



TNM 8th edition

Lung Cancer Stage Classification (8th Edition)

General Note:

All Stage I-III tumors are M0

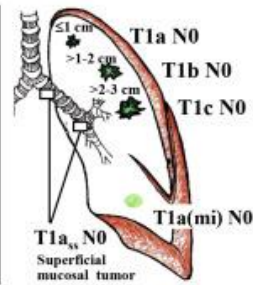
Tx, Nx should be used only if no information at all is available about T or N stage (including no clinical staging information).

Mx is not allowed, because symptoms and physical exam information is always available.

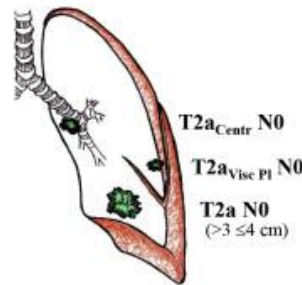
Stage 0



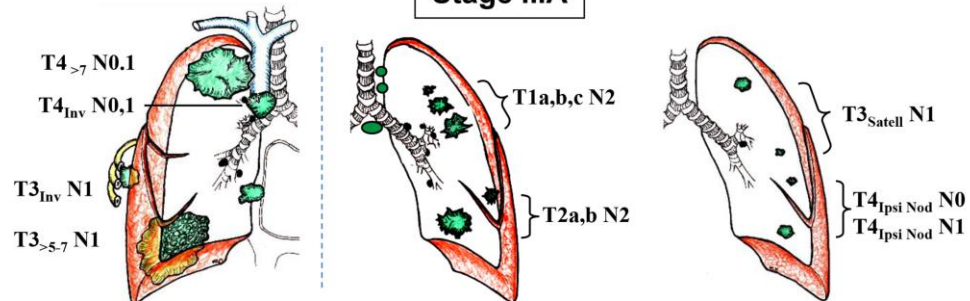
Stage IA



Stage IB



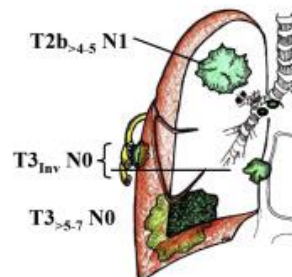
Stage IIIA



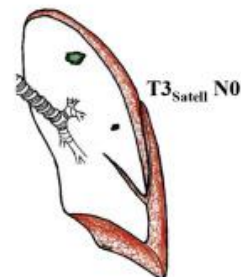
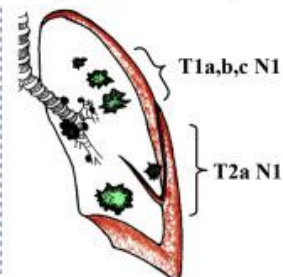
Specific Notes:

Tumor size defined as largest dimension of the solid (imaging, c-stage) or invasive (p-stage) component
Direct extension of the primary tumor into an adjacent node counts as nodal involvement
Extension of a nodal metastasis into a T structure does not count for the T category
The highest T category is used when there is a discrepancy between T by size or by other factors

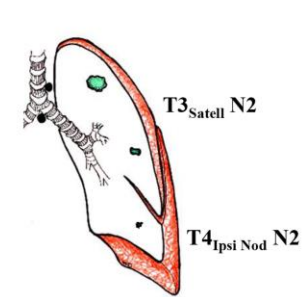
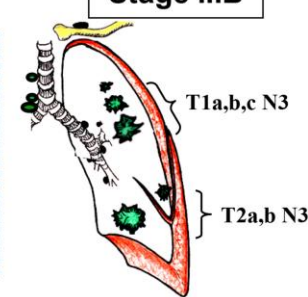
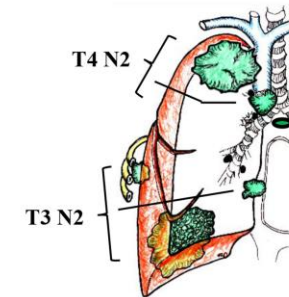
Stage IIA



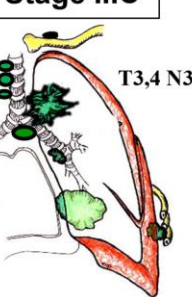
Stage IIB

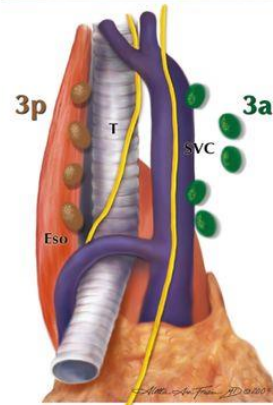
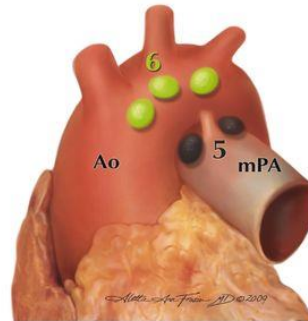
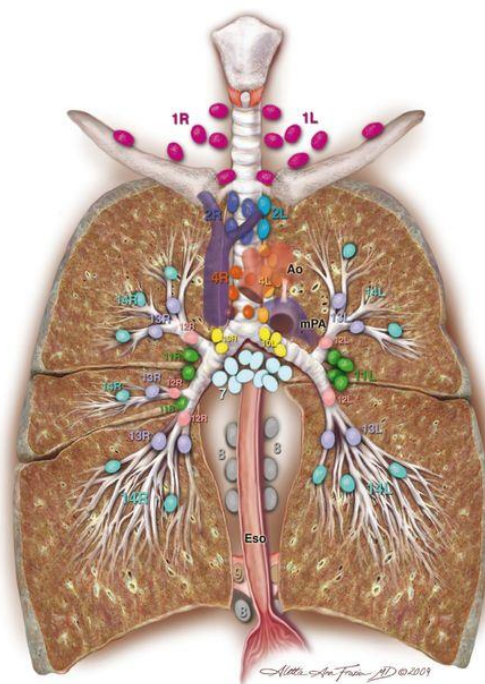


Stage IIIB



Stage IIIC





Supraclavicular zone

- 1 Low cervical, supraclavicular, and sternal notch nodes

SUPERIOR MEDIASTINAL NODES

Upper zone

- 2R Upper Paratracheal (right)
- 2L Upper Paratracheal (left)
- 3a Prevascular
- 3p Retrotracheal
- 4R Lower Paratracheal (right)
- 4L Lower Paratracheal (left)

AORTIC NODES

AP zone

- 5 Subaortic
- 6 Para-aortic (ascending aorta or phrenic)

INFERIOR MEDIASTINAL NODES

Subcarinal zone

- 7 Subcarinal

Lower zone

- 8 Paraesophageal (below carina)
- 9 Pulmonary ligament

N1 NODES

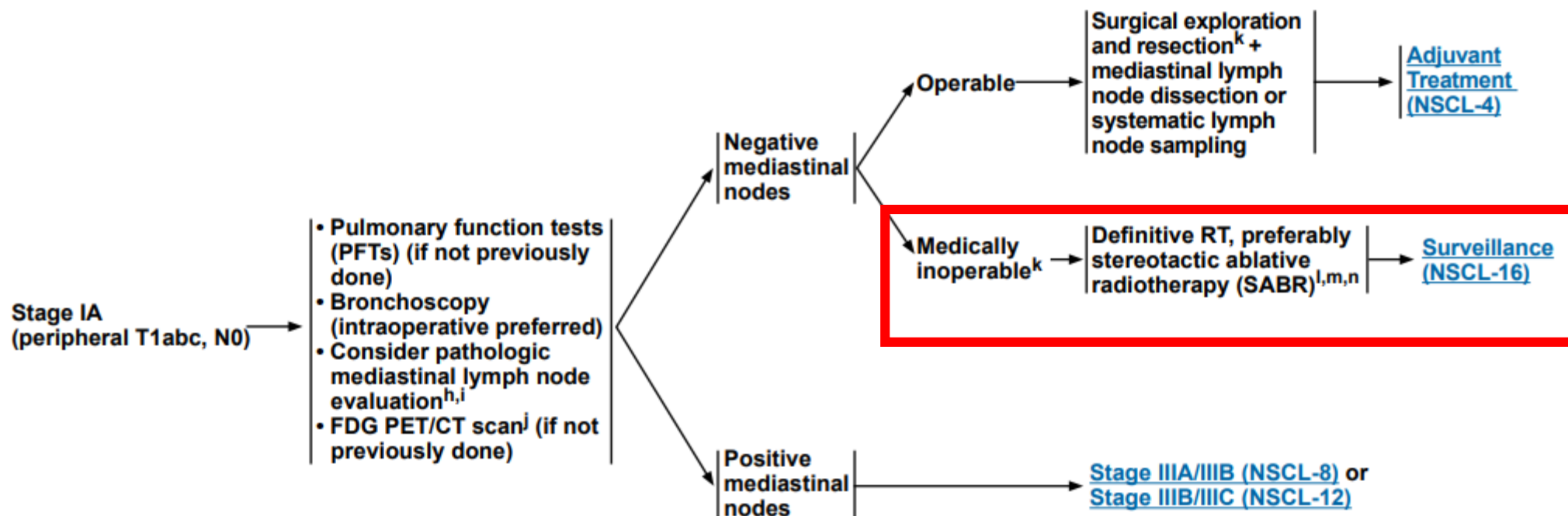
Hilar/interlobar zone

- 10 Hilar
- 11 Interlobar

Peripheral zone

- 12 Lobar
- 13 Segmental
- 14 Subsegmental

CLINICAL ASSESSMENT PRETREATMENT EVALUATION^g



^g Testing is not listed in order of priority and is dependent on clinical circumstances, institutional processes, and judicious use of resources.

^h Methods for evaluation include mediastinoscopy, mediastinotomy, EBUS, EUS, and CT-guided biopsy. An EBUS-TBNA negative for malignancy in a clinically (PET and/or CT) positive mediastinum should undergo subsequent mediastinoscopy prior to surgical resection.

ⁱ There is low likelihood of positive mediastinal lymph nodes when these nodes are CT and PET negative in solid tumors <1 cm and purely non-solid tumors <3 cm. Thus, pre-resection pathologic mediastinal evaluation is optional in these settings.

^j PET/CT performed skull base to knees or whole body. Positive PET/CT scan findings for distant disease need pathologic or other radiologic confirmation. If PET/CT scan is positive in the mediastinum, lymph node status needs pathologic confirmation.

^k [Principles of Surgical Therapy \(NSCL-B\)](#).

^l [Principles of Radiation Therapy \(NSCL-C\)](#).

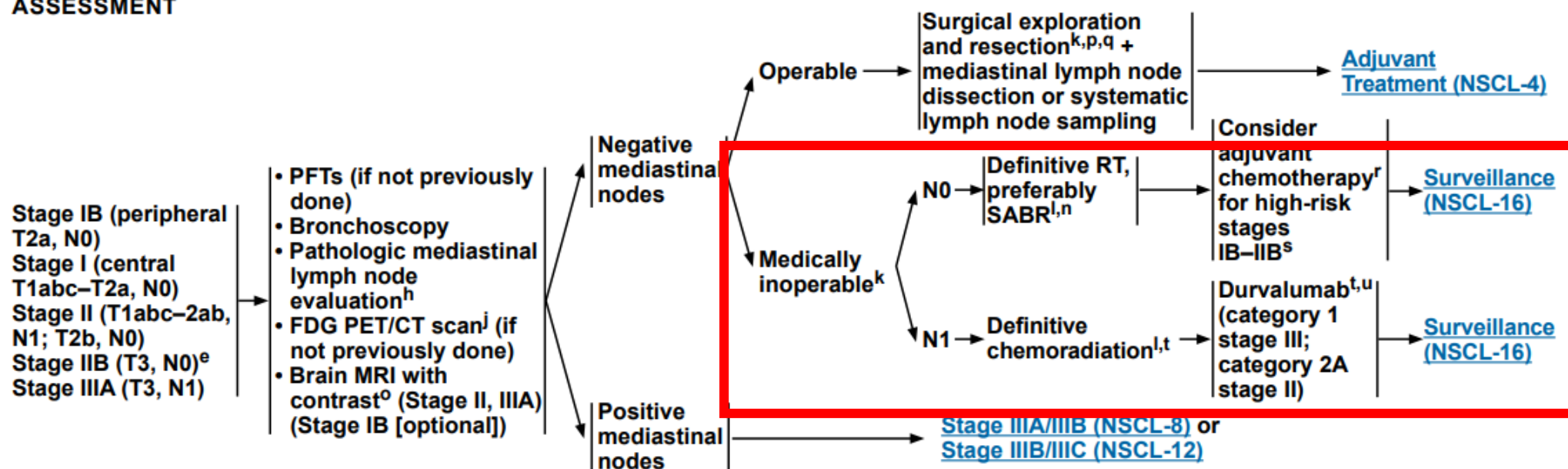
^m Image-guided thermal ablation (IGTA) therapy (eg, cryotherapy, microwave, radiofrequency) may be an option for select patients not receiving SABR or definitive RT. [Principles of Image-Guided Thermal Ablation Therapy \(NSCL-D\)](#).

ⁿ If empiric therapy is contemplated without tissue confirmation, multidisciplinary evaluation that at least includes interventional radiology, thoracic surgery, and interventional pulmonology is required to determine the safest and most efficient approach for biopsy, or to provide consensus that a biopsy is too risky or difficult and that the patient can proceed with therapy without tissue confirmation. (Jsseldijk MA, et al. J Thorac Oncol 2019;14:583-595.)

CLINICAL ASSESSMENT

PRETREATMENT EVALUATION^g

INITIAL TREATMENT



^e T3, N0 related to size or satellite nodules.

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^o If MRI is not possible, CT of head with contrast.

^p After surgical evaluation, patients likely to receive adjuvant chemotherapy may be treated with induction chemotherapy or chemoimmunotherapy as an alternative. If an immune checkpoint inhibitor is used in the pre-operative setting, an immune checkpoint inhibitor should not be used in the adjuvant setting. [Systemic Therapy Regimens for Neoadjuvant and Adjuvant Therapy \(NSCL-E\)](#).

^q Test for *EGFR* mutation (stages IB-IIIa) and PD-L1 status (stages II-IIIa) on surgical tissue or biopsy. [Principles of Molecular and Biomarker Analysis \(NSCL-H\)](#).

^r [Systemic Therapy Regimens for Neoadjuvant and Adjuvant Therapy \(NSCL-E\)](#).

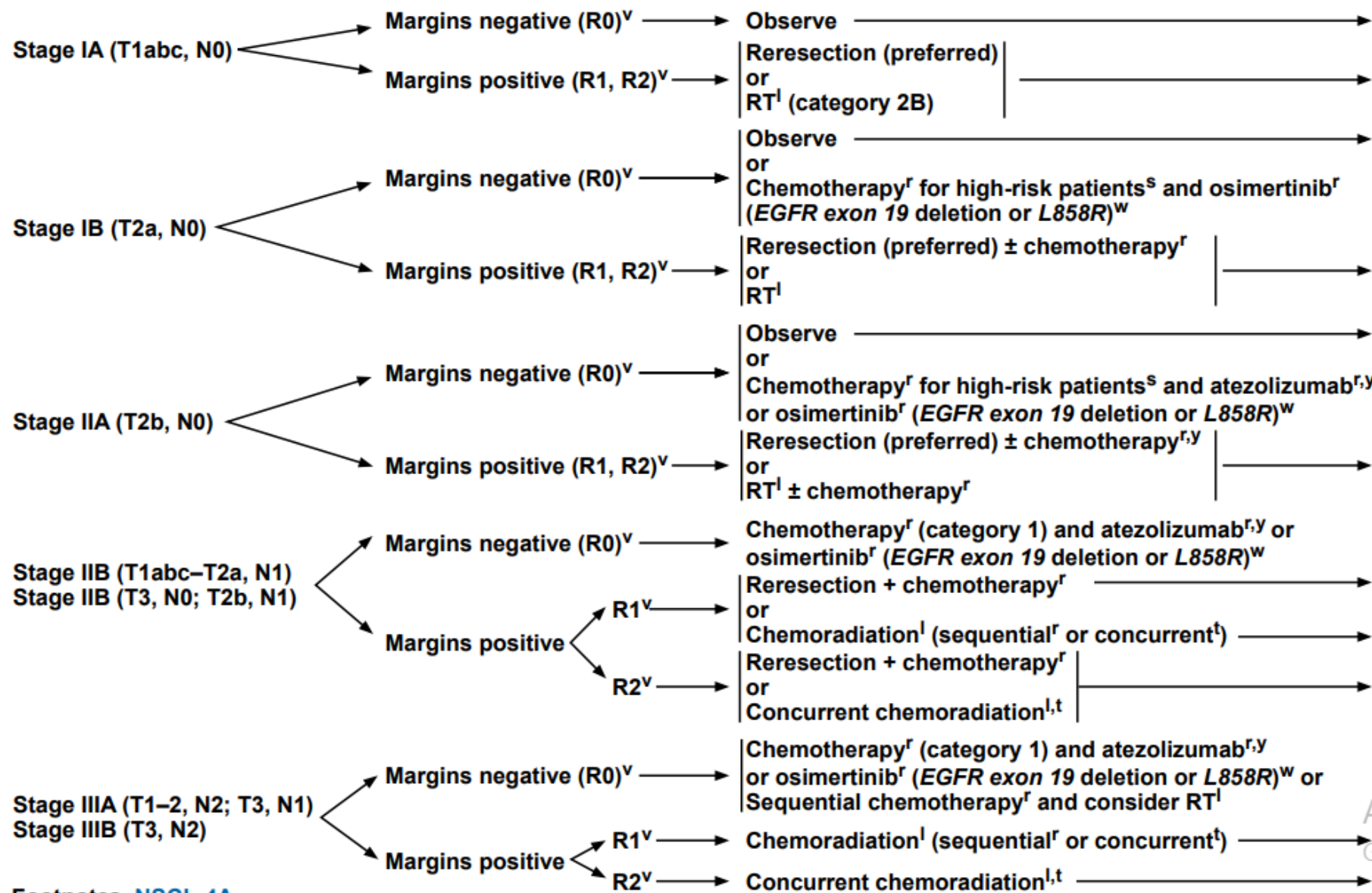
^s Examples of high-risk factors may include poorly differentiated tumors (including lung neuroendocrine tumors [excluding well-differentiated neuroendocrine tumors]), vascular invasion, wedge resection, tumors >4 cm, visceral pleural involvement, and unknown lymph node status (Nx). These factors independently may not be an indication and may be considered when determining treatment with adjuvant chemotherapy.

^t [Concurrent Chemoradiation Regimens \(NSCL-F\)](#).

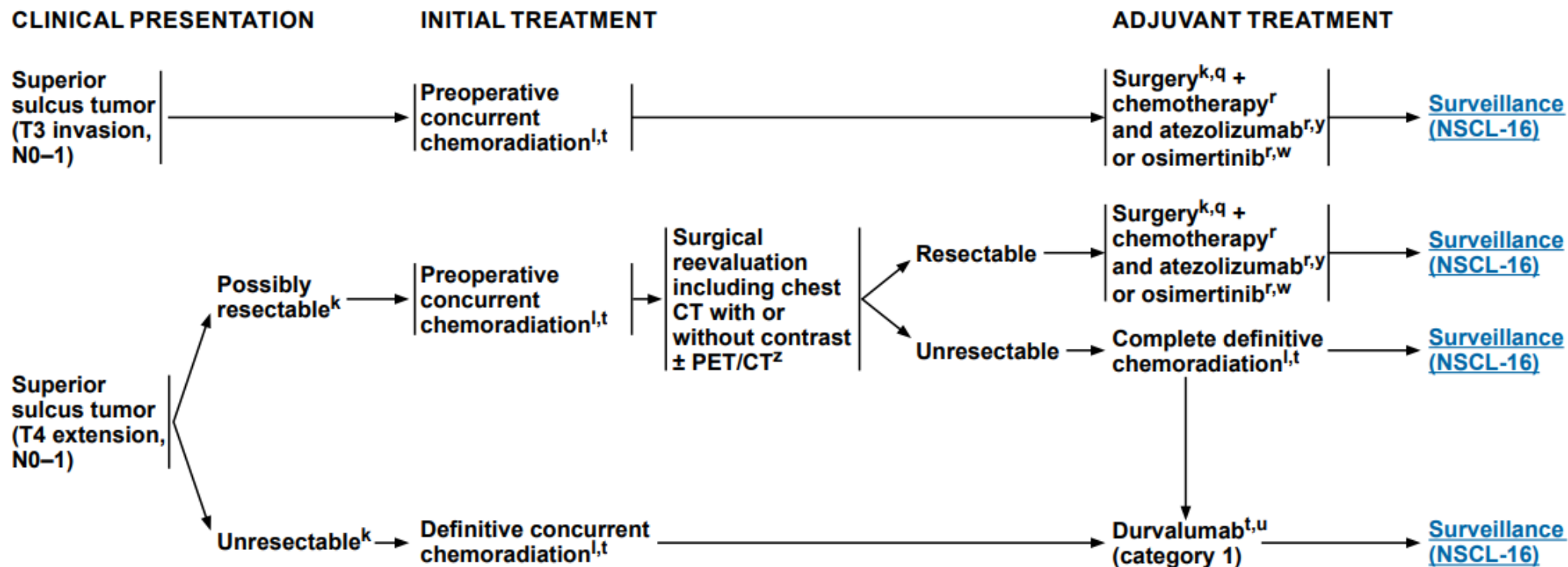
^u Durvalumab is not recommended for patients following definitive surgical resection.

FINDINGS AT SURGERY

ADJUVANT TREATMENT



[Surveillance \(NSCL-16\)](#)



^k [Principles of Surgical Therapy \(NSCL-B\)](#).

^l [Principles of Radiation Therapy \(NSCL-C\)](#).

^q Test for *EGFR* mutation (stages IB–IIIA) and PD-L1 status (stages II–IIIA) on surgical tissue or biopsy. [Principles of Molecular and Biomarker Analysis \(NSCL-H\)](#).

^r [Systemic Therapy Regimens for Neoadjuvant and Adjuvant Therapy \(NSCL-E\)](#).

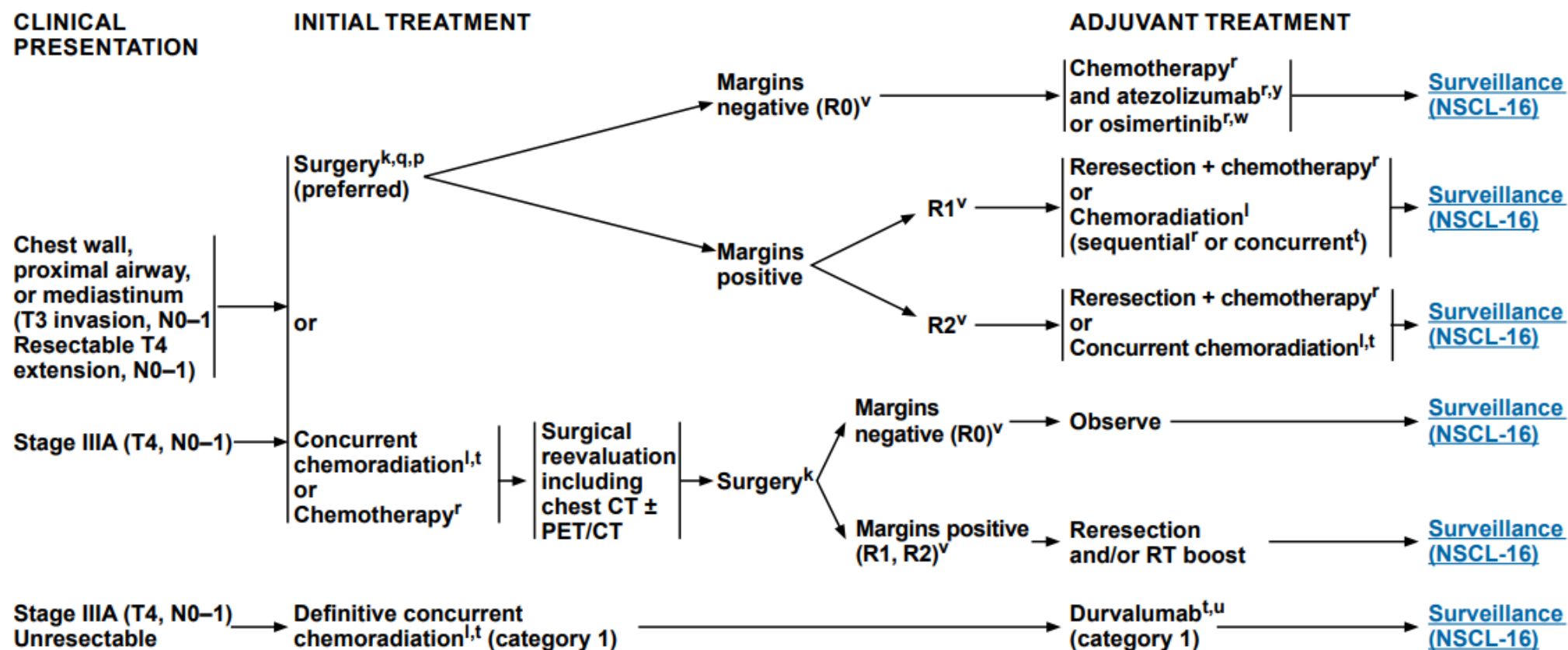
^t [Concurrent Chemoradiation Regimens \(NSCL-F\)](#).

^u Durvalumab is not recommended for patients following definitive surgical resection.

^w For patients with *EGFR* exon 19 deletion or L858R who received previous adjuvant chemotherapy or are ineligible to receive platinum-based chemotherapy.

^y For patients with PD-L1 ≥1% NSCLC who received previous adjuvant chemotherapy.

^z MRI with contrast of spine + thoracic inlet for superior sulcus lesions abutting the spine, subclavian vessels, or brachial plexus.



^k [Principles of Surgical Therapy \(NSCL-B\)](#).

^l [Principles of Radiation Therapy \(NSCL-C\)](#).

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^v R0 = no residual tumor, R1 = microscopic residual tumor, R2 = macroscopic residual tumor.

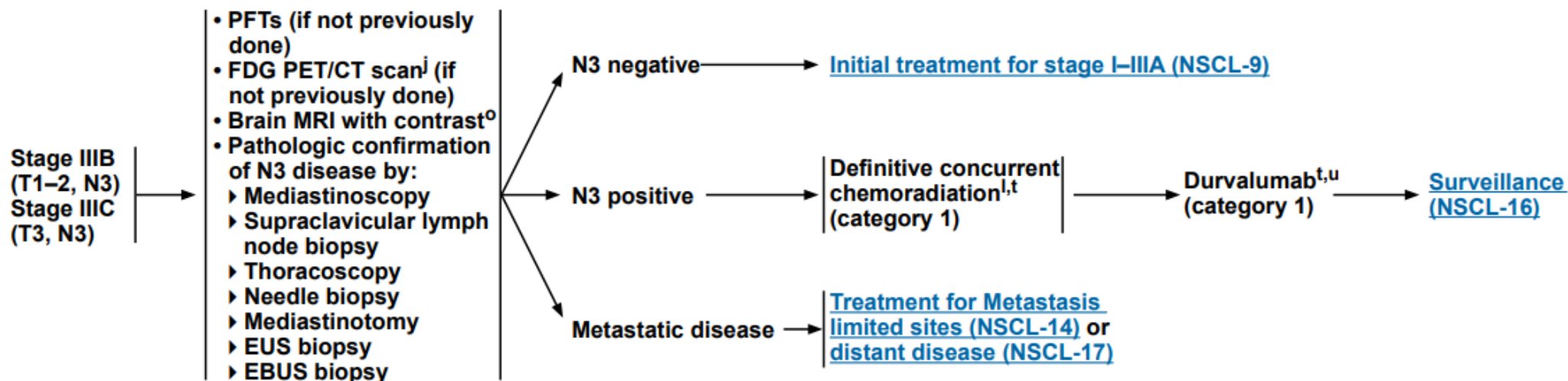
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**CLINICAL
ASSESSMENT**

PRETREATMENT EVALUATION

INITIAL TREATMENT



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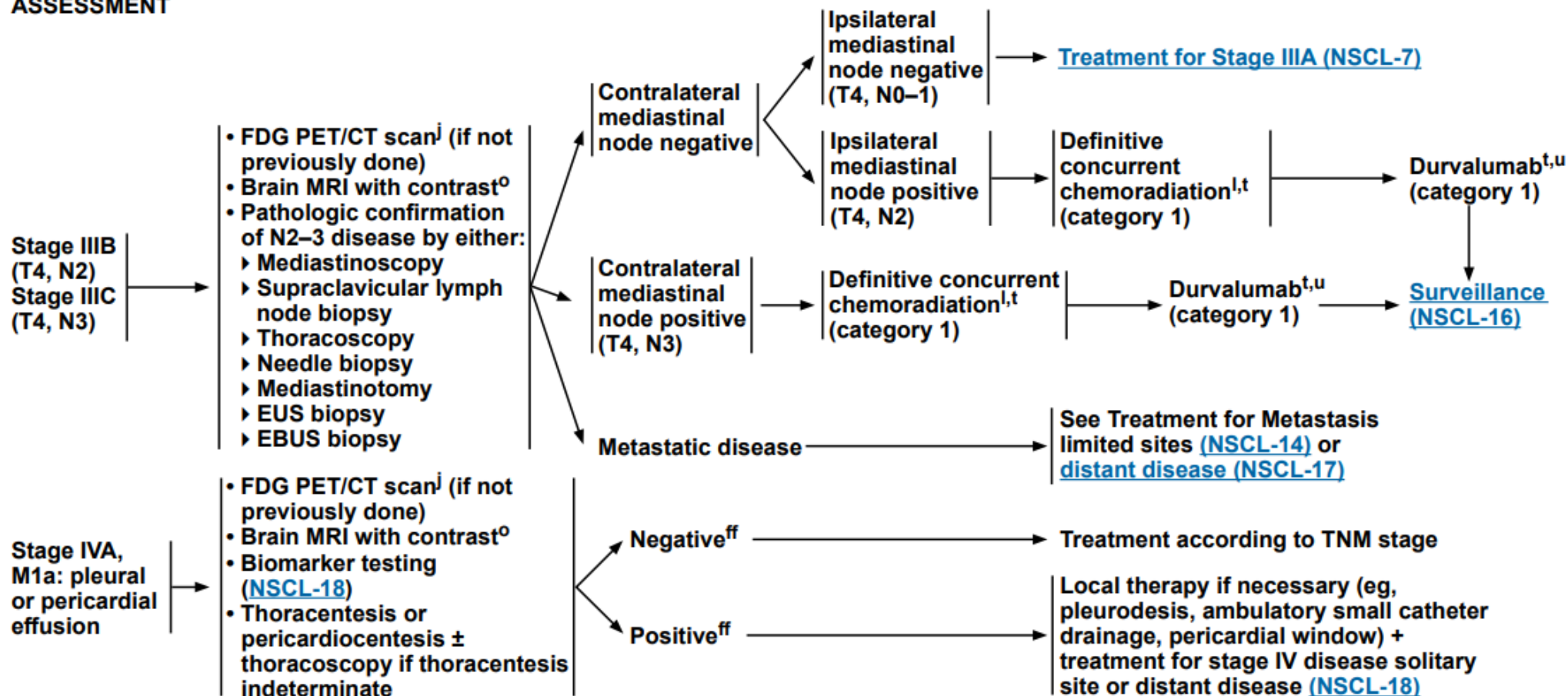
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**CLINICAL
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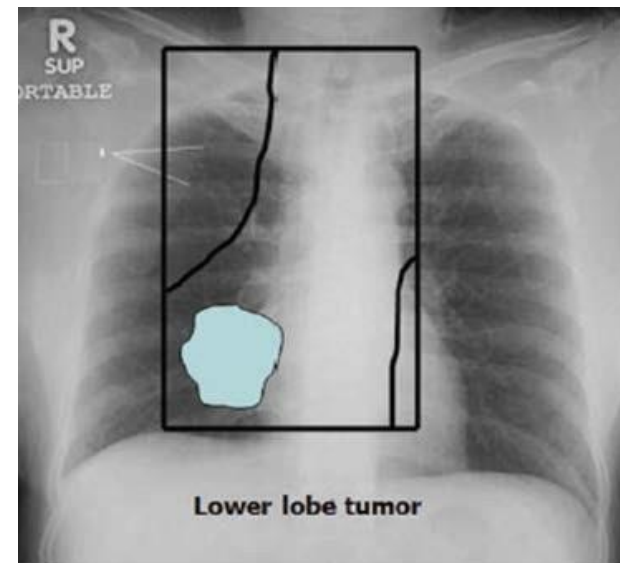
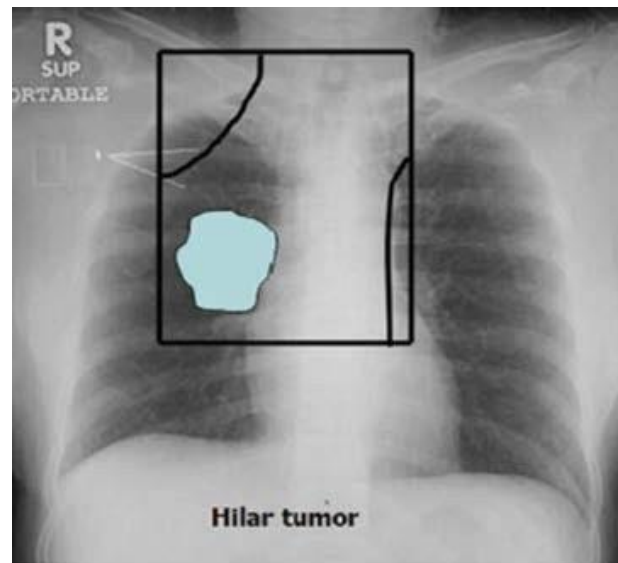
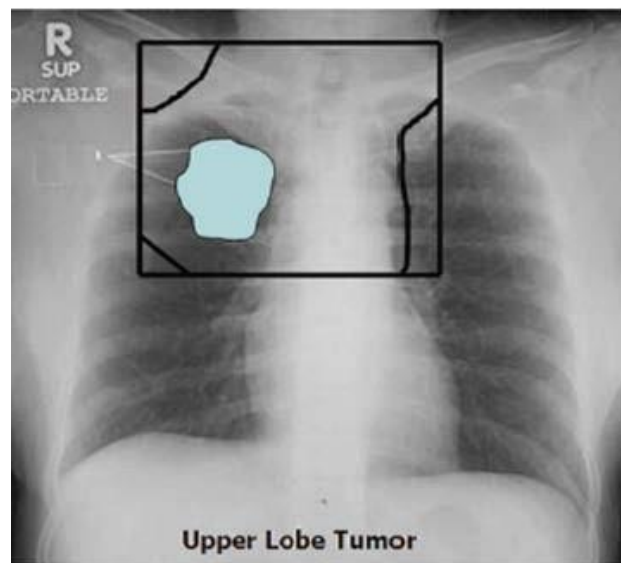
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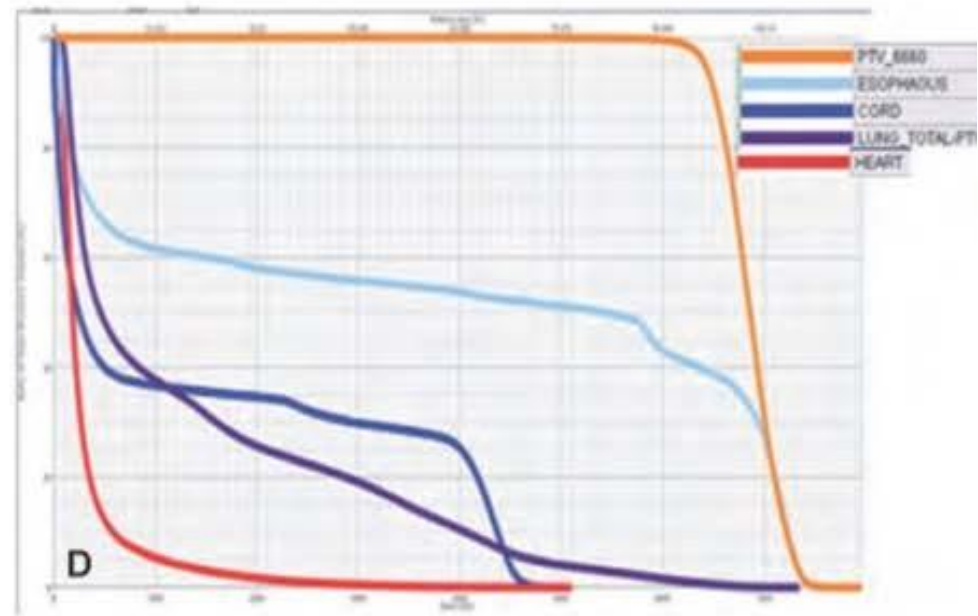
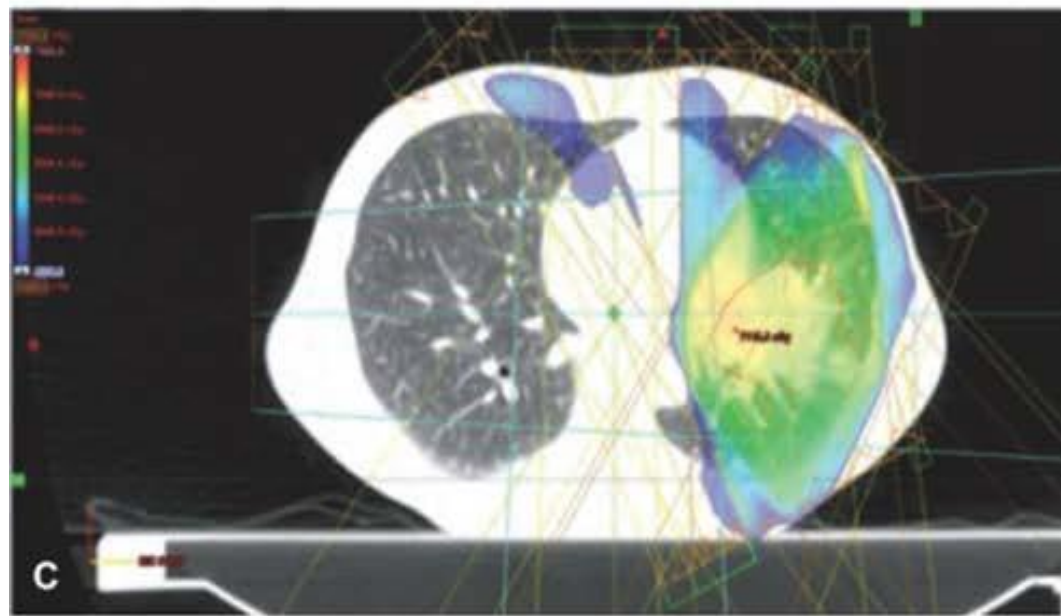
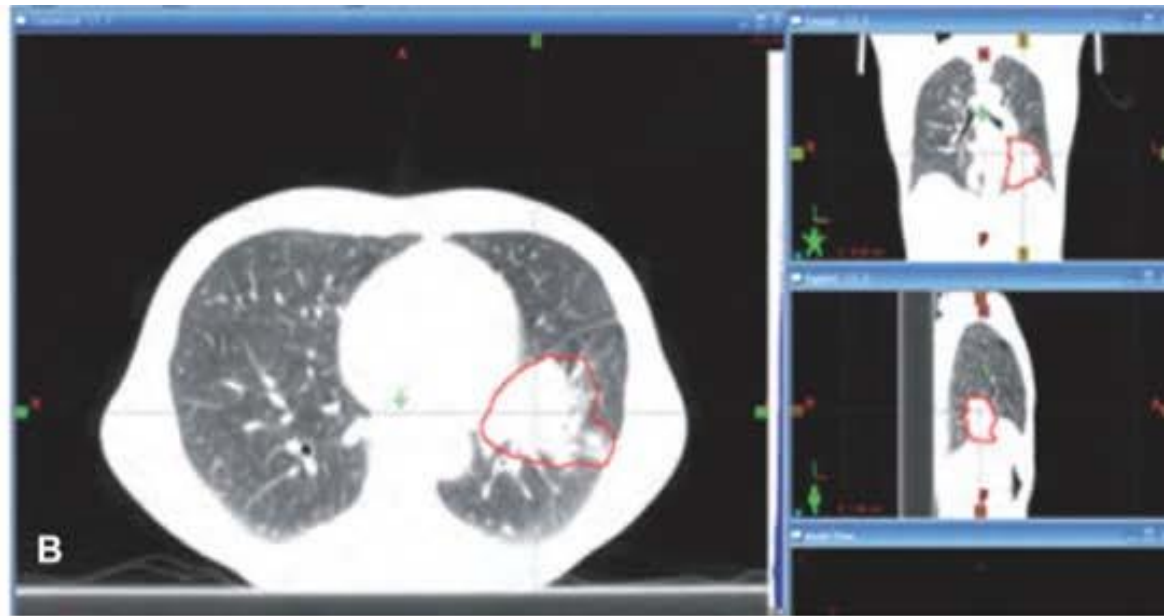
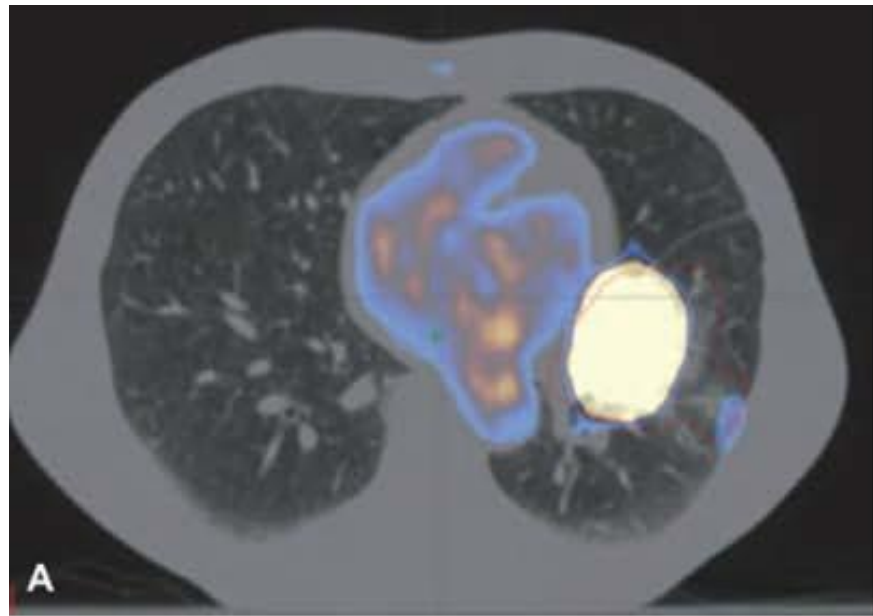
^{ff} Most pleural (pericardial) effusions with lung cancer are a result of the tumor. In a few patients, however, multiple microscopic examinations of pleural (pericardial) fluid are negative for tumor, and fluid is non-bloody and not an exudate. If these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging descriptor.

1D, 2D

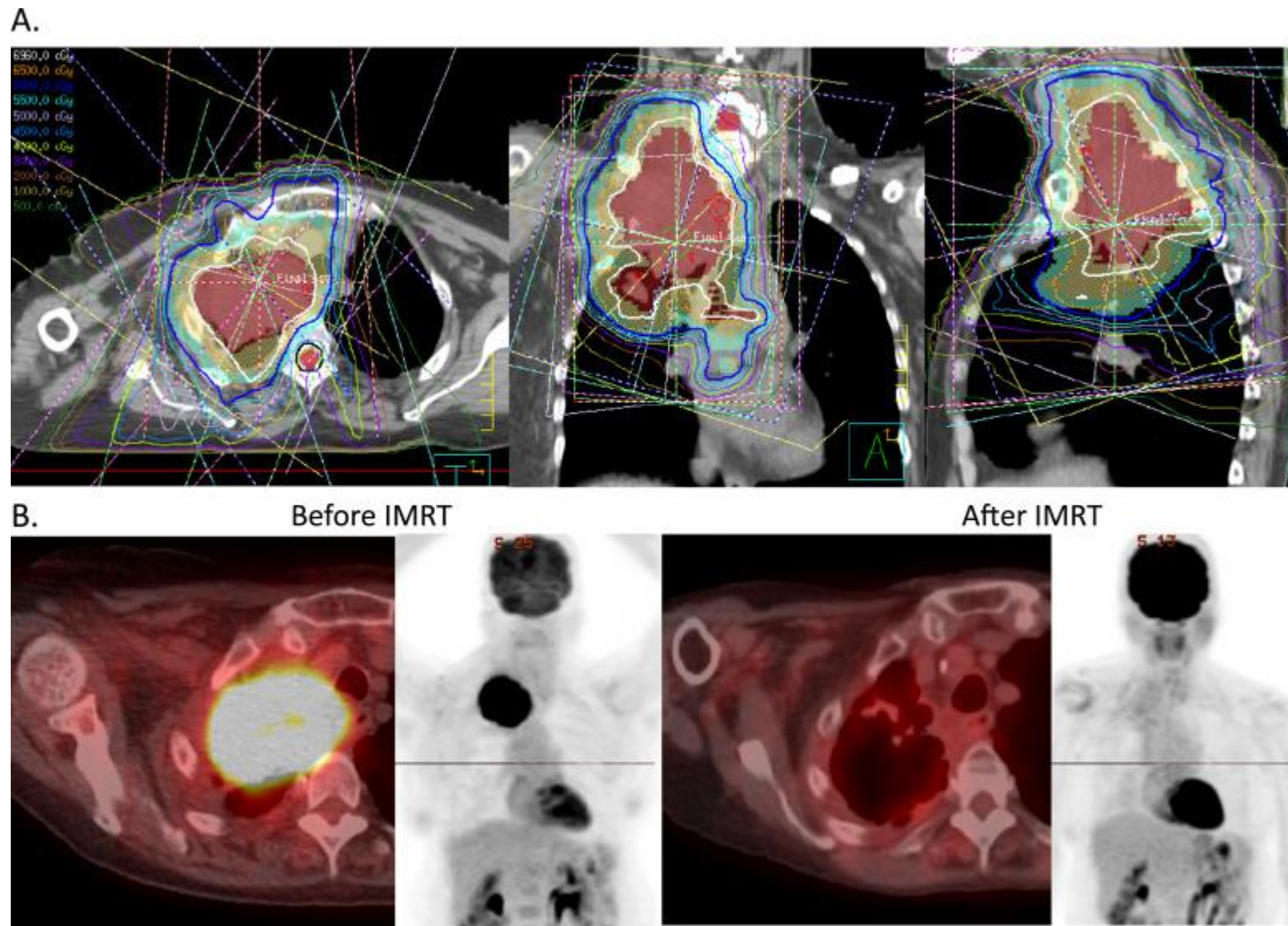


3D CRT

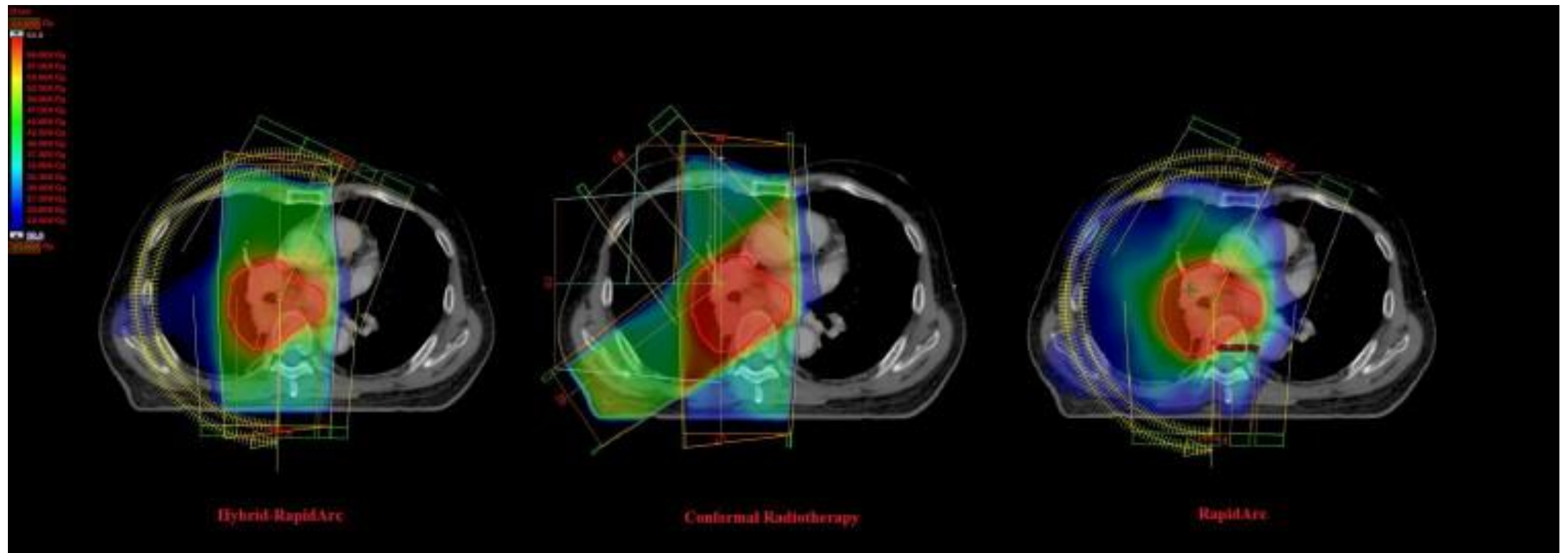
- 3D CRT – delineation of target volumes and OARs. Target volumes - "involved field" approach (IFRT)
- Elective lymph node radiotherapy is not advised due to higher toxicity, low likelihood of relapse in elective lymph node regions, and evidence that even with IFRT, elective regions receive a high dose of radiation. The RTOG recommendations stipulate that when applying the IFRT technique, the ipsilateral hilar lymph nodes should be included.
- 3D-CRT planning involves delineation of the visible tumor mass (GTV), a clinically significant target volume that includes likely locoregional routes of spread (CTV) and the planned target volume (PTV), as well as organs at risk (OAR). If the planning does not include Breath hold or Respiratory gating, it is necessary to define the Internal target volume (ITV), which includes the margin added to the CTV due to target movement.
- GTV- represents a macroscopic disease, includes the primary tumor (on the lung window) and affected lymphatics (mediastinal window). When possible, GTV should always be performed in co-registration with PET-CT (atelecase). If HT was applied before radiation therapy, the GTV should include the post-chemotherapy volume, and the coverage of the pre-chemotherapy disease with the CTV, while the affected lymphatics are delineated in the GTV as the post-chemotherapy volume, and the entire level of lymph nodes as the CTV.
- CTV- GTV + region containing microscopic disease - in the case of the IFRT technique in non-small cell carcinoma, this volume includes the entire region in which the affected lymph node is located. In relation to GTV, a margin of 5–10 mm is added (according to the works - in non-small cell carcinoma, a margin of 9 mm covers in 95% of cases microscopic expansion in adenocarcinoma, while in squamous cell carcinomas, this margin is 6 mm, in lymph nodes up to 2 cm, this margin is 3 mm) . CTV is corrected according to pre-chemotherapy GTV.
- ITV- CTV+ margin due to respiratory movements - when delineating the ITV, anatomical borders should be respected. Margins due to initiation depend on the location and size of the tumor.
- PTV- CTV+ margin due to daily variations in positioning. A typical margin is 5-10mm if ITV is used due to respiratory drift compensation and diurnal drift control (IGRT).



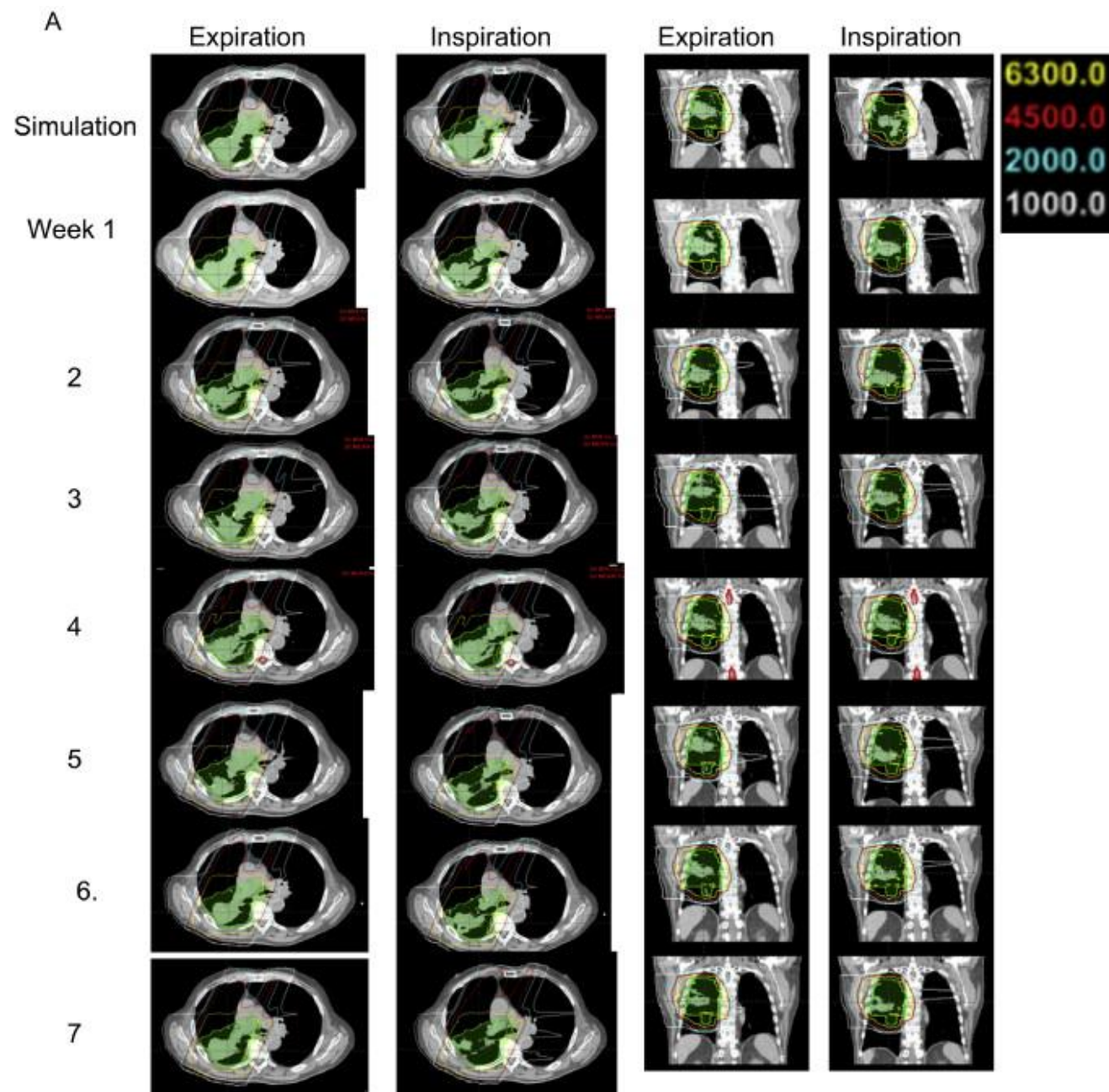
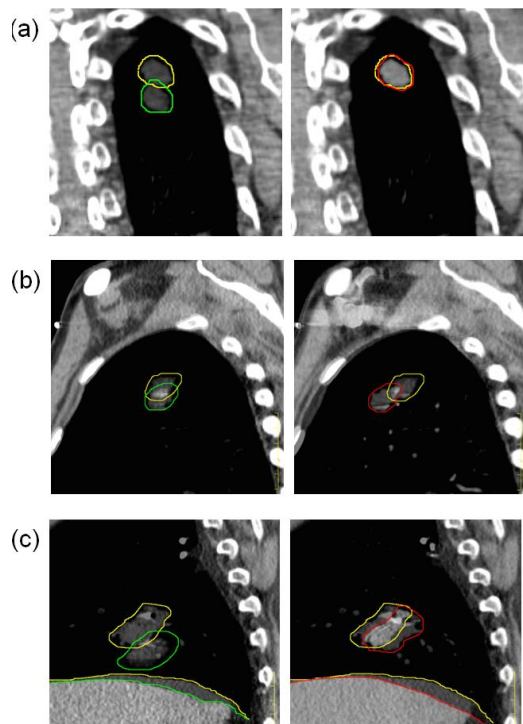
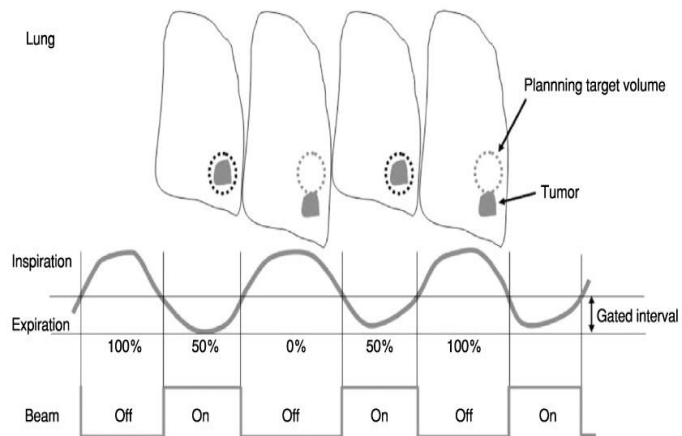
IMRT



VMAT



Oscar S.H. Chan et al. 52nd Annual Meeting of American Society for Radiation Oncology, San Diego, US.



PRINCIPLES OF RADIATION THERAPY

Please note: Tables 2–5 provide doses and constraints used commonly or in past clinical trials as useful references rather than specific recommendations.

Table 4. Commonly Used Doses for Conventionally Fractionated and Palliative RT

Treatment Type	Total Dose	Fraction Size	Treatment Duration
Definitive RT with or without chemotherapy	60–70 Gy	2 Gy	6–7 weeks
Preoperative RT	45–54 Gy	1.8–2 Gy	5 weeks
Postoperative RT			
• Negative margins	50–54 Gy	1.8–2 Gy	5–6 weeks
• Extracapsular nodal extension or microscopic positive margins	54–60 Gy	1.8–2 Gy	6 weeks
• Gross residual tumor	60–70 Gy	2 Gy	6–7 weeks
Palliative RT			
• Obstructive disease (SVC syndrome or obstructive pneumonia)	30–45 Gy	3 Gy	2–3 weeks
• Bone metastases with soft tissue mass	20–30 Gy	4–3 Gy	1–2 weeks
• Bone metastases without soft tissue mass	8–30 Gy	8–3 Gy	1 day–2 weeks
• Brain metastases	CNS GLs*	CNS GLs*	CNS GLs*
• Symptomatic chest disease in patients with poor PS	17 Gy**	8.5 Gy**	1–2 weeks**
• Any metastasis in patients with poor PS	8–20 Gy	8–4 Gy	1 day–1 week

* [NCCN Guidelines for Central Nervous System Cancers](#)

** This regimen includes one dose per week, as the phase 3 study included day 1 & 8 treatments.

Table 5. Normal Tissue Dose-Volume Constraints for Conventionally Fractionated RT with Concurrent Chemotherapy^{†,‡}

OAR	Constraints in 30–35 fractions
Spinal cord	Max ≤50 Gy
Lung	V20 ≤35%–40%; [§] MLD ≤20 Gy
Heart	V50 ≤25%; Mean ≤20 Gy
Esophagus	Mean ≤34 Gy; Max ≤105% of prescription dose; V60 ≤17%; contralateral sparing is desirable
Brachial plexus	Median dose ≤69 Gy

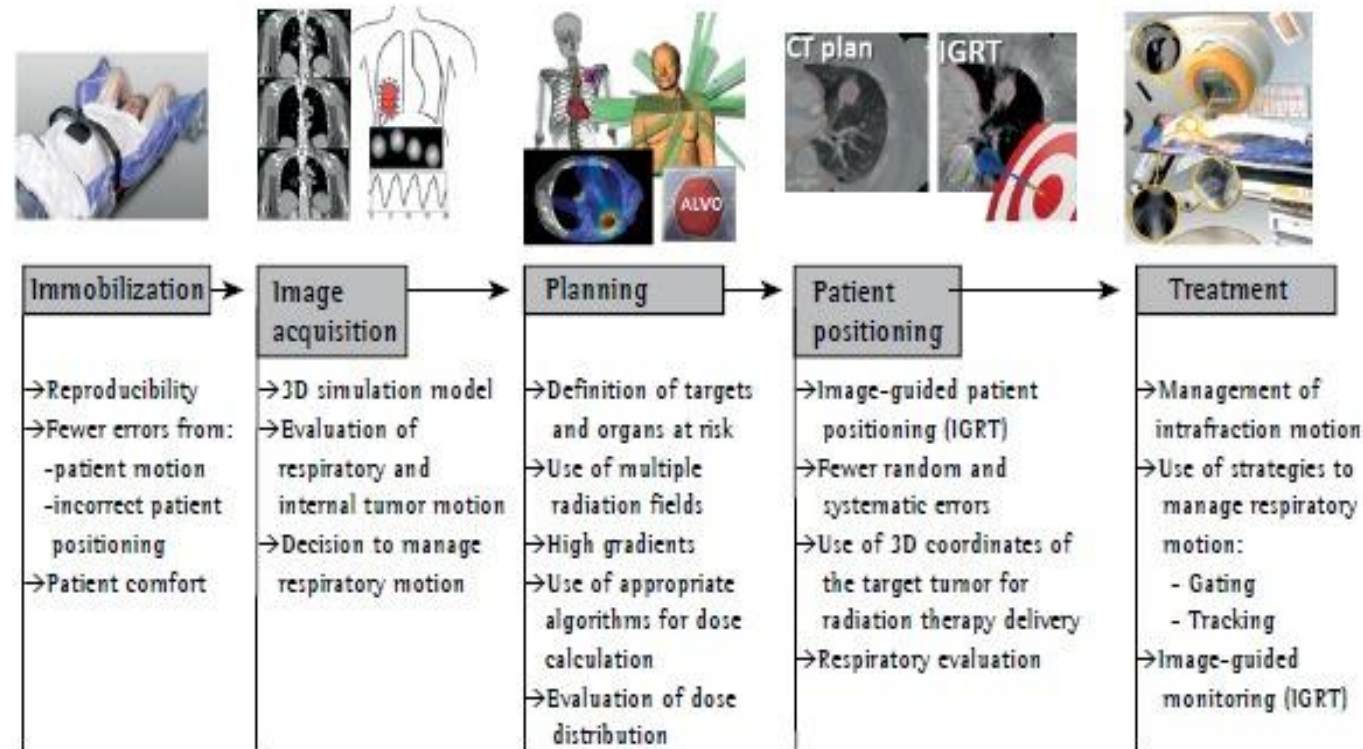
Vxx = % of the whole OAR receiving ≥xx Gy.

[†]These constraints represent doses that generally should not be exceeded, based on a consensus survey of NCCN Member Institutions. Because the risk of toxicity increases progressively with dose to normal tissues, a key principle of radiation treatment planning is to keep normal tissue doses "as low as reasonably achievable" while adequately covering the target. The doses to any given organ at risk should typically be lower than these constraints, approaching them only when there is close proximity to the target volume.

[‡] Speirs CK, et al. J Thorac Oncol 2017;12:293-301; Wang K, et al. J Clin Oncol 2017;35:1387-1394; Amini A, et al. Int J Radiat Oncol Biol Phys 2012;82:e391-398; Graham MV, et al. Int J Radiat Oncol Biol Phys 1999;45:323-329; Palma DA, et al. Int J Radiat Oncol Biol Phys 2013;85:444-450; Kamran SC, et al. JAMA Oncol 2021;7:910-914.

[§] Use V20 <35%, especially for the following: elderly ≥70 years, taxane chemotherapy, and poor PFTs (such as FEV1 or DLCO <50% normal). Use more conservative limits with a diagnosis or radiologic evidence of idiopathic pulmonary fibrosis (IDP)/usual interstitial pneumonia (UIP) (the tolerance of these patients is lower though not well characterized).

Stereotactic Body Radiotherapy, SBRT



PRINCIPLES OF RADIATION THERAPY

Please note: Tables 2–5 provide doses and constraints used commonly or in past clinical trials as useful references rather than specific recommendations.

Table 2. Commonly Used Doses for SABR

Total Dose	# Fractions	Example Indications
25–34 Gy	1	Peripheral, small
45–60 Gy	3	Peripheral tumors
48–50 Gy	4	Central or peripheral tumors <4–5 cm
50–55 Gy	5	Central or peripheral tumors
60–70 Gy	8–10	Central tumors

Table 3. Maximum Dose Constraints for SABR*

OAR/Regimen	1 Fraction	3 Fractions	4 Fractions	5 Fractions
Spinal cord	14 Gy	18 Gy (6 Gy/fx)	26 Gy (6.5 Gy/fx)	30 Gy (6 Gy/fx)
Esophagus	15.4 Gy	27 Gy (9 Gy/fx)	30 Gy (7.5 Gy/fx)	105% of PTV prescription^
Brachial plexus	17.5 Gy	24 Gy (8 Gy/fx)	27.2 Gy (6.8 Gy/fx)	32 Gy (6.4 Gy/fx)
Heart/ pericardium	22 Gy	30 Gy (10 Gy/fx)	34 Gy (8.5 Gy/fx)	105% of PTV prescription^
Great vessels	37 Gy	NS	49 Gy (12.25 Gy/fx)	105% of PTV prescription^
Trachea & proximal bronchi	20.2 Gy	30 Gy (10 Gy/fx)	34.8 Gy (8.7 Gy/fx)	105% of PTV prescription^
Rib	30 Gy	30 Gy (10 Gy/fx)	40 Gy (10 Gy/fx)	NS
Skin	26 Gy	24 Gy (8 Gy/fx)	36 Gy (9 Gy/fx)	32 Gy (6.4 Gy/fx)
Stomach	12.4 Gy	NS	27.2 Gy (6.8 Gy/fx)	NS

*Based on constraints used in recent RTOG SABR trials (RTOG 0618, 0813, & 0915).

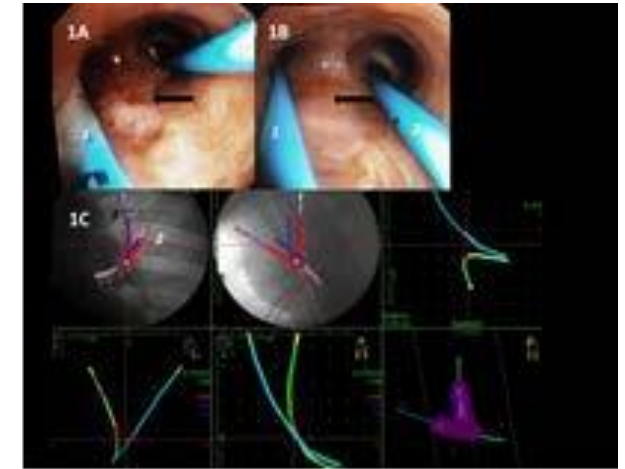
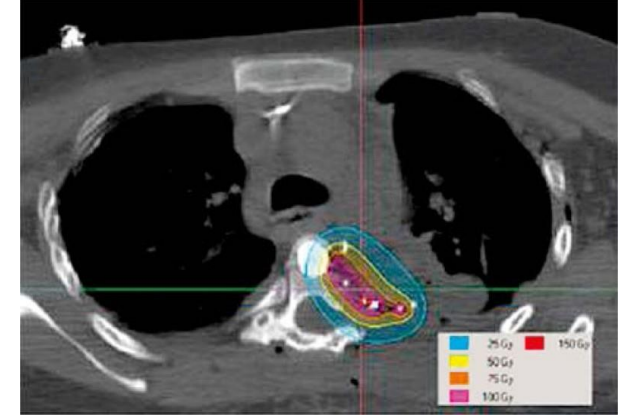
^For central tumor location. NS = not specified.

LUNG CANCER BRACHYTHERAPY

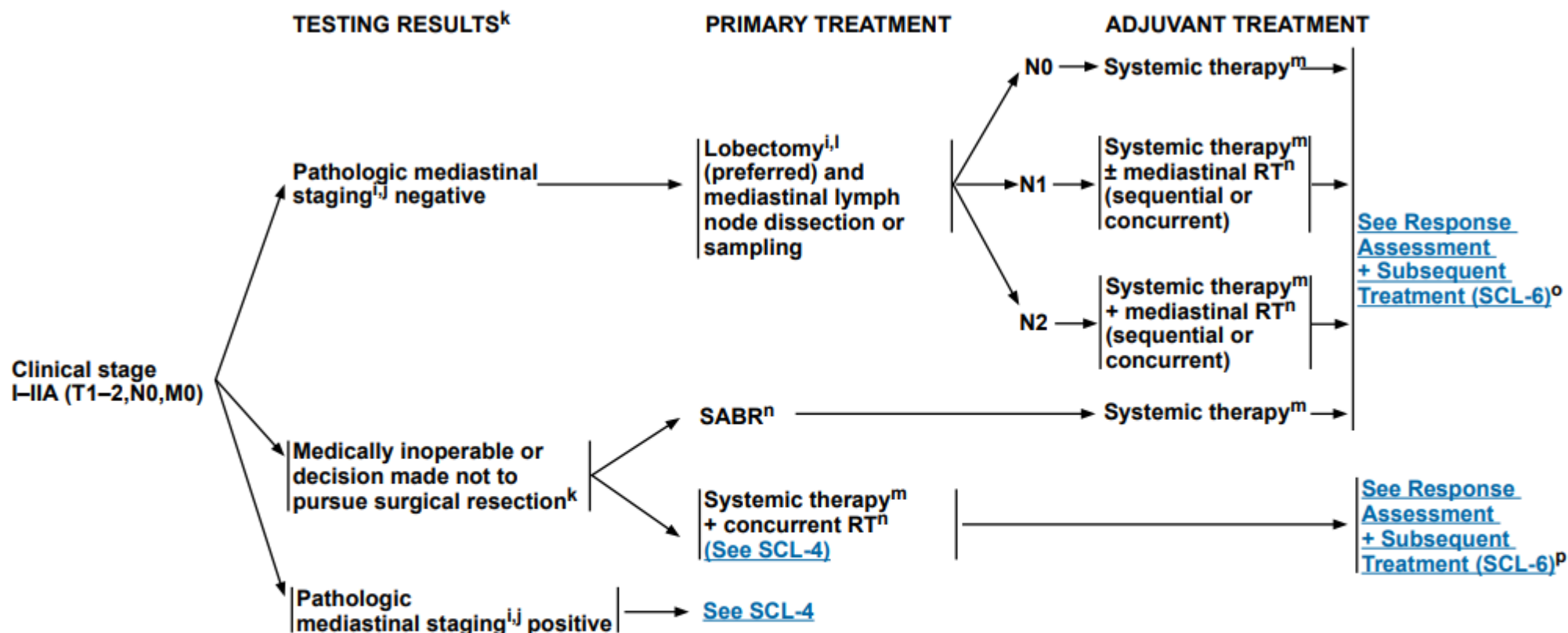
- The progress of brachytherapy follows the introduction of interstitial brachytherapy for early and locally advanced stages of lung cancer, intraoperative irradiation and brachytherapy for endobronchial lesions and palliation.
- In order to treat locally advanced lung cancer, endoluminal and interstitial brachytherapy can be applied. The application of brachytherapy can help in turning an unresectable or marginally resectable tumor into a tumor that can be appropriately resected in an oncological sense.
- Interstitial brachytherapy
- Placement of permanent radioactive sources or HDR brachytherapy. Placement of permanent radioactive sources is the method of choice in high-risk or inoperable patients.
- It can be applied in case of sublobular, i.e. maximum safe surgical resection to the region with increased risk (positive or close margins), in case of advanced disease in the area of residual tumor or positive lymph node and increases local control of the disease with prolonged survival.
- It is suitable for irradiation of locally invasive paraspinal tumors.
- For permanent implantation, ^{125}I , ^{103}Pd and ^{131}Cs are used (dose rate 0.01 to 0.3 Gy/h) due to their low energy, small size or short half-life.
- The toxicity resulting from the application of this type of treatment is low and amounts to about 8% for grades 3 to 4 that require surgical treatment. Special types of toxicity such as hydropneumothorax, radiation pneumonitis or esophageal fistulas occur rarely.

INTRALUMINAL BT

- Intraluminal (endobronchial) brachytherapy in order to recanalize the airways.
- Lesions must be visible bronchoscopically and usually localized in the trachea, main bronchi or lobar bronchi. Applying this method achieves a longer-lasting palliative effect with a significant improvement in the quality of life of patients.
- Indications: palliative treatment for symptoms caused by bronchial obstruction (dyspnea, hemoptysis, cough, obstructive pneumonia and atelectasis), salvage treatment for recurrent endoluminal disease after EBRT, boost after EBRT for centrally located tumors.
- The dose is prescribed at 1 cm from the center of the source with a 1-2 cm linear margin.
- If brachytherapy is administered alone for palliative purposes, the most common regimens are 5Gy x 3-4 fractions or 7Gy x 3 fractions (HDR).
- Application of the boost dose after EBRT is in 2-3 fractions for a week, 5-7Gy/fraction. The method of fractionation is individual.



SCLC



ⁱ See Principles of Surgical Resection (SCL-C).

^j Mediastinal staging procedures include mediastinoscopy, mediastinotomy, endobronchial or esophageal ultrasound-guided biopsy, and video-assisted thoracoscopy. If endoscopic lymph node biopsy is positive, additional mediastinal staging is not required.

^k Pathologic mediastinal staging is not required if the patient is not a candidate for surgical resection or if non-surgical treatment is pursued.

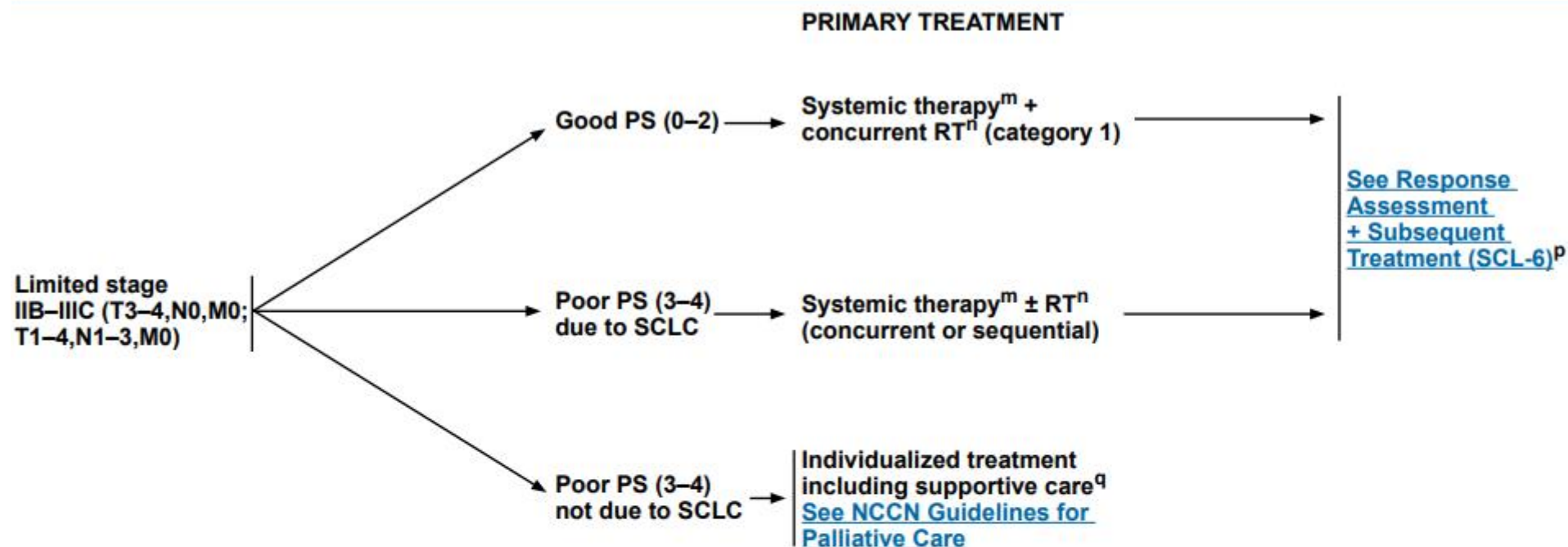
^l Select patients may be treated with systemic therapy/RT as an alternative to surgical resection.

^m See Principles of Systemic Therapy (SCL-E).

ⁿ See Principles of Radiation Therapy (SCL-F).

^o For patients receiving adjuvant systemic therapy ± RT, response assessment should occur only after completion of adjuvant therapy ([SCL-6](#)); do not repeat scans to assess response during adjuvant treatment.

^p For patients receiving systemic therapy + concurrent RT, response assessment should occur only after completion of initial therapy ([SCL-6](#)); do not repeat scans to assess response during initial treatment. For patients receiving systemic therapy alone or sequential systemic therapy followed by RT, response assessment by chest/abdomen/pelvis CT with contrast should occur after every 2 cycles of systemic therapy and at completion of therapy ([SCL-6](#)).



^m See [Principles of Systemic Therapy \(SCL-E\)](#).

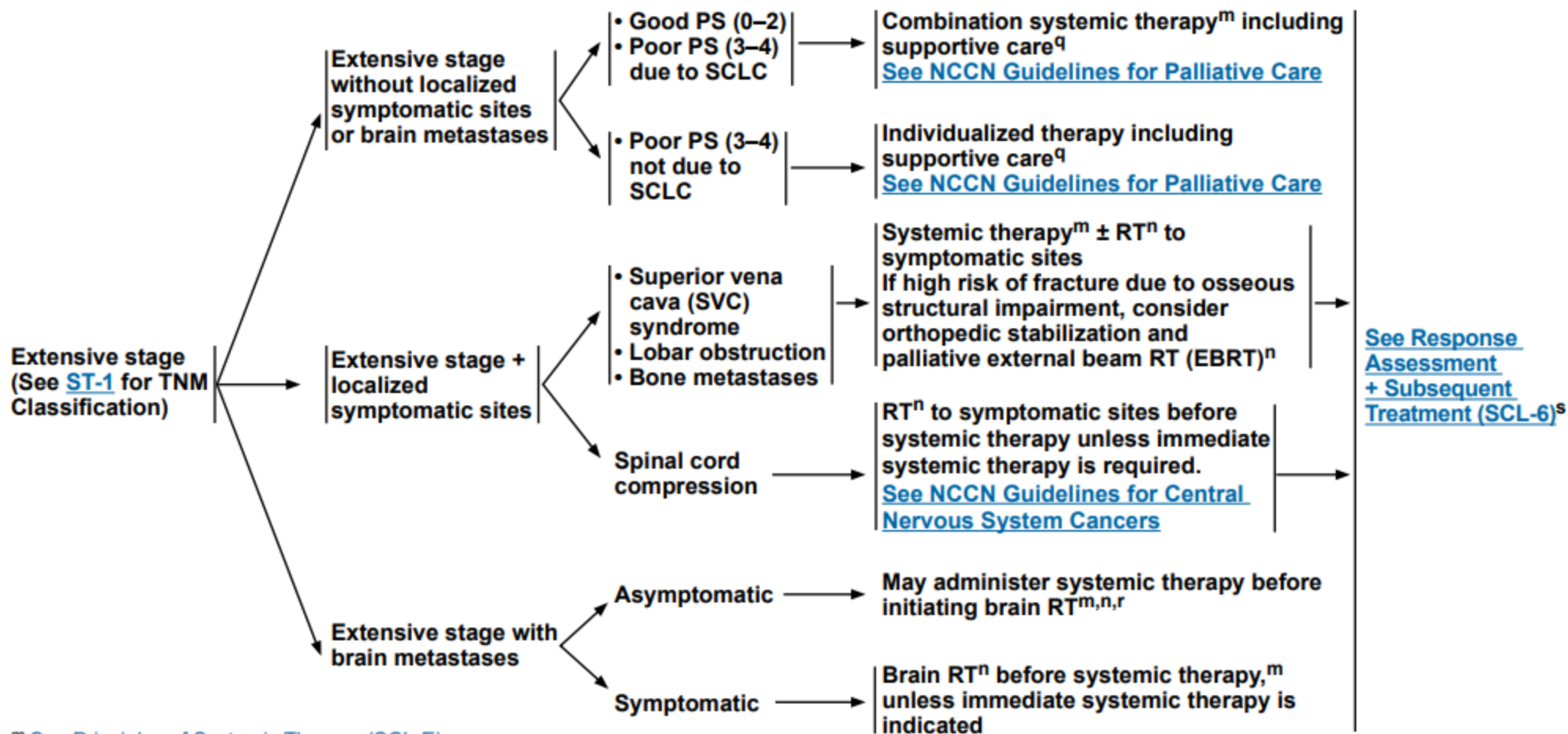
ⁿ See [Principles of Radiation Therapy \(SCL-F\)](#).

^p For patients receiving systemic therapy + concurrent RT, response assessment should occur only after completion of initial therapy ([SCL-6](#)); do not repeat scans to assess response during initial treatment. For patients receiving systemic therapy alone or sequential systemic therapy followed by RT, response assessment by chest/abdomen/pelvis CT with contrast should occur after every 2 cycles of systemic therapy and at completion of therapy ([SCL-6](#)).

^q See [Principles of Supportive Care \(SCL-D\)](#).

STAGE

PRIMARY TREATMENT^q



^m See Principles of Systemic Therapy (SCL-E).

ⁿ See Principles of Radiation Therapy (SCL-F).

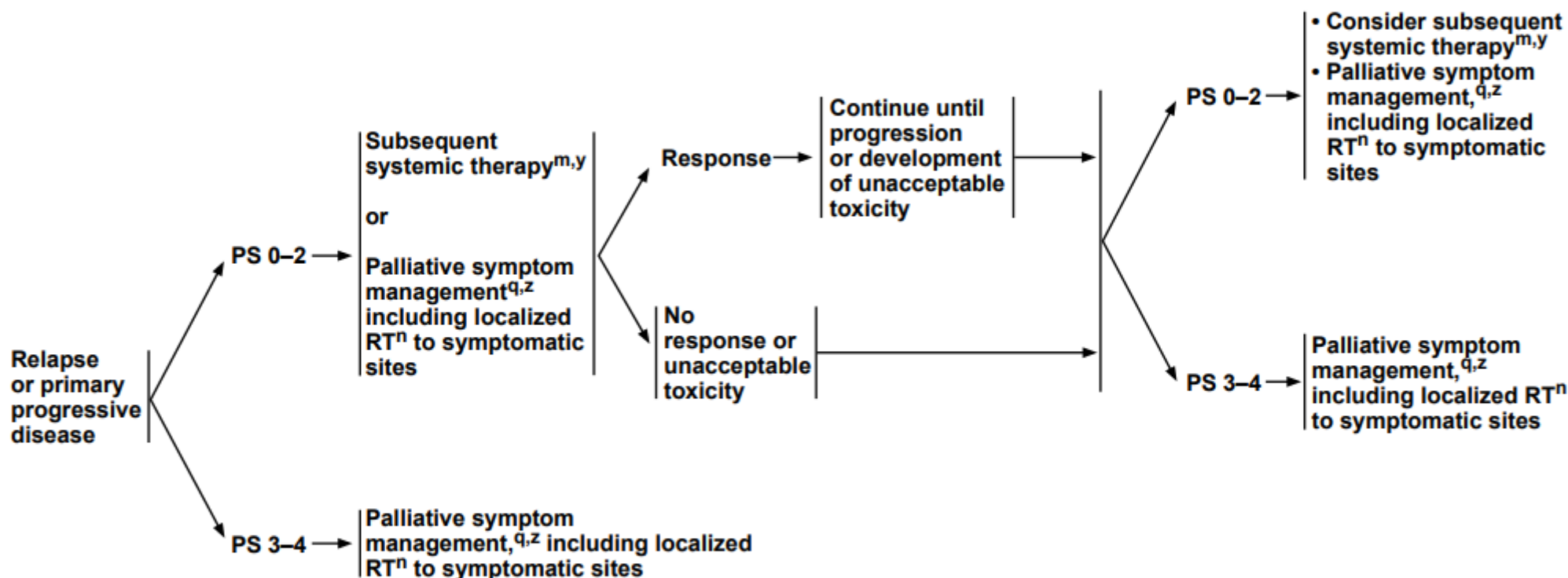
^q See Principles of Supportive Care (SCL-D).

^r Brain MRI (preferred) or CT with contrast should be repeated after every 2 cycles of systemic therapy until brain RT is initiated or systemic therapy is completed, whichever is first (see SCL-6). If brain metastases progress while on systemic therapy, brain RT should be initiated before completion of systemic therapy. See Principles of Radiation Therapy (SCL-F).

^s During systemic therapy, response assessment by chest/abdomen/pelvis CT with contrast should occur after every 2–3 cycles of systemic therapy and at completion of therapy (SCL-6).

PROGRESSIVE DISEASE

SUBSEQUENT THERAPY/PALLIATIVE THERAPY



^m See Principles of Systemic Therapy (SCL-E).

ⁿ See Principles of Radiation Therapy (SCL-F).

^q See Principles of Supportive Care (SCL-D).

^y Response assessment by chest/abdomen/pelvis CT with contrast should occur after every 2–3 cycles of systemic therapy.

^z See NCCN Guidelines for Palliative Care.



PRINCIPLES OF RADIATION THERAPY

General Principles:

- General principles of RT for lung cancer—including commonly used abbreviations; standards for clinical and technologic expertise and quality assurance; and principles of RT simulation, planning, and delivery—are provided in the NCCN Guidelines for Non-Small Cell Lung Cancer ([see NSCL-C](#)) and are applicable to RT for SCLC.
- RT has a potential role in all stages of SCLC, as part of either definitive or palliative therapy. Radiation oncology input, as part of a multidisciplinary evaluation or discussion, should be provided for all patients early in the determination of the treatment strategy.
- To maximize tumor control and to minimize treatment toxicity, critical components of modern RT include appropriate simulation, accurate target definition, conformal RT (CRT) planning, and ensuring accurate delivery of the planned treatment. A minimum standard is CT-planned 3D-CRT conformal RT. Multiple fields should be used, with all fields treated daily.
- Use of more advanced technologies is appropriate when needed to deliver adequate tumor doses while respecting normal tissue dose constraints. Such technologies include (but are not limited to) 4D-CT and/or PET/CT simulation, intensity-modulated RT (IMRT)/volumetric modulated arc therapy (VMAT), image-guided RT (IGRT), and motion management strategies. IMRT is preferred over 3D conformal EBRT on the basis of reduced toxicity in the setting of concurrent chemotherapy/RT.¹ Quality assurance measures are essential and are covered in the NCCN Guidelines for Non-Small Cell Lung Cancer ([see NSCL-C](#)).
- Useful references include the ACR Appropriateness Criteria at: <http://www.acr.org/quality-safety/appropriateness-criteria>

General Treatment Information:

• Limited stage:

- ▶ In patients with clinical stage I–IIA (T1–2, N0, M0) who have undergone lobectomy and are found to have regional nodal involvement on final pathology, postoperative RT is recommended in pathologic N2 and may be considered in pathologic N1 stage, either sequentially or concurrently with chemotherapy. Principles of postoperative RT for NSCLC, including target volumes and doses, are recommended.
- ▶ Selected patients with stage I–IIA (T1–2, N0, M0) SCLC who are medically inoperable or in whom a decision is made not to pursue surgery may be candidates for stereotactic ablative RT (SABR) to the primary tumor followed by adjuvant systemic therapy. Principles of SABR for SCLC are similar to those for NSCLC ([see NCCN Guidelines for Non-Small Cell Lung Cancer: NSCL-C](#)).^{2–4}
- ▶ Timing: RT concurrent with systemic therapy is standard and preferred to sequential chemo/RT.⁵ RT should start early, with cycle 1 or 2 of systemic therapy (category 1).⁶ A shorter time from the start of any therapy to the end of RT (SER) is significantly associated with improved survival.⁷
- ▶ Target definition: RT target volumes should be defined based on the pretreatment PET scan and CT scan obtained at the time of RT planning. PET/CT should be obtained, preferably within 4 weeks and no more than 8 weeks, before treatment. Ideally, PET/CT should be obtained in the treatment position.



PRINCIPLES OF RADIATION THERAPY

- **Limited stage (continued):**

- ▶ Historically, clinically uninvolved mediastinal nodes have been included in the RT target volume, whereas uninvolved supraclavicular nodes generally have not been included. Consensus on elective nodal irradiation (ENI) is evolving.⁸ Several more modern series, both retrospective and prospective, suggest that omission of ENI results in low rates of isolated nodal recurrences (0%–11%, most <5%), particularly when incorporating PET staging/target definition (1.7%–3%).^{9–14} ENI has been omitted in current prospective clinical trials (including CALGB 30610/RTOG 0538 and the EORTC 08072 [CONVERT] trial). Inclusion of the ipsilateral hilum in the target volume, even if not grossly involved, differs between these trials but may be reasonable.
- ▶ In patients who start systemic therapy before RT, the gross tumor volume (GTV) can be limited to the post-induction systemic therapy volume to avoid excessive toxicity. Initially involved nodal regions (but not their entire pre-systemic therapy volume) should be covered.^{11,15}
- ▶ Dose and schedule: For limited-stage SCLC, the optimal dose and schedule of RT have not been established.
 - ◊ Based on the randomized phase III trial, INT 0096, 45 Gy in 3 weeks (1.5 Gy twice daily [BID]) is superior (category 1) to 45 Gy in 5 weeks (1.8 Gy daily).^{16,17} When BID fractionation is used, there should be at least a 6-hour interfraction interval to allow for repair of normal tissue.
 - ◊ Retrospective and randomized phase II studies suggest that similarly accelerated doses of 40–42 Gy in 3 weeks but given in once-daily fractionation produce similar outcomes as 45 Gy in 3 weeks in BID fractionation.^{18,19}
 - ◊ If using once-daily conventionally fractionated RT, higher doses of 66–70 Gy should be used.^{20–23} Two randomized phase II trials did not demonstrate superiority of 66 Gy in 6.5 weeks/2 Gy daily (the European CONVERT trial) or 70 Gy in 7 weeks/2 Gy daily (CALGB 30610/RTOG 0538) over 45 Gy in 3 weeks/1.5 Gy BID, but overall survival and toxicity were similar.^{24,25}
 - ◊ Recent randomized phase II trials suggest that higher dose accelerated RT of 60–65 Gy in 4–5 weeks given in BID or daily fractionation may produce increased overall or progression-free survival compared to 45 Gy in 3 weeks in BID fractionation.^{26,27}

- **Extensive stage:**

- ▶ Consolidative thoracic RT is beneficial for selected patients with ES-SCLC with complete response or good response to systemic therapy, especially with residual thoracic disease and low-bulk extrathoracic metastatic disease. Studies have demonstrated that consolidative thoracic RT up to definitive doses is well-tolerated, results in fewer symptomatic chest recurrences, and improves long-term survival in some patients.^{28,29} The Dutch CREST randomized trial of modest-dose thoracic RT (30 Gy in 10 fractions) in patients with ES-SCLC that responded to systemic therapy demonstrated significantly improved 2-year overall survival and 6-month progression-free survival, although the protocol-defined primary endpoint of 1-year overall survival was not significantly improved.³⁰ Subsequent exploratory analysis found the benefit of consolidative thoracic RT is limited to the majority of patients who had residual thoracic disease after systemic therapy.³¹



PRINCIPLES OF RADIATION THERAPY

- **Extensive stage: (continued)**
 - ▶ Dosing and fractionation of consolidative thoracic RT should be individualized within the range of 30 Gy in 10 daily fractions to 60 Gy in 30 daily fractions, or equivalent regimens in this range.
 - ▶ Based on two randomized trials, immunotherapy during and after chemotherapy is a first-line approach,^{32,33} but these studies did not include consolidative thoracic RT. Nevertheless, consolidative thoracic RT after chemoimmunotherapy can be considered for selected patients as above, during or before maintenance immunotherapy (there are no data on optimal sequencing or safety).

Normal Tissue Dose Constraints:

- Normal tissue dose constraints depend on tumor size and location. For similar RT prescription doses, the normal tissue constraints used for NSCLC are appropriate ([see NSCL-C](#)).
- When administering accelerated RT schedules (eg, BID) or lower total RT doses (eg, 45 Gy), more conservative constraints should be used. When using accelerated schedules (eg, 3–5 weeks), the spinal cord constraints from the CALGB 30610/RTOG 0538 protocol should be used as a guide: ie, the maximum spinal cord dose should be limited to ≤41 Gy (including scatter irradiation) for a prescription of 45 Gy BID in 3 weeks and limited to ≤50 Gy for more protracted schedules.

Prophylactic Cranial Irradiation:

- In patients with LS-SCLC who have a good response to initial therapy, PCI decreases brain metastases and increases overall survival^{34,35}. In patients with ES-SCLC that has responded to systemic therapy, PCI decreases brain metastases. A randomized trial conducted by the EORTC found improved overall survival with PCI.³⁶ However, a Japanese randomized trial found that in patients who had no brain metastases on baseline MRI, PCI did not improve overall survival compared with routine surveillance MRI and treatment of asymptomatic brain metastases upon detection.³⁷ Surveillance imaging for brain metastases is recommended for all patients regardless of PCI status.
- The preferred dose for PCI to the whole brain is 25 Gy in 10 daily fractions. A shorter course (eg, 20 Gy in 5 fractions) may be appropriate in selected patients with extensive-stage disease. In a large randomized trial (PCI 99-01), patients receiving a dose of 36 Gy had higher mortality and higher chronic neurotoxicity compared to patients treated with 25 Gy.^{38,39}
- Neurocognitive function: Increasing age and higher doses are the most predictive factors for development of chronic neurotoxicity. In trial RTOG 0212, 83% of patients older than 60 years of age experienced chronic neurotoxicity 12 months after PCI versus 56% of patients younger than 60 years of age ($P = .009$).³⁹ Concurrent systemic therapy and high total RT dose (>30 Gy) should be avoided in patients receiving PCI.



PRINCIPLES OF RADIATION THERAPY

Prophylactic Cranial Irradiation: (continued)

- Administer PCI after resolution of acute toxicities of initial therapy. PCI is not recommended in patients with poor performance status or impaired neurocognitive functioning.
- When administering PCI, consider adding memantine during and after RT, which has been shown to decrease neurocognitive impairment following whole brain radiation therapy (WBRT) for brain metastases.⁴⁰ The dose of memantine used on RTOG 0614 was as follows: week 1 (starting on day 1 of WBRT), 5 mg each morning; week 2, 5 mg each morning and evening; week 3, 10 mg each morning and 5 mg each evening; and weeks 4–24, 10 mg each morning and evening.
- Hippocampal-avoidance (HA) PCI using IMRT may be considered as a potential strategy to improve cognitive preservation. A phase III randomized trial of HA-WBRT vs. conventional WBRT demonstrated improved cognitive preservation and patient-reported outcomes with HA-WBRT in patients with brain metastases from mixed histologies.⁴¹ Conflicting data have been reported with HA-PCI vs. conventional PCI in SCLC with one trial reporting no differences in cognition⁴² and a separate trial reporting improved cognitive preservation with HA-PCI.⁴³ A larger randomized trial of HA-PCI vs. conventional PCI, NRG CC003, is ongoing.⁴⁴
- An ongoing randomized trial, SWOG S1827/MAVERICK, is evaluating whether brain MRI surveillance alone is non-inferior to MRI surveillance plus PCI with regard to overall survival for LS-SCLC and ES-SCLC.⁴⁵

Brain Metastases:

- Brain metastases should typically be treated with WBRT; however, selected patients with a small number of metastases may be appropriately treated with stereotactic radiotherapy (SRT)/radiosurgery (SRS).⁴⁶ A current randomized trial, NRG CC009, is comparing SRS to hippocampal-sparing WBRT plus memantine in this setting.
- Recommended dose for WBRT is 30 Gy in 10 daily fractions. Consider adding memantine during and after RT (see Prophylactic Cranial Irradiation for memantine dosing).⁴⁰
- In patients who develop brain metastases after PCI, repeat WBRT may be considered in carefully selected patients.^{47,48} SRS is preferred, if feasible.^{49,50} For patients with a better prognosis (eg, ≥ 4 months), hippocampal-sparing WBRT using IMRT plus memantine is preferred because it produces less cognitive function failure than conventional WBRT plus memantine.⁴¹

Palliative Radiation for Extracranial Metastases:

- Common radiation dose-fractionation regimens (eg, 30 Gy in 10 fractions, 20 Gy in 5 fractions, 8 Gy in 1 fraction) used for palliation of other solid tumors are appropriate for palliation of SCLC metastases in most patients.
- Conformal techniques, such as IMRT, and/or higher dose intensity approaches, including SABR or SRS, may be appropriate in selected patients (eg, tumors with close proximity to organs at risk, re-irradiation, or better prognosis).

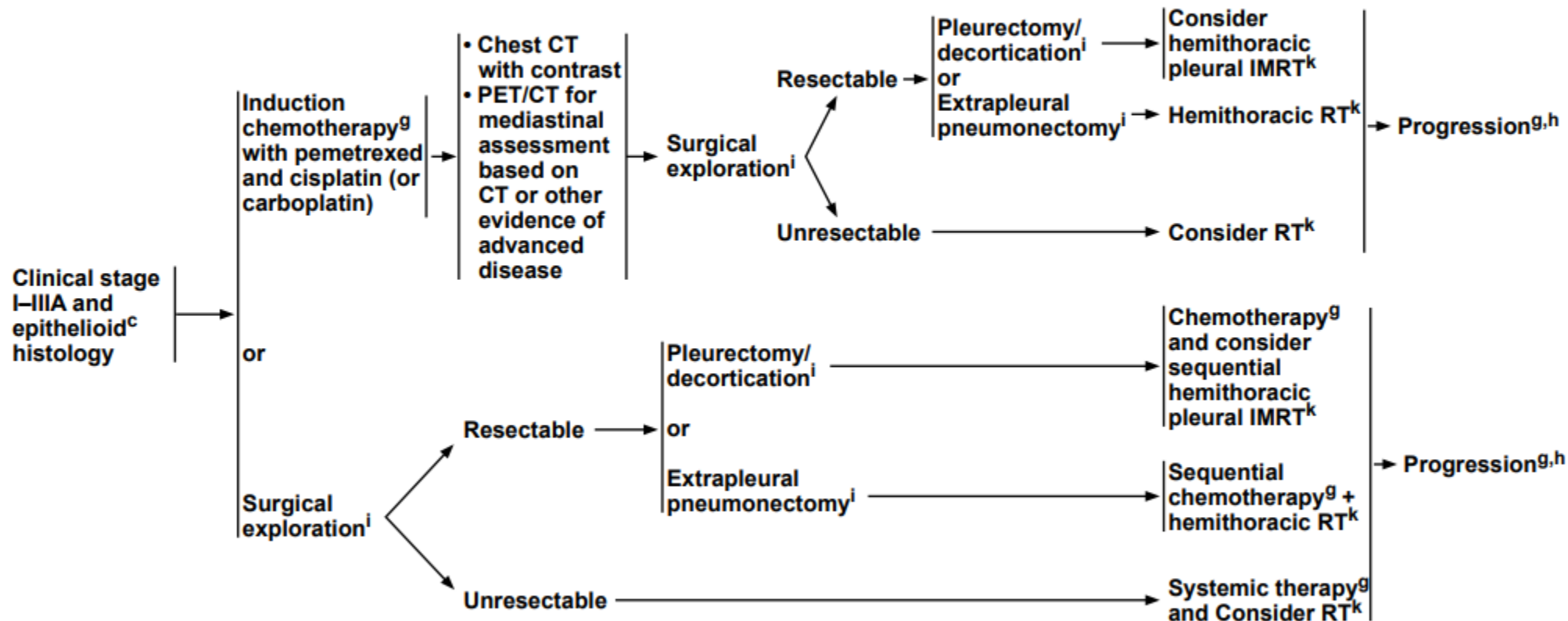
Mezothelioma



CLINICAL STAGE

PRIMARY TREATMENT^h

ADJUVANT TREATMENT^j



^c Surgery may be considered for biphasic histology if the patient has early-stage disease.

^g See Principles of Systemic Therapy (MPM-B).

^h See Principles of Supportive Care (MPM-C).

ⁱ See Principles of Surgery (MPM-D).

^j See NCCN Guidelines for Survivorship.

^k See Principles of Radiation Therapy (MPM-E).



PRINCIPLES OF RADIATION THERAPY

General Principles

- Recommendations regarding RT should be made by radiation oncologists with experience in managing MPM.
- The best timing for delivering RT after surgical intervention and/or in conjunction with chemotherapy should be discussed in a multidisciplinary team including radiation oncologists, surgeons, medical oncologists, diagnostic imaging specialists, and pulmonologists.
- For patients with resectable MPM who undergo EPP, adjuvant RT can be recommended for patients with good performance status (PS) to improve local control.¹⁻⁶
- PET scanning for treatment planning can be used as indicated.
- Prophylactic RT is not routinely recommended to prevent instrument-tract recurrence after pleural intervention.⁷
- RT is an effective palliative treatment for relief of chest pain, bronchial or esophageal obstruction, or other symptomatic sites associated with mesothelioma.
- A randomized phase III trial in patients with non-metastatic MPM who underwent non-radical lung-sparing surgery found substantially greater overall survival with radical hemithoracic intensity-modulated RT (IMRT) compared to palliative RT.⁸ Hemithoracic pleural IMRT after P/D in the presence of an intact lung may be considered in centers with experience and expertise in these methods, given the technical difficulty of this treatment.^{9,10,11}
- Acronyms and abbreviations related to RT are the same as listed in the Principles of Radiation Therapy for [NCCN Guidelines for Non-Small Cell Lung Cancer](#).
- Advanced technologies may be used, such as image-guided RT (IGRT) for treatment involving IMRT/stereotactic radiosurgery (SRS)/stereotactic body RT (SBRT), and intensity-modulated proton therapy (IMPT).¹²

Radiation Dose and Volume

- The dose of radiation should be based on the purpose of the treatment.
See [Recommended Doses for Radiation Therapy \(MPM-E 2 of 3\)](#).
- The dose of radiation for adjuvant therapy following EPP should be 45–60 Gy in 1.8–2.0 Gy based on the margin status. A dose of 54 Gy given to the entire hemithorax, the thoracotomy incision, and sites of chest drains was well-tolerated.^{6,13} When it is challenging to deliver 45 Gy, every effort should be made to deliver a minimum dose of 40 Gy.¹
- A dose ≥ 60 Gy should be delivered to macroscopic residual tumors if the doses to adjacent normal structures are limited to their tolerances. In addition to covering the surgical bed within the thorax, the volume of postoperative radiation should also include the surgical scars and biopsy tracks in the chest wall.¹⁴⁻¹⁶
- Daily doses of 4 Gy appear to be more efficacious than fractions of less than 4 Gy in providing relief from chest pain associated with mesothelioma,^{15,17} although the optimal daily and total dose of RT for palliative purposes remains unclear.
- For patients with residual tumors, some experienced investigators have used brachytherapy or intraoperative external beam RT (EBRT) in combination with surgery.

PRINCIPLES OF RADIATION THERAPY

Recommended Doses for Radiation Therapy

Treatment type	Total dose	Fraction size	Treatment duration
Postoperative after EPP Higher dose to higher risk areas	45–60 Gy	1.8–2 Gy	5–6 weeks
Palliative			
Chest wall pain from recurrent nodules	20–40 Gy or 30 Gy	≥4 Gy 3 Gy	1–2 weeks 2 weeks
Multiple brain or bone metastases	30 Gy	3 Gy	2 weeks
Post pleurectomy/decortication Higher dose to higher risk areas	45–60 Gy	1.8–2 Gy	5–6 weeks

After EPP, RT should only be considered for patients who meet the following criteria: ECOG PS ≤1; good functional pulmonary status; good function of contralateral kidney confirmed by renal scan; and absence of disease in abdomen, contralateral chest, or elsewhere. Patients who are on supplemental oxygen should not be treated with adjuvant RT.

Radiation Techniques

- A minimum technological standard is CT-planned 3D-CRT using photon or photon/electron beams.
- Use of highly conformal radiation technology (IMRT) is the preferred choice based on comprehensive consideration of target coverage and clinically relevant normal tissue tolerance.^{10,18} Advanced technologies are appropriate when needed to deliver curative RT safely. These technologies include (but are not limited to) 4D-CT and/or PET/CT simulation, IMRT/VMAT, IGRT, motion management, and proton therapy.
- Special attention should be paid to minimize radiation to the contralateral lung,¹⁹ as the risk of fatal pneumonitis with IMRT is excessively high when strict limits are not applied.²⁰ The contralateral uninvolved mean lung dose should be kept as low as possible, preferably <8.5 Gy. The low-dose volume should be minimized.²¹
- The gross tumor volume (GTV) should include any grossly visible tumor. Surgical clips (indicative of gross residual tumor) should be included for postoperative adjuvant RT.
- The clinical target volume (CTV) for adjuvant RT after EPP or P/D should encompass the entire pleural surface (for partial resection cases), surgical clips, and any potential sites with residual disease.
- Extensive elective nodal irradiation (ENI) (entire mediastinum and bilateral supraclavicular nodal regions) is not recommended.
- The planning target volume (PTV) should consider the target motion and daily setup errors. The PTV margin should be based on the individual patient's motion, simulation techniques used (with and without inclusion motion), and reproducibility of each clinic's daily setup.

THYMOMAS AND THYMIC CANCER

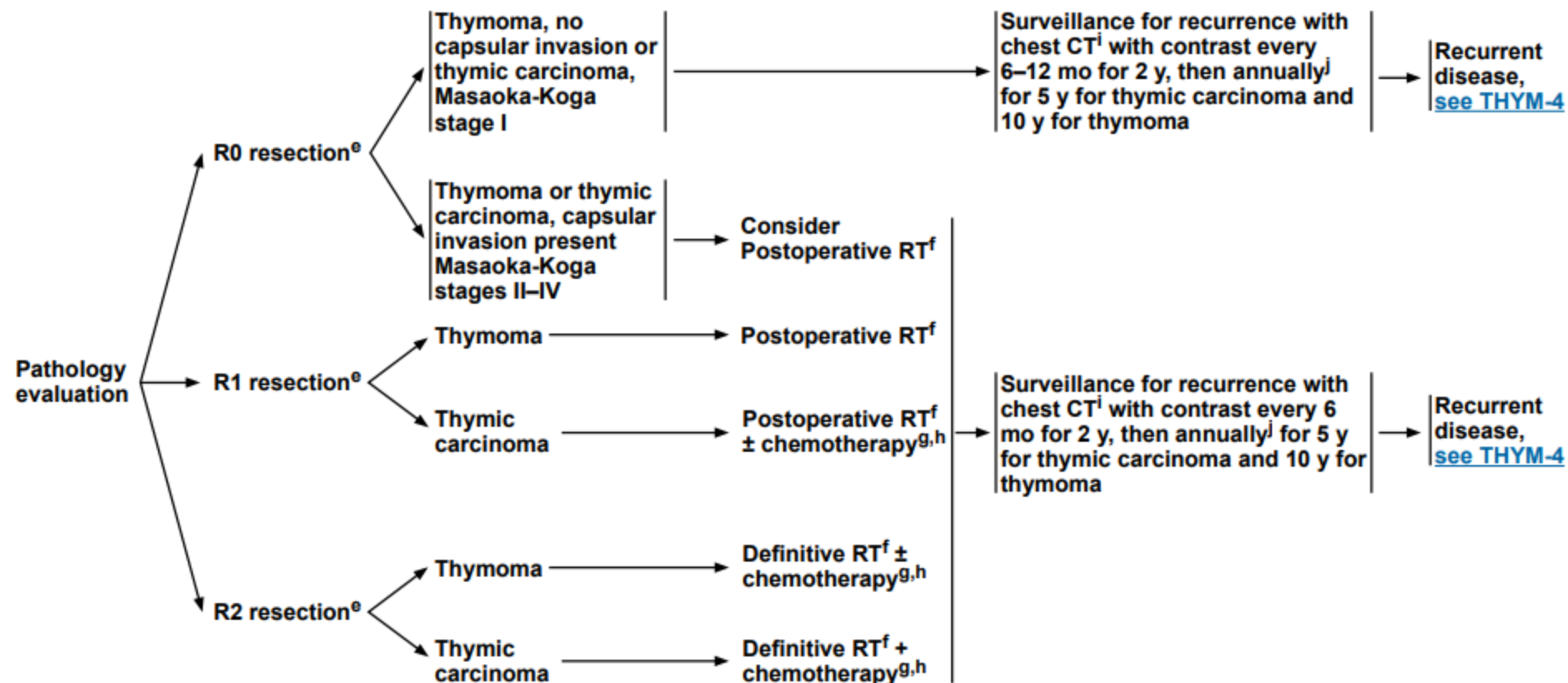
- When it comes to resectable tumors, surgical treatment is the method of choice. Complete resection is achieved in 60-75% and represents a positive prognostic factor. R1 resection leads to a poor outcome, even when adjuvant therapy is applied.
- Neoadjuvant HT can be used to improve resectability. HT is the main form of treatment for palliative purposes.
- Adjuvant radiotherapy is applied, and in stage II and III it has a significant effect on local control of the disease. After complete surgical resection in stage I, adjuvant radiotherapy is not indicated
- In case surgical treatment is not feasible definitive radiotherapy, with or without HT achieves satisfactory local control. RT can also be used as a "salvage" therapy.



NCCN Guidelines Version 2.2022 Thymomas and Thymic Carcinomas

POSTOPERATIVE TREATMENT

POSTOPERATIVE MANAGEMENT

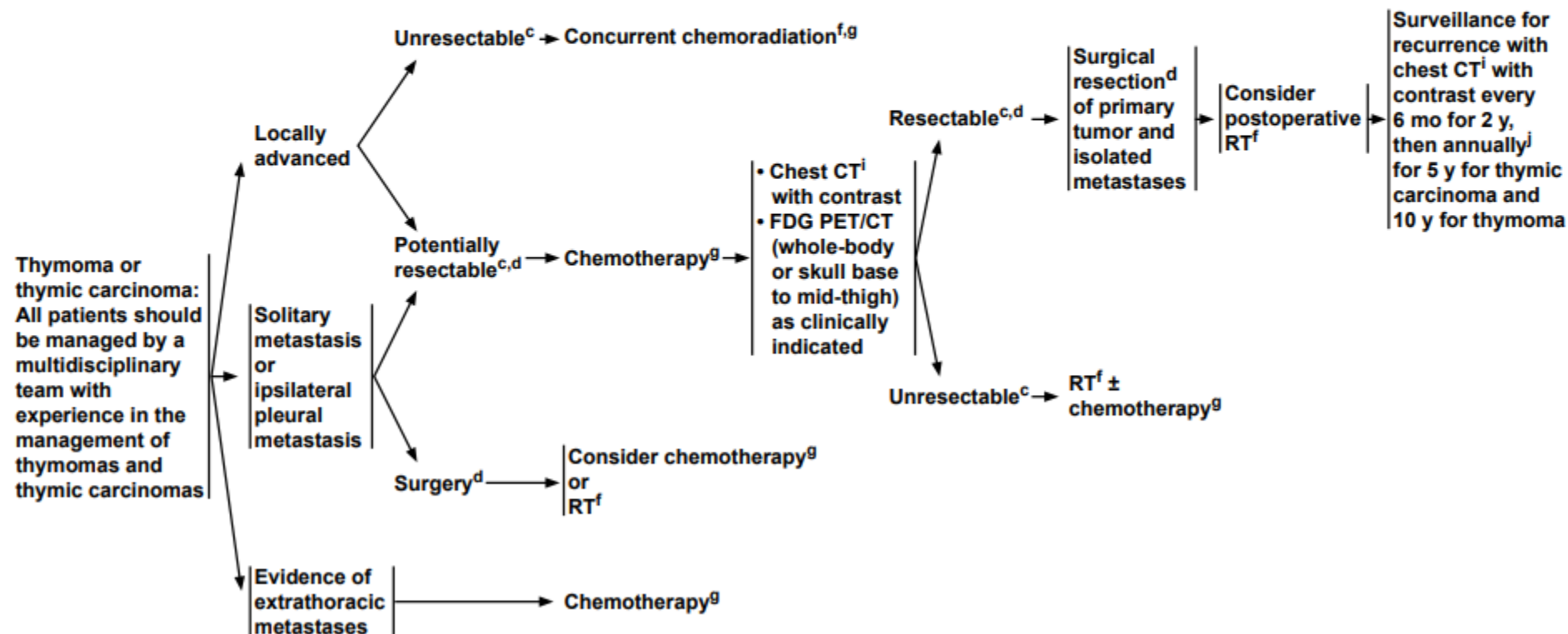




NCCN Guidelines Version 2.2022 Thymomas and Thymic Carcinomas

LOCALLY ADVANCED, ADVANCED, OR RECURRENT DISEASE

TREATMENT





PRINCIPLES OF RADIATION THERAPY^{1,2}

General Principles

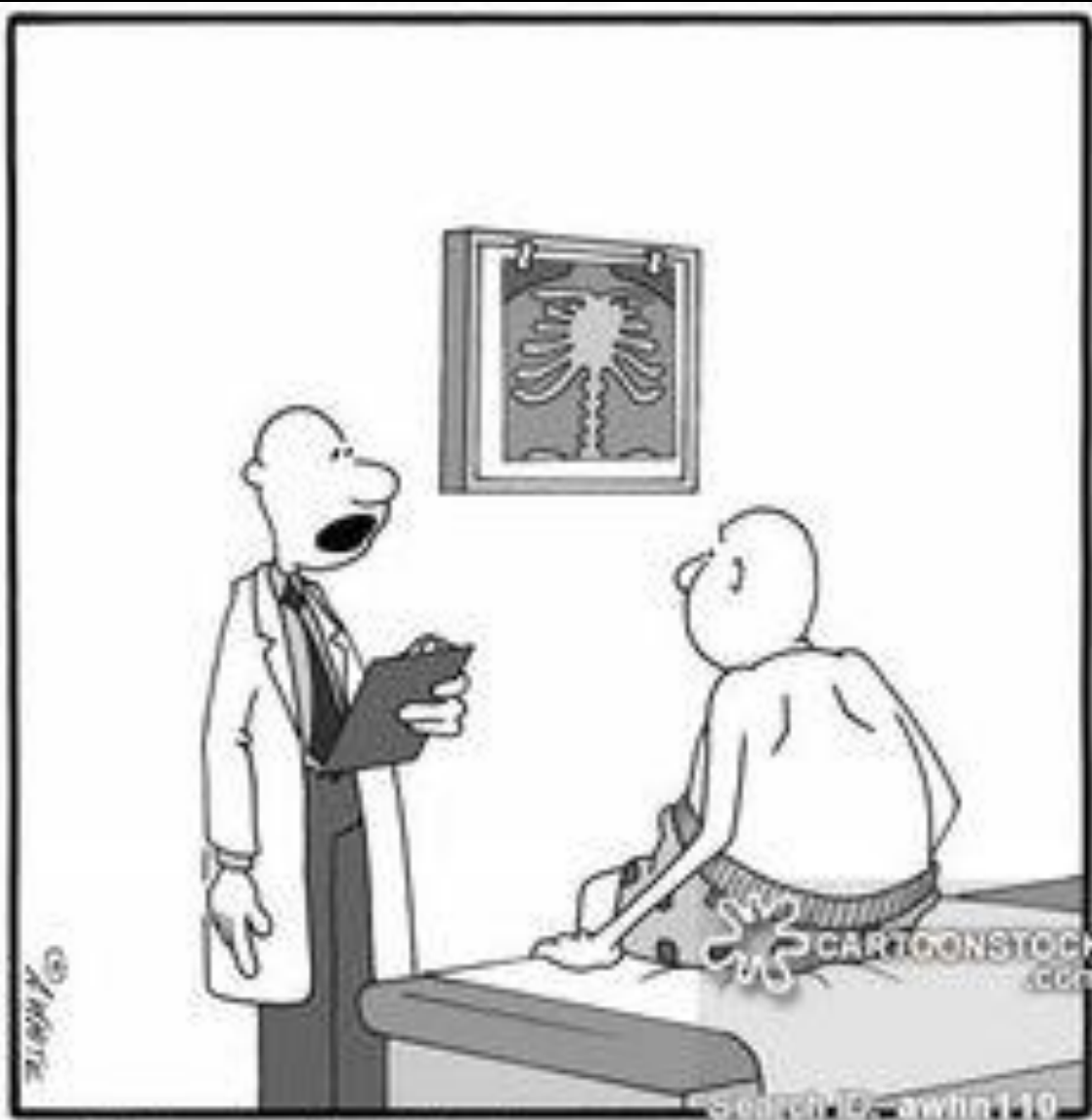
- Recommendations regarding RT should be made by radiation oncologists with experience in managing thymomas and thymic carcinomas.
- Definitive RT should be given for patients with unresectable disease (if disease progresses on induction chemotherapy), incompletely resected invasive thymoma or thymic carcinoma, or as adjuvant therapy after chemotherapy and surgery for patients with locally advanced disease.
- Radiation oncologists need to communicate with the surgeon to review the operative findings and to help determine the target volume at risk. They also need to communicate with the pathologist regarding the detailed pathology on histology, disease extent such as extracapsular extension, and surgical margins.
- The review of preoperative imaging and co-registration of preoperative imaging into the planning system are helpful in defining treatment volumes.
- Acronyms and abbreviations for RT are the same as listed in the Principles of Radiation Therapy for the [NCCN Guidelines for Non-Small Cell Lung Cancer](#).

Radiation Dose

- The dose and fractionation schemes of RT depend on the indication of the radiation and the completeness of surgical resection in postoperative cases.
- A dose of 60 to 70 Gy should be given to patients with unresectable disease.
- For adjuvant treatment, the radiation dose consists of 45 to 50 Gy for clear/close margins and 54 Gy for microscopically positive resection margins. A total dose of 60–70 Gy should be given to patients with gross residual disease (similar to patients with unresectable disease),^{3,4} when conventional fractionation (1.8–2.0 Gy per daily fraction) is applied.
- Depending on the treatment objectives in the palliative setting, typical palliative doses (eg, 8 Gy in a single fraction, 20 Gy in 5 fractions, 30 Gy in 10 fractions) up to definitive doses for more durable local control and highly conformal techniques for limited volume metastases may be appropriate, given the relatively long natural history of even metastatic thymoma.

Radiation Volume

- The gross tumor volume should include any grossly visible tumor. Surgical clips indicative of gross residual tumor should be included for postoperative adjuvant RT.
- The clinical target volume (CTV) for postoperative RT should encompass the entire thymus (for partial resection cases), surgical clips, and any potential sites with residual disease. The CTV should be reviewed with the thoracic surgeon.
- Extensive elective nodal irradiation (ENI) (entire mediastinum and bilateral supraclavicular nodal regions) is not recommended, as thymomas do not commonly metastasize to regional lymph nodes.⁵
- The planning target volume (PTV) should consider the target motion and daily setup error. The PTV margin should be based on the individual patient's motion, simulation techniques used (with and without inclusion motion), and reproducibility of daily setup of each clinic.



**"Those 'light' cigarettes have given
you 'light' cancer."**

FOR MORE INFORMATION ON
LUNG CANCER...KEEP SMOKING!

