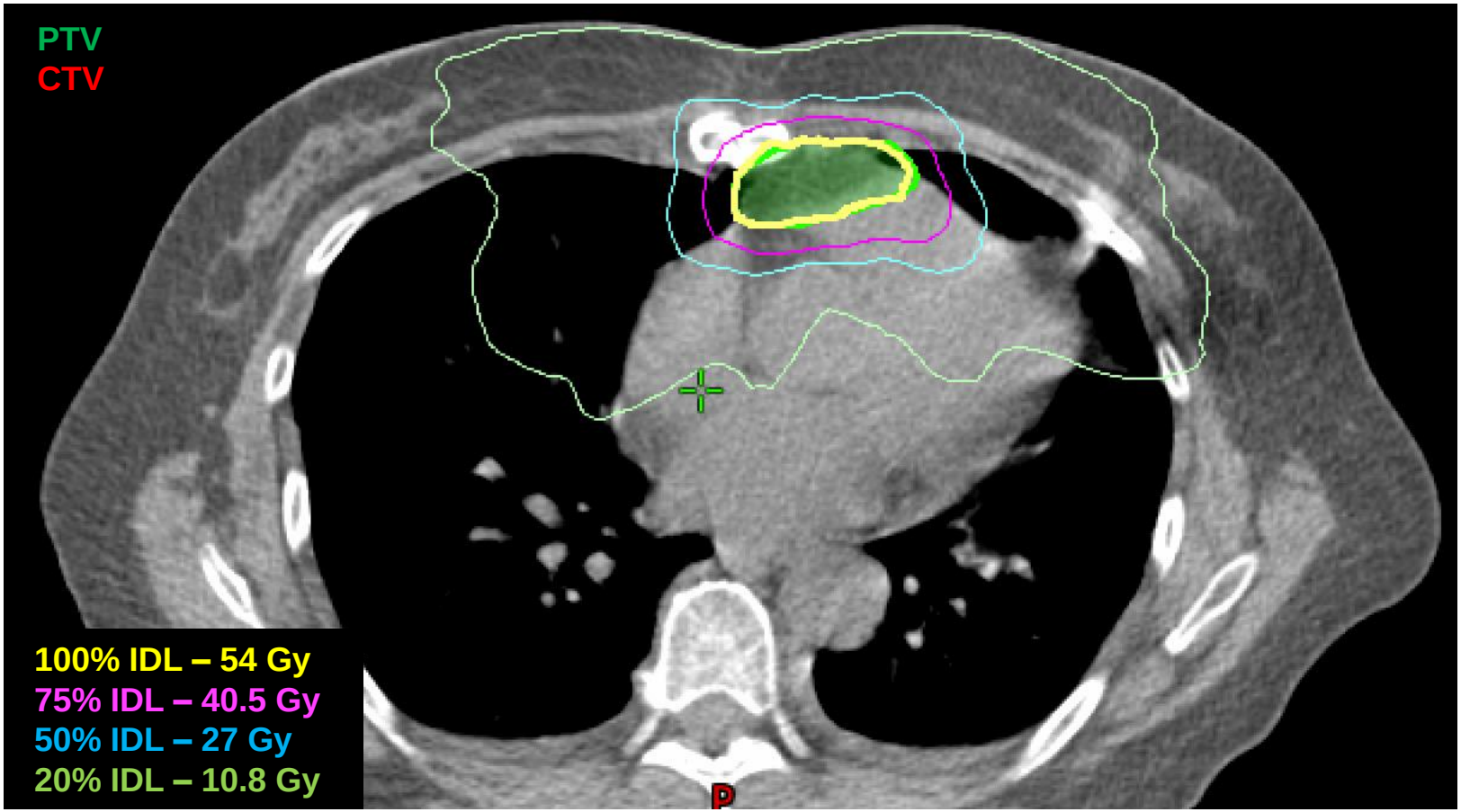
Postoperative Radiotherapy: Plan



Postoperative Radiotherapy: Plan

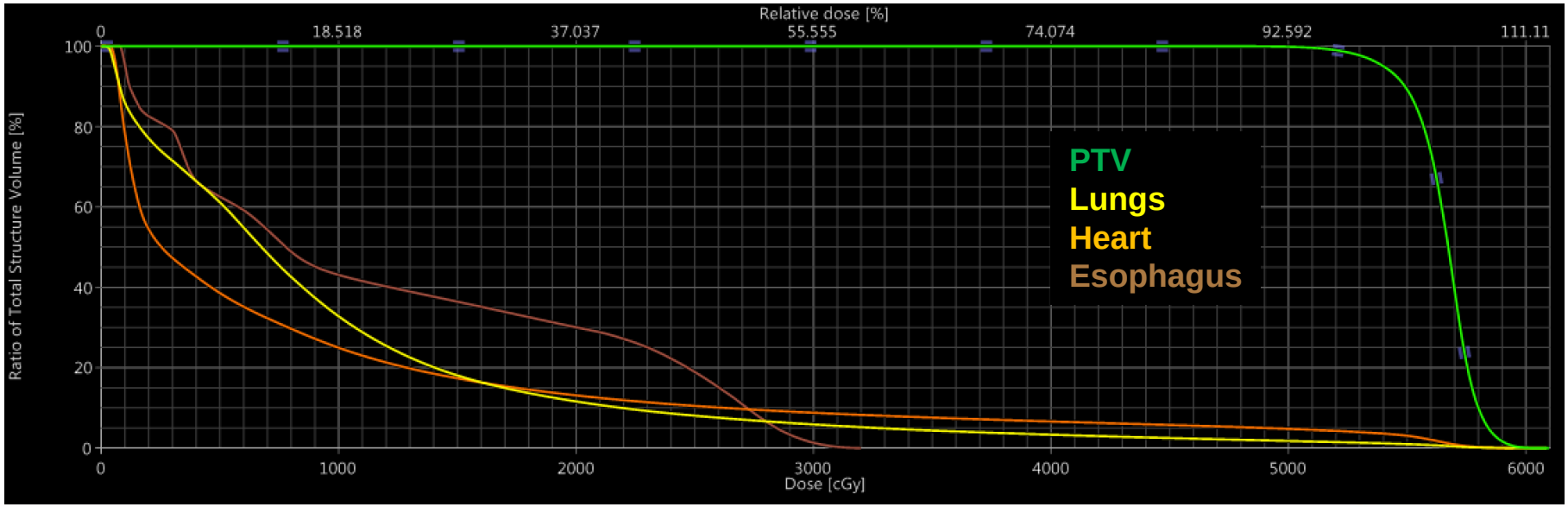


Postoperative Radiotherapy: Plan



Postoperative Radiotherapy: Plan

- **VMAT plan:**
  - **Fields:** Two arcs, 6 MeV, 54 Gy in 30 fractions prescribed to 95% PTV coverage
  - **Lungs:** Mean 9.7 Gy; V30=6%; V20=12%; V5=61%
  - **Heart:** Mean 8.9 Gy; V30=9%; V10=25%
  - **Esophagus:** Dmax 32 Gy; mean 12 Gy
  - **Great vessels:** D0.03cc <=108%
  - **Proximal tracheobronchial tree:** D0.03cc <=108%
  - **Full list of proposed constraints:** Gomez et al. **[3]**



Radiotherapy Course and Follow-Up

- She experienced grade 1 fatigue during radiotherapy, with no dyspnea, esophagitis, or weight loss.
- A surveillance chest CT with contrast was completed six months after radiotherapy per NCCN guidelines, with no evidence of intrathoracic recurrence.
  - Recurrence patterns defined in Gomez et al. **[3]**
- NCCN guidelines for follow-up: **[2]**
  - Chest CT with contrast every 6 months for the first two years, then annually for 5 years (thymic carcinoma) or 10 years (thymoma)

Thymic Masses: Presentation

- **Symptoms:**
  - **Myasthenic symptoms:** ptosis, diplopia, dysphagia, difficulty chewing, dysarthria, hypophonia, facial weakness, dyspnea**.** 30-50% of patients with thymomas have myasthenic symptoms. 10-20% of patients with myasthenia gravis have a thymoma.
  - **Mass effect:** dyspnea, chest pain, cough, odynophagia, SVC syndrome, pleural/pericardial effusions, restrictive lung physiology
  - **Phrenic nerve involvement:** dyspnea, diaphragmatic paralysis
  - **Other paraneoplastic syndromes:** variety of other common and uncommon autoimmune diseases have been associated with thymomas, including pure red cell aplasia, immunodeficiencies, and thymoma-associated multiorgan autoimmunity.
    - **Management:** short- and long-term immunosuppression, thymectomy, pyridostigmine/IVIG (MG), supportive transfusions (PRCA). Thymectomy alone may not reverse these syndromes.
- **Epidemiology: [2]**
  - Incidence: 1.5 cases per million, similar incidence between men and women
  - Most common adult primary thymic neoplasm
  - Highest incidence between 40-60 years of age

Thymic Masses: Work-Up

- **NCCN 1.2020 recommended work-up: [2]**
  - **Required:** Chest CT with contrast, beta-HCG+AFP (rule out germ cell tumors), CBC/CMP, AChR antibodies
  - **Optional:** PFTs, PET/CT, MRI (for equivocal CT, may help distinguish thymoma vs. thymic carcinoma vs. thymic cyst vs. other histologies)
  - **Biopsy:**
    - **Upfront resection without biopsy** can be pursued if a primary thymic neoplasm is felt to be likely (well-defined anterior mediastinal mass, negative beta-HCG/AFP, absence of adenopathy, absence of continuity with thyroid).
    - For **unresectable** tumors or if there is **uncertainty** regarding histology, core biopsy should be performed (CT-guided, open, or thoracoscopic). Thoracentesis and cytology can also be pursued to establish diagnosis.

Thymic Neoplasms: Classification

WHO Type	Muller-Hermelink	Levine and Rosai	Distribution
Type A	Medullary type thymoma	Encapsulated	4-7% (17% MG*)
Type AB	Mixed type thymoma	Encapsulated	28-34% (16% MG)
Type B1	Predominantly cortical	Malignant type I	9-20% (57% MG)
Type B2	Cortical type	Malignant type I	20-36% (71% MG)
Type B3	Well-differentiated carcinoma	Malignant type I	10-14% (46% MG)
Type C (thymic carcinoma)	Thymic carcinoma	Malignant type II	5-10% (<10% MG)

*Incidence of Myasthenia Gravis by WHO Type.

Thymic Neoplasms: Staging

Masaoka-Koga Staging [2]		5-Year OS [7]
I	Macroscopically encapsulated, no microscopic transcapsular invasion	96%
IIA	Microscopic transcapsular invasion	86%
IIB	Macroscopic invasion into surrounding fatty tissue, or grossly adherent to but not breaking through mediastinal pleura or pericardium	
IIIA	Macroscopic invasion of neighboring organ (e.g., pericardium or lung) **without** great vessel invasion	69%
IIIB	Macroscopic invasion of neighboring organ (e.g., pericardium or lung) **with** great vessel invasion	
IVA	Pleural or pericardial dissemination	50%
IVB	Lymphogenous or hematogenous metastasis	

Thymic Neoplasms: Staging

AJCC 8th Edition Staging	
T category	**TX:** primary tumor cannot be assessed **T0:** no evidence of primary tumor **T1:** tumor encapsulated or extending into mediastinal fat **T2:** direct invasion of the pericardium (partial or full-thickness) **T3:** direct invasion into any of the following: lung, brachiocephalic vein, superior vena cava, phrenic nerve, chest wall, or extrapericardial pulmonary artery or veins **T4:** invasion into any of the following: aorta, arch vessels, intrapericardial pulmonary artery, myocardium, trachea, esophagus
N category	**NX:** regional nodes cannot be assessed **N0:** no regional nodal metastases **N1:** metastasis in anterior (perithymic) lymph nodes **N2:** metastasis in deep intrathoracic or cervical lymph nodes
M category	**M0:** no pleural, pericardial, or distant metastases **M1a:** separate pleural or pericardial nodule(s) **M1b:** pulmonary intraparenchymal nodule or distant organ metastasis
Group Stage	**I:** T1N0M0 **II:** T2N0M0 **IIIA:** T3N0M0 **IIIB:** T4N0M0 **IVA:** N1 or M1a **IVB:** N2 or M1b

Management

- Given rarity, there is no randomized evidence to guide management.
- Resectable tumors (with or without initial biopsy) should proceed to initial resection by a team with experience in the management of thymic neoplasms. **[2]**
  - Myasthenic symptoms should be managed and optimized prior to resection with immunosuppression, pyridostigmine, and/or IVIG.
- Initially unresectable tumors should first be treated with chemotherapy +/- radiotherapy. **[2]**
  - **Potentially-resectable tumors:** chemotherapy → restaging
    - Resectable after restaging: resection +/- PORT
    - Unresectable after restaging: definitive RT +/- chemotherapy
  - **Unresectable tumors:** concurrent chemoradiotherapy
- **Systemic therapy: [2]**
  - **First-line thymoma:** CAP q3 weeks (cisplatin, doxorubicin, cyclophosphamide)
  - **First-line thymic carcinoma:** Carboplatin/paclitaxel q3 weeks
  - **Second-line thymoma**: everolimus, octreotide, pemetrexed, gemcitabine
  - **Second-line thymic carcinoma:** sunitinib, pemetrexed, everolimus, pembrolizumab
  - **Concurrent chemotherapy:** cisplatin+etoposide or carboplatin+paclitaxel

Management: PORT

- **Controversial.** Given rarity, there is no randomized evidence to guide management. **[2-4]**
  - **Masaoka stage I, R0:** no PORT
  - **Masaoka stage II, R0:** consider PORT for high-risk features (e.g., large size, WHO type B3/C)
  - **Masaoka stage III:** PORT
  - **Masaoka stage IV:** individualized based on resectability, symptoms
  - **R1-2 resection:** PORT +/- chemotherapy (e.g., for R2 resection or thymic carcinoma)
  - **Thymic carcinoma:** PORT (even if stage I-II)
- **Conflicting evidence for LC, DFS, and OS benefit in different subgroups**
  - **NCDB (PMID: 28126540):** PORT improved OS for Masaoka stage IIB, III, and positive margins. No SS benefit for OS among stage I-IIA **[5]**
  - **Japanese Consortium (PMID: 25565590):** PORT improved RFS but not OS for stage II-III thymic carcinoma, and did not improve RFS or OS for stage II-III thymoma. **[6]**
  - **ITMIG (PMID: 27346413):** PORT improved OS in stage II-III R0 thymoma. **[7]**
  - **Meta-analysis (PMID: 27026316):** PORT improved OS in stage III/IV but not stage II thymoma. **[8]**
  - All observational series are subject to selection biases in PORT vs. no PORT cohorts.

Management: PORT

- **Treatment planning:** consensus atlas is not available, but reporting guidelines exist **[3]**, with lower inter-rater agreement in postoperative cases relative to definitive cases **[9]**
- **Radiotherapy:**
  - **Target volumes: [3]**
    - Fuse pre-resection imaging and contour **pre-resection GTV**
    - Postoperative **CTV** encompasses entire surgical bed, clips, anterior mediastinum, and areas of pericardial/pleural contact with the preoperative GTV at risk for microscopic disease. Discussion with surgeon encouraged.
    - Motion-inclusive **ITV** vs. breath hold
    - Elective nodal irradiation not recommended by NCCN
    - **CTV-to-PTV** margin dictated by image-guidance and LINAC
  - **Prescription dose:**
    - R0: 45-50 Gy at 1.8-2 Gy per fraction
    - R1: 54 Gy at 1.8-2 Gy per fraction
    - R2: 60-70 Gy at 1.8-2 Gy per fraction, similar to unresectable disease
    - Hemithoracic RT with boost to high-risk areas is rarely used **[3]**
  - **Motion management:** inspiration breath hold vs. respiratory gating during treatment to exclude extreme breaths with daily CBCT.
- **Postoperative chemotherapy:** can be considered for thymic carcinoma or R2 resection

Management: Unresectable Disease

- **Potentially-resectable tumors:** induction chemotherapy → resection (if feasible) → risk-adapted PORT **[10]**
- **Unresectable tumors / R2 resection:** Definitive concurrent chemoradiotherapy **[2]**
  - **Target volumes (definitive):**
    - Fuse pre-radiotherapy CT/MRI/PET and contour **GTV**
    - No routine **GTV-to-CTV** expansion, but CTV should include areas of pericardial/pleural contact with the GTV at risk for microscopic disease. If chemotherapy precedes radiotherapy, CTV should include pre-chemotherapy extent of disease adapted to anatomy at time of simulation.
    - Motion-inclusive **ITV**
    - Elective nodal irradiation not recommended by NCCN
    - **CTV-to-PTV** margin dictated by image-guidance and LINAC
  - **Prescription dose:** 60-70 Gy at 1.8-2 Gy per fraction
  - **Motion management:** inspiration breath hold vs. respiratory gating during treatment to exclude extreme breaths with daily CBCT

Management: Unresectable Disease

- **Potentially-resectable tumors:** induction chemotherapy → resection (if feasible) → risk-adapted PORT **[10]**
- **Unresectable tumors / R2 resection:** Definitive concurrent chemoradiotherapy **[2]**
  - **Evidence:**
    - Kim et al: phase II trial of 22 patients with unresectable thymoma treated with CAP q 3-4 weeks x 3 → surgical resection (76% R0) → PORT → CAP q 3-4 weeks x 3 **[11]**
    - Loehrer: phase II trial of 26 patients with unresectable thymoma treated with CAP q 3 weeks x 2-4 → definitive radiotherapy (54 Gy) **[12]**
    - Fan et al: phase II trial of 56 patients with unresectable thymoma/thymic carcinoma treated with definitive chemoradiotherapy (60 Gy) with concurrent EP q 4 weeks x 2 → adjuvant EP q 4 weeks x 2 **[13]**
- **Concurrent chemotherapy:**
  - Generally indicated for suitable candidates in the definitive setting
  - Cisplatin+etoposide or carboplatin+paclitaxel

Surveillance

- **NCCN 1.2020:** Chest CT+contrast every 6 months for 2 years, and then annually for 5 years for thymic carcinomas and 10 years for thymomas.
- **Late toxicity:** given long life expectancy in most cases, late toxicities can include pneumonitis, dyspnea, cardiac toxicity, and secondary malignancies.
- **Recurrence: [2]**
  - Most common site of recurrence is along the pleura/pericardium.
  - Nodal recurrence is uncommon, but thymic carcinomas may metastasize to the bone, liver, kidneys, and lymph nodes.
  - Resection of limited pleural/pericardial metastases can lead to long-term disease control, with prognosis associated with WHO Grade. **[14]**

References

- **[1]** Tumours of the lung, pleura, thymus and heart. In: *World Health Organization Classification of tumours*, Travis WD, Brambilla E, Muller-Hermelink HK, Harris CC (Eds), IARC Press, Lyon, France 2004.
- **[2]** NCCN Clinical Practice Guidelines in Oncology. Thymomas and Thymic Carcinomas. Version 1.2020. November 2019.
- **[3]** Gomez et al. J Thorac Oncol . 2011 Jul;6(7 Suppl 3):S1743-8. PMID: 21847057.
- **PORT:**
  - **[4]** Ahmad et al. J Thorac Cardiovasc Surg. 2015;149(1):95. Epub 2014 Oct 5. PMID: 25524678.
  - **[5]** Jackson et al. J Thorac Oncol. 2017;12(4):734. Epub 2017 Jan 25. PMID: 28126540.
  - **[6]** Omasa et al. Cancer. 2015;121(7):1008. Epub 2015 Jan 6. PMID: 25565590.
  - **[7]** Rimner et al. J Thorac Oncol. 2016;11(10):1785. Epub 2016 Jun 23. PMID: 27346413.
  - **[8]** Lim et al. Int J Radiat Oncol Biol Phys . 2016 Apr 1;94(5):1129-36. PMID: 27026316.
  - **[9]** Holliday et al. J Radiat Oncol. 2016 Mar; 5(1): 55–61. PMID: 27570583.
- **Unresectable Disease:**
  - **[10]** Hamaji et al. Ann Thorac Surg. 2015;99(5):1848. PMID: 25770014.
  - **[11]** Kim et al. Lung Cancer 2004 Jun;44(3):369-79. PMID: 15140551.
  - **[12]** Loehrer et al. J Clin Oncol. 1997 Sep;15(9):3093-9. PMID: 9294472.
  - **[13]** Fan et al. Int J Radiat Oncol Biol Phys. 2020 May 1;107(1):98-105. PMID: 31987968.
- **Recurrent Disease:**
  - **[14]** Okumura et al. J Surg Oncol. 2007;95(1):40. PMID: 17192865.
- **ESMO Thymic Guidelines: [15]** Ann Oncol . 2015 Sep;26 Suppl 5:v40-55. PMID: 26314779

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