Chapter 15
Non-small Cell Lung Cancer

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IV

PEARLS

- #1 non-cutaneous cancer in the world.
- #2 most common cancer in the United States, behind prostate in men and breast in women.
- #1 cause of cancer death in the United States and worldwide.
- >90% of cases are associated with active or passive smoking. Second most common cause in the United States is radon. Asbestos exposure is associated with 3–4% of cases.
- Screening with low-dose CT is standard of care for strong smoking history.
- After initial cancer, risk of tobacco-induced second primary is ~2–3% per year.
- Surgical lymph node levels 1–9 correspond to N2 nodes, and levels 10–14 correspond to N1 nodes. International Association for the Study of Lung Cancer lymph node definition contouring atlas has been published (Lynch, PRO 2013) (Fig. 15.1).

Eric K. Hansen and M. Roach III (eds.), *Handbook of Evidence-Based Radiation Oncology*, https://doi.org/10.1007/978-3-319-62642-0_15

- Pathology
  - Adenocarcinoma comprises 40–50% of cases. It tends to be peripherally located; squamous cell carcinoma tends to be centrally located.
  - TTF-1 is positive only in adenocarcinomas of primary lung and thyroid origin (not metastases); napsin is differentiating as it is positive in 80% of lung and only 10% of thyroid adenocarcinomas.
  - Large cell carcinoma behaves similarly to small cell lung cancer, with high propensity to metastasize, especially to brain.
  - Adenocarcinoma in situ (AIS) or minimally invasive adenocarcinoma (MIS), formerly referred to as bronchoalveolar carcinoma, is a subtype of adenocarcinoma with weak association with smoking. Frequently harbor EGFR or ALK mutations (sensitive to gefitinib, erlotinib, crizotinib, etc.).
- Pancoast tumor = apical (superior sulcus) tumor + either chest wall (rib) invasion or Pancoast syndrome [shoulder pain or brachial plexus palsy, ±Horner's syndrome (ptosis, meiosis, and ipsilateral anhidrosis)].
- Carcinoid tumors are rare. Tend to be endobronchial. Most common site is GI tract, but 25% in lung. 70–90% are typical carcinoids, which rarely metastasize and are not associated with smoking. 10–30% are atypical carcinoids, which more frequently metastasize and are associated with smoking, and have poorer prognosis. Only 10–15% of patients with carcinoid tumors present with carcinoid syndrome (flushing, diarrhea, and wheezing), but up to 2/3 eventually develop symptoms.
- Presentation: stage I 10%, II 20%, III 30%, IV 40%.
- Prognostic factors: stage, weight loss (>10% body weight over 6 months), KPS, pleural effusion.
  - RTOG RPA analysis (Werner-Wasik IJROBP 2000): KPS <90, use of chemo, age > 70 years, pleural effusion, N stage. Worst survival in patients with malignant pleural effusion (5 months).
  - For N2, single station disease has more favorable outcomes than multi-station (5-year OS 34% vs 11%, Andre JCO 2000).

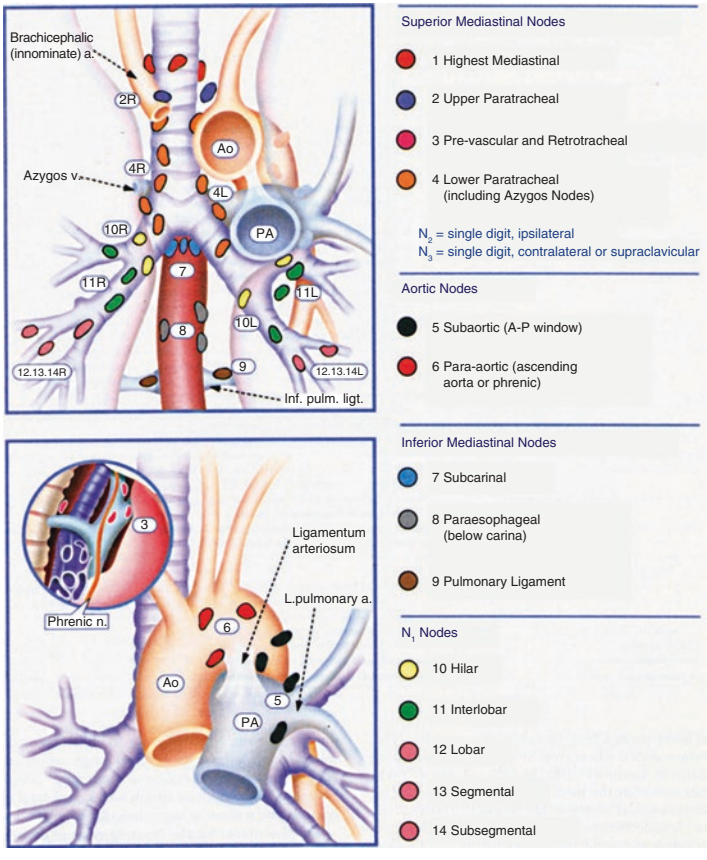

Fig. 15.1 Pulmonary and mediastinal lymph node atlas (From Rusch et al. (2009). Reprinted with permission from Elsevier)

WORKUP

- H&P, including performance status, weight loss, and smoking status.
- Cough, dyspnea, hemoptysis, postobstructive pneumonia, pleural effusion, pain, hoarseness (left recurrent

laryngeal nerve), SVC syndrome, clubbing, Pancoast syndrome.
- Labs: CBC, BUN, Cr, LFTs, alkaline phosphatase, LDH.
- Imaging:
  - CT chest and abdomen (to rule out adrenal or liver metastasis).
    - Mediastinal LN sensitivity ~60%, specificity ~80% (Gould 2003).
    - Approximately 10–20% false negative rate for CT depending on T stage and size.
  - PET/CT: Mediastinal LN sensitivity 77%, specificity 90% (Schmidt-Hansen 2014).
  - Brain MRI for stage II–IV, or for neurologic symptoms.
  - MRI of the thoracic inlet for superior sulcus tumors to assess vertebral body and/or brachial plexus invasion.
  - Octreotide scan for carcinoid tumor.
- Pathology: Thoracentesis for pleural effusions. For central lesions, bronchoscopy because sputum cytology has ~65–80% sensitivity. For peripheral lesions, CT-guided biopsy. Endobronchial ultrasound (EBUS)-guided biopsy to reach peripheral lesions less invasively. Thoracoscopic (surgical) biopsy can be diagnostic and therapeutic.
  - Molecular testing for Kras activation, EGFR mutation, ROS/ALK rearrangements.
- Many prescribe SBRT without pathologic confirmation for FDG-avid nodules that are new or growing (<6% false positive rate).
- Pathologic mediastinal staging recommended for all patients per NCCN, but not universally performed for cN0 patients. Mediastinoscopy or bronchoscopic biopsy to confirm any CT+ or PET+ nodes, and for all superior sulcus tumors. If T3 or central T1–2, perform mediastinoscopy to evaluate superior mediastinal nodes.
  - Cervical mediastinoscopy assesses nodal levels 1–4R.
  - Anterior (Chamberlain) mediastinoscopy assesses levels 4 L (left lower paratracheal), 5, 6, and 7.
  - Endobronchial Ultrasound (EBUS): Levels 2, 3, 4, 7, 10.
  - Esophageal Ultrasound (EUS): Levels 4 L, 7, 8, 9.
- Pulmonary function testing for presurgical and/or preradiotherapy evaluation:

- Desire FEV1 ≥ 1.2–2 L (if pneumonectomy >2.5 L, if lobectomy >1.2 L) or >75% predicted or predicted post-op FEV1 > 0.8 L; also DLCO >60%.
- Medically inoperable is generally FEV1 < 40% or <1.2 L, DLCO <60%, FVC <70% but less restrictive if wedge/segmentectomy is planned.

- Paraneoplastic syndromes.
  - Hypercalcemia (SqCC).
  - Hypertrophic pulmonary osteoarthropathy (adenocarcinoma).
  - Hypercoagulable (adenocarcinoma).
  - Gynecomastia (large cell).
  - VIP-induced diarrhea (carcinoid).

STAGING: NON-SMALL CELL LUNG CANCER

Editors' note: All TNM stage and stage groups referred to elsewhere in this chapter reflect the 2010 AJCC staging nomenclature unless otherwise noted.

STAGING (AJCC 7TH ED., 2010)

Primary tumor (T)

TX:	Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings, but not visualized by imaging or bronchoscopy
T0:	No evidence of primary tumor
Tis:	Carcinoma in situ
T1:	Tumor 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion, more proximal than the lobar bronchus (i.e., not in the main bronchus)*
T1a:	Tumor 2 cm or less in greatest dimension
T1b:	Tumor more than 2 cm but 3 cm or less in greatest dimension
T2:	Tumor more than 3 cm but 7 cm or less or tumor with any of the following features (T2 tumors with these features are classified T2a if 5 cm or less); involves main bronchus, 2 cm or more distal to the carina; invades visceral pleura (pl1 or pl2); associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung

continued

T2a: Tumor more than 3 cm but 5 cm or less in greatest dimension

T2b: Tumor more than 5 cm but 7 cm or less in greatest dimension

T3: Tumor more than 7 cm or one that directly invades any of the following: parietal pleural (PL3) chest wall (including superior sulcus tumors), diaphragm, phrenic nerve, mediastinal pleura, and parietal pericardium; or tumor in the main bronchus (less than 2 cm distal to the carina*) but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung or separate tumor nodule(s) in the same lobe

T4: Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, separate tumor nodule(s) in a different ipsilateral lobe

*The uncommon superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximally to the main bronchus, is also classified as T1a

Regional lymph nodes (N)

NX: Regional lymph nodes cannot be assessed

N0: No regional lymph node metastases

N1: Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension

N2: Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)

N3: Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

Distant metastasis (M)

M0: No distant metastasis

M1: Distant metastasis

M1a: Separate tumor nodule(s) in a contralateral lobe tumor with pleural nodules or malignant pleural (or pericardial) effusion

M1b: Distant metastasis

Anatomic stage/prognostic groups

Occult carcinoma: TX N0 M0

0: Tis N0 M0

IA: T1a N0 M0

T1b N0 M0

IB: T2a N0 M0

IIA: T2b N0 M0

T1a N1 M0

T1b N1 M0

T2a N1 M0

IIB: T2b N1 M0

T3 N0 M0

IIIA: T1a N2 M0

T1b N2 M0

T2a N2 M0

T2b N2 M0

T3 N1 M0

T3 N2 M0

T4 N0 M0

T4 N1 M0

IIIB:	T1a N3 M0
	T1b N3 M0
	T2a N3 M0
	T2b N3 M0
	T3 N3 M0
	T4 N2 M0
	T4 N3 M0
IV:	Any T Any N M1a
	Any T Any N M1b

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~5-year survival	~Median survival
IA:50–70%	IA:5–10 years
IB:40–60%	IB:3–7 years
IIA:34–55%	IIA:3–4 years
IIB:20–40%	IIB:1.5–3 years
IIIA:10–25%	IIIA:14–23 months
IIIB:7–9%	IIIB:10–16 months
IV:2–13%	IV:6–18 months (best supportive care 3–6 months; better with chemo; even better with targetable mutations)
Superior sulcus: 3 years 50%	

*Range represents clinical vs pathologic staging

STAGING (AJCC 8TH ED., 2017)

Definitions of AJCC TNM

Definition of primary tumor (T)

T category	T criteria
TX	Primary tumor that cannot be assessed or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0	No evidence of primary tumor
Tis	Carcinoma in situ Squamous cell carcinoma in situ (SCIS) Adenocarcinoma in situ (AIS): adenocarcinoma with pure lepidic pattern, ≤3 cm in the greatest dimension
T1	Tumor ≤3 cm in the greatest dimension, surrounded by the lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)
T1mi	Minimally invasive adenocarcinoma: adenocarcinoma (<3 cm in the greatest dimension) with a predominantly lepidic pattern and ≤5 mm invasion in the greatest dimension

continued

T1a	Tumor ≤1 cm in the greatest dimension. A superficial, spreading tumor of any size whose invasive component is limited to the bronchial wall and may also extend proximal to the main bronchus is classified as T1a, but this tumor is uncommon
T1b	Tumor >1 cm but ≤2 cm in the greatest dimension
T1	Tumor >2 cm but ≤3 cm in the greatest dimension
T2	Tumor >3 cm but ≤5 cm or having any of the following features: Involves the main bronchus regardless of the distance to the carina but without involvement of the carina Invades the visceral pleura (PL1 or PL2) Associated with atelectasis or obstructive pneumonitis that extends to the hilar region, involving part or all of the lung T2 tumors with these features are classified as T2a if ≤4 cm or if the size cannot be determined and T2b if >4 cm but ≤5 cm
T2a	Tumor >3 cm but ≤4 cm in the greatest dimension
T2b	Tumor >4 cm but ≤5 cm in the greatest dimension
T3	Tumor >5 cm but ≤7 cm in the greatest dimension or directly invading any of the following—parietal pleura (PL3), chest wall (including superior sulcus tumors), phrenic nerve, and parietal pericardium—or separate tumor nodule(s) in the same lobe as the primary
T4	Tumor >7 cm or tumor of any size invading one or more of the following—diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, or carina—separate tumor nodule(s) in an ipsilateral lobe different from that of the primary

DEFINITION OF REGIONAL LYMPH NODE (N)

N category	**N criteria**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

DEFINITION OF DISTANT METASTASIS (M)

M category	M criteria
M0	No distant metastasis
M1	Distant metastasis
M1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural or pericardial nodules or malignant pleural or pericardial effusion. 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 the fluid is nonbloody 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
M1b	Single extrathoracic metastasis in a single organ (including involvement of a single nonregional node)
M1c	Multiple extrathoracic métastases in a single organ or in multiple organs

AJCC PROGNOSTIC STAGE GROUPS

When T is...	And N is...	And M is...	Then the stage group is...
TX	N0	M0	Occult carcinoma
Tis	N0	M0	0
T1mi	N0	M0	IA1
T1a	N0	M0	IA1
T1a	N1	M0	IIB
T1a	N2	M0	IIIA
T1a	N3	M0	IIIB
T1b	N0	M0	IA2
T1b	N1	M0	IIB
T1b	N2	M0	IIIA
T1b	N3	M0	IIIB
T1c	N0	M0	IA3
T1c	N1	M0	IIB
T1c	N2	M0	IIIA
T1c	N3	M0	IIIB
T2a	N0	M0	IB
T2a	N1	M0	IIB
T2a	N2	M0	IIIA
T2a	N3	M0	IIIB
T2b	N0	M0	IIA
T2b	N1	M0	IIB
T2b	N2	M0	IIIA
T2b	N3	M0	IIIB
T3	N0	M0	IIB
T3	N1	M0	IIIA
T3	N2	M0	IIIB
T3	N3	M0	IIIC

continued

T4	N0	M0	IIIA
T4	N1	M0	IIIA
T4	N2	M0	IIIB
T4	N3	M0	IIIC
Any T	Any N	M1a	IVA
Any T	Any N	M1b	IVA
Any T	Any N	M1c	IVB

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TREATMENT RECOMMENDATIONS

Stage	Recommended treatment	Outcome
I–II operable	Lobectomy (~2–3% mortality) preferred over pneumonectomy (~5–7% mortality) if anatomically feasible Wedge resection only if physiologically compromised LN sampling or dissection generally indicated because ~15% of cT1–2N0 found to have +LN For resected T1–2N1, adjuvant chemo For resected T2N0, consider adjuvant chemo esp if >4 cm For resected T3N0, give adjuvant chemo For close/+ margin, re-resect or consider post-op RT	LRF: lobectomy 6%, wedge 18% 5-year OS stage I: 70–80%
I–II inoperable	T1-2N0: Definitive SBRT not 3D Consider adjuvant chemo for T2N0 > 4 cm T3N0: Definitive chemo-RT or hypofractionated RT or SBRT T1-2N1: Definitive chemo-RT to 60–66 Gy	SBRT: 2–3-year LC 85–95%, OS 55%
IIIA operable or marginally operable	If candidate for lobectomy and non-bulky N2 disease: Concurrent chemo-RT (45 Gy) → restage → if no progression → surgery → chemo Alternatively, chemo alone → restage → if no progression → surgery → chemo and post-op RT for +margin or N2 disease Otherwise, definitive concurrent chemo-RT (60–66 Gy)	5-year OS 20–25%, MS 16–17 months Induction chemo-RT pCR 15–30% and mediastinal clearance rate ~ 50% Induction chemo pCR 5–10% and mediastinal clearance rate ~ 30–35%
IIIA inoperable	Concurrent chemo-RT (60–66 Gy) If unacceptable risk of pneumonitis with upfront RT, may consider mid-course replanning or alternatively induction chemo for downstaging → concurrent chemo-RT (to postchemo volume) if no progression	~5-year OS and MS Concurrent chemo-RT: 20–25%, 16–17 mo Sequential chemo-RT: 20%, 13–15 mo RT alone: <10%, 10–12 mo

Stage	Recommended treatment	Outcome
IIIB	Concurrent chemo-RT (60–66 Gy) If unacceptable risk of pneumonitis with upfront RT, consider mid-course replanning or alternatively induction chemo for downstaging → concurrent chemo-RT (to postchemo volume) if no progression If T4N0-1, may treat with surgery → chemo ± RT (if +margin or N2), or chemo ± RT → surgery → chemo	
Typical chemo	*Postsurgery* Cisplatin 100 mg/m² d1 and etoposide 100 mg/m² d1–3 every 4 weeks × 4 cycles Other cisplatin combinations with vinorelbine, vinblastine, gemcitabine, pemetrexed, and docetaxel may be considered Alternative if not able to tolerate cisplatin: carboplatin, paclitaxel every 3 weeks for 4 cycles *Concurrent with RT* Cisplatin 50 mg/m² d1, 8, 29, and 36 and etoposide 50 mg/m² d1–5 and 29–33 Carboplatin AUC 2 and paclitaxel 45 mg/m2 weekly then after RT completion, carboplatin AUC 6 and paclitaxel 200 mg/m2 every 3 weeks × 2 cycles Alternatives: cisplatin week 1 and 4, vinblastine weekly; or carboplatin and paclitaxel weekly; or for nonsquamous, cisplatin and pemetrexed *Sequential chemo → RT* Cisplatin 100 mg/m² d1, 29 and vinblastine 5 mg/m² weekly × 5 weeks Alternative: carboplatin and paclitaxel every 3 weeks × 2 cycles *Consolidation chemo after chemo-RT* Carboplatin and paclitaxel every 3 weeks × 2 cycles	
IV	If EGFR mutation or ALK/ROS1 translocation detected, initial therapy with appropriate targeted agent. If PD-L1 tumor expression >50%, pembrolizumab Otherwise: ECOG PS 0–2: platinum-based chemo ± palliative RT ECOG PS 3–4: best supportive care Immune checkpoint inhibitors (anti-PD1, anti-PDL1) for disease progression after a platinum doublet Phase 3 data on combination regimens containing immunotherapy in 1st and subsequent lines are forthcoming	

continued

Stage	Recommended treatment	Outcome
Superior sulcus	If operable or marginally resectable, concurrent chemo-RT (45 Gy) → restage → if no progression → surgery → chemo If unresectable (initially or after restaging), complete definitive concurrent chemo-RT (60–66 Gy)	50% achieve pCR or minimal microscopic residual after initial chemo-RT. 5-year OS 45%. Most common site failure in brain (40%)
Pulmonary carcinoid	For stage I–III, surgery preferred (lobectomy or other anatomic resection +/– mediastinal LN dissection or sampling) Adjuvant RT considered for atypical histology, involved LN, +margin, subtotal resection No definite role for chemo since response rate is only 20–30%, but many institutions consider cisplatin/etoposide with RT For stage III, if surgery is not feasible, definitive RT (for typical) or chemo-RT (for atypical) For stage IV, systemic therapy is used. Octreotide considered if octreotide scan positive or symptoms of carcinoid syndrome	5-year OS: Resected typical carcinoid >70–90% Resected atypical carcinoid: 25–70% Metastatic carcinoid: 20–40%

STUDIES

SCREENING

- National Lung Screening Trial (Aberle NEJM 2011): 53,454 patients aged 55–74, current or former smokers with >30 pack-year history randomized to annual CXR vs low-dose CT × 3 years. CT-based screening reduced mortality from lung cancer and from any cause (20% and 6.7% relative improvement, respectively).

SURGERY

- For T1–2 N0, surgery has 80–90% LRC and 50–70% CSS. 25–35% percent pathologic upstaging from clinical stage.
- Video-assisted thoracoscopic surgery (VATS) + lymphadenectomy may have equivalent oncologic results as open thoracotomy in properly selected cases.
- LCSG 821 (Ginsberg, Ann Thorac Surg 1995): 247 patients with peripheral T1 N0 randomized to lobectomy vs wedge resection with a 2 cm margin of normal lung. Wedge resection tripled LRF (6 → 18%).

SBRT

- Indiana (Timmerman JCO 2006; Fakiris, IJROBP 2009): 70 patients with T1–3N0 (≤7 cm) treated with 60–66 Gy in 3 fx over 1–2 weeks. Three-year LC 88%, CSS 82%, OS 43%, regional failure 9%, and distant failure 13%. Patients with central tumors had increased risk of grade 3–5 toxicity (27% vs 10%). Established "no-fly-zone" of 2 cm surrounding proximal bronchial tree for 3-fraction treatment.
- Onishi (Cancer, 2004): 245 patients with T1–2N0 treated with 18–75 Gy in 1–22 fx. LF was 8% for BED ≥100 Gy vs 26% for BED <100 Gy. Three-year OS was 88% for BED ≥100 Gy vs 69% for BED <100 Gy.
- RTOG 0236 (Timmerman 2010): Phase II study of patients with T1–3N0 (≤5 cm) medically inoperable tumors >2 cm from proximal bronchial tree treated with SBRT 20 Gy × 3 over 1.5–2 weeks (54 Gy applying heterogeneity correction). GTV = CTV. PTV = 0.5 cm axial margin and 1 cm superior/inferior margin. 5-year LC 93%, LRC 62%, 31% DM, DFS 26%, OS 40%.
- RTOG 0915 (Videtic IJROBP 2015): Phase II randomized study of 34 Gy in 1 fraction vs 48 Gy in 4 fractions for medically inoperable T1-3N0 (≤5 cm) NSCLC. Single fraction arm had lower risk of serious adverse events (10.3 vs 13.3%). 2-year primary control, OS, and DFS were 97% vs 93%, 61% vs 77%, and 56% vs 71%, respectively.
- RTOG 0618 (Timmerman ASCO 2013): Patients with medically operable T1-T3N0 (≤5 cm) NSCLC >2 cm from proximal bronchial tree treated with 60 Gy in 3 fractions (54 Gy with heterogeneity correction). 2-year primary failure rate 7.8%, local failure (including ipsilateral lobe) 19.2%, OS 84%. 16% grade 3 toxicity.
- RTOG 0813 (Bezjak ASTRO 2016) Phase I/II dose escalation trial for medically inoperable early-stage NSCLC with centrally located lesions (<2 cm from the bronchial tree). Dose escalated from 50 Gy in 5 fractions to 60 Gy in 5 fractions. 38 pts 57.5 Gy, 33 pts 60 Gy. 2 yr LC 88–89%, PFS 52–55%, OS 70–73%, grade 3 toxicity 6–7%.
- VUMC (Senthi, Lancet Oncol 2012). 676 pts with PET+ clinical stage T1–2 N0 NSCLC. 65% no histology attained. 2/5-yr LF 5/11%, regional failure 8/13%, DM 15/20%. Earlier report from same institution (Verstegen, Radiother Oncol 2011) compared 209 pts with pathologic

confirmation vs 382 with clinical diagnosis only treated with SBRT and reported no difference in LC, regional control, DM, or OS, suggesting that SBRT results are unlikely to be biased substantially by inclusion of benign lesions.

SBRT VS SURGERY

- Two randomized trials of surgery vs SBRT for operable early-stage NSCLC failed to accrue (STARS and ROSEL).
- Combined ROSEL/STARS analysis (Chang Lancet Oncol 2015): 58 patients from two trials with T1-T2 (<4 cm) N0 medically operable NSCLC. Randomized to SBRT (54 Gy in 3 fractions, 50 Gy in 4 fractions if central) vs lobectomy and mediastinal lymph node dissection. 3-year OS improved for SBRT (95%) vs surgery (79%). Grade 3–4 toxicity 10% for SBRT vs 44% for surgery.
- New randomized trials: JoLT-Ca STABLE-MATES trial (NCT02468024), VALOR (Veterans Affairs Lung cancer surgery Or stereotactic Radiotherapy trial, NCT02984761) in the United States, SABRTOOTH (NCT02629458) in the United Kingdom.

PERIOPERATIVE CHEMOTHERAPY

- Multiple trials report that adjuvant chemotherapy after surgery improves survival for LN+ (stage II–III disease) and high-risk IB tumors >4 cm.
  - LACE (Pignon JCO 2008): Meta-analysis of 5 largest adjuvant chemotherapy trials (>4000 patients). 5.4% absolute overall survival benefit at 5 years with the addition of chemotherapy. Benefit most pronounced in stage II/III disease.
- Several trials also report that preoperative chemo is beneficial for stage II–III disease.
  - Meta-analysis (Song, J Thorac Oncol 2010) of 13 randomized trials reported that preoperative chemo improved survival vs surgery alone.
- Some studies suggest that preoperative chemo is as effective and better tolerated than adjuvant chemo, but a randomized trial for early-stage disease found no survival or quality of life difference (Westeel, Eur J Cancer 2013).

PRE-OP RT

- There is no improvement in survival with pre-op RT alone (without chemo) as noted in two collaborative studies from 1970s (VA and NCI).
- ASTRO guideline (Rodrigues, PRO 2015):
  - There is no level 1 evidence for pre-op chemo-RT (≥45 Gy) for operable pts, but it may be considered for pts with minimal N2 disease, treatable with lobectomy, with good PS, and no/minimal weight loss.
  - Pre-op chemo-RT is recommended for resectable superior sulcus tumors.
- German trial (Thomas, Lancet Oncol 2008): 524 patients with IIIA/IIIB (69% IIIB) treated with neoadjuvant cisplatin/etoposide × 3c, then randomized to pre-op hyperfractionated chemo-RT vs immediate surgery → post-op RT. Pre-op chemo-RT was 1.5 b.i.d./45 Gy with carboplatin/vindesine × 3c → surgery if possible → RT boost (1.5 b.i.d./24 Gy) if inoperable or R1/R2 resection. Post-op RT was 1.8/54 Gy or 1.8/68.4 Gy if inoperable or R1/R2 resection.
  - No difference in 5-year OS or PFS (16% vs 14%).
  - Pre-op chemo-RT increased complete resection rates (37% vs 32%), and in those with complete resection, increased mediastinal downstaging (46% vs 29%).
  - Pre-op chemo-RT increased G3-4 hematologic toxicity and esophagitis, and was associated with 14% treatment-related mortality in pts undergoing pneumonectomy.

POST-OP RT

- Historically, post-op RT (PORT) utilized large fields covering comprehensive nodal fields. Multiple older studies showed no survival benefit to PORT, and PORT meta-analysis (Lancet 1998, 2005) showed a survival detriment, leading to PORT falling out of favor. Analysis criticized because 25% of patients were N0, many pts were treated with Co-60, older studies used inadequate staging, and unpublished data were included.

- PORT is detrimental for pN0-1 pts with negative margins.
- Recent data suggest benefit of modern linear accelerator PORT for pN2 pts:
  - *SEER* (Lally JCO 2006): 7465 patients with stage II–III resected NSCLC, 48% received PORT. PORT used most often for patients <50 years, T3–4, larger T size, increased N stage. PORT improved 5-year OS for N2 patients (20 → 27%, HR 0.85), but reduced OS for N0 (41 → 31%, HR 1.2), and N1 (34 → 30%, HR 1.1) patients.
  - ANITA subgroup analysis (Douillard IJROBP 2008): Retrospective analysis of data from ANITA adjuvant chemotherapy trial. 232 of 840 patients on the trial received PORT. Median survival detriment to PORT seen in pN1 patients receiving chemo (94 → 47 months), but improved MS in pN1 not receiving chemo (26 → 50 months) and for pN2 regardless of chemo (24 → 47 months for if chemo, 12 → 13 months if no chemo). PORT reduced local/regional failure (first site) for both N1 and N2 patients.
  - National Cancer Database – N2 (Robinson JCO 2015): 4483 pts with pN2 disease, 48% underwent PORT, all received adjuvant chemo. PORT improved 5-year OS (35% → 39%) and remained prognostic of OS on multivariate analysis.
  - Patel (Lung Cancer 2014). Review of 3 prospective and 8 retrospective studies of 2728 N2 pts treated with linear accelerator PORT or not. PORT improved OS and locoregional recurrence free survival.
  - Lung ART (EORTC 22055–08053, ongoing): Randomizes patients with resected N2 disease to post-op conformal RT 54 Gy vs observation. Pre-op or post-op chemo allowed before RT, but not concurrent with RT.
- ASTRO guideline (Rodrigues, PRO 2015):
  - PORT (50–54 Gy) after R0 resection for pN2 pts should be delivered sequentially after adjuvant chemo.
  - PORT (54–60 Gy) may be considered after R1 resection or for extracapsular nodal extension, with either concurrent or sequential chemo.

- National Cancer Database – Positive Margins (Wang JCO 2015): 3395 pts with positive margins after surgery, 36% underwent PORT, all received adjuvant chemo. PORT improved 5-year OS (24% → 32%) and remained prognostic of OS on MVA.
  - PORT (at least 60 Gy) is indicated after R2 resection, with concurrent or sequential chemo.

ROLE OF SURGERY FOR N2 PTS

- The role of surgery for N2 disease is controversial, but this population is heterogeneous and there could be a benefit for selected pts [e.g., single station N2 nodes <3 cm, planned lobectomy (vs pneumonectomy), good PS, no/minimal weight loss, or other subsets].
- Intergroup/RTOG 0139 (Albain, Lancet 2009): 396 patients with T1–3pN2M0 treated with concurrent chemo × 2c + 45 Gy → restaging → randomized to [surgery (if no progression) → chemo × 2c] vs [concurrent chemo-RT to 61 Gy (no surgery)) → chemo × 2c]. Chemo was cisplatinum and etoposide. Surgery improved 5-year PFS (11% → 22%) and median PFS (10.5 → 12.8 months) with fewer local-only relapses (10% vs 22%). There was no significant difference in MS (23.6 vs 22.2 months, $p = 0.24$), although there was a 5-year OS trend in favor of surgery (20% vs 27%, $p = 0.1$). Increased treatment-related deaths with surgery (8% vs 2%), particularly when pneumonectomy required. 14% pCR rate, with 42% 5-year OS if pCR. In unplanned exploratory subgroup analysis, MS was improved for pts undergoing lobectomy compared to matched cohort undergoing non-operative treatment (MS 22 → 33 months).
- EORTC 08941 (Van Meerbeeck, JNCI 2007): 579 patients with initially unresectable pIIIA(N2) disease treated with induction cisplatin-based chemo. 332 patients (61%) showing response randomized to surgery or definitive RT. Post-op RT (56 Gy) given to 40% of pts with an incomplete resection. pCR was 5%, and 47% had pneumonectomy. 4% surgical mortality. Definitive RT was to tumor and involved mediastinum to 60–62 Gy with 46 Gy to uninvolved mediastinum. One RT patient died of RT pneumonitis. No difference in MS (16–17 months) or PFS

(9–11 months). Fewer local/regional failures (32% vs 55%), but more DM (61% vs 39%) with surgery. Patients with pneumonectomy, incomplete resection, or persistent pN2 disease fared worst.

- ESPATUE (Eberhardt JCO 2015): 246 patients with resectable IIIA(N2) or IIIB disease (70% IIIB) received induction chemo (cisplatin/paclitaxel x 3c) → chemo-RT (45 Gy/1.5 Gy BID with cisplatin/vinorelbine). Patients then randomized to surgery (2/3 received lobectomy) vs chemo-RT boost (20 Gy in 10 fractions with cisplatin/vinorelbine). Trial closed early due to non-accrual. No significant difference in 5-year PFS (32–35%) or OS (40–44%). 33% pCR rate in surgery arm.

DEFINITIVE RT AND CHEMO FOR LOCALLY ADVANCED NSCLC

- ASTRO has published a practice guideline for locally advanced NSCLC (Rodrigues PRO 2015).
- *RT alone*: MS 10–12 months, 5-year OS 7%.
  - RT alone is superior to observation or chemo alone at the cost of side effects (e.g., esophagitis, pneumonitis).
  - Consider for pts not eligible for chemo (e.g., poor PS, comorbidities, extensive weight loss, or pt preference).
  - Dose options: 60 Gy/30 fx, 45 Gy/15 fx (hypofractionation), 54 Gy/36 fx TID (CHART), 60 Gy/40 fx TID (CHARTWEL).
- *Sequential chemo → RT*: MS 13–15 months, 5-year OS 20%
  - For pts who cannot tolerate concurrent chemo-RT, sequential chemo-RT improves survival vs RT alone [e.g., CALGB 8433 (Dillman, NEJM 1990) and RTOG 8808 (Sause, Chest 2000)].
  - With sequential chemo and RT, optimal RT dose is unknown, although accelerated hyperfractionated RT (CHARTWEL 60 Gy/40 fx TID over 18 days) may improve LC vs standard RT (66 Gy/33 fx over 6.5 wks) at cost of toxicity.
- *Concurrent chemo-RT*: MS 16–17 months, 5-year OS 20–30%.
  - Multiple randomized studies report improved survival, local control, and response rate with concurrent over sequential treatment. For example:

- RTOG 9410 (Curran, JNCI 2011). 610 pts with unresectable or inoperable II/III (98% III) treated with sequential cisplatin/vinblastine then 63 Gy vs concurrent cisplatin/vinblastine +63 Gy QD vs concurrent cisplatin/etoposide +69.6 Gy / 1.2 Gy BID. Concurrent chemo-RT improved MS: 14.6 mo vs 17 mo vs 15.2 mo, respectively.
- Auperin (JCO 2010): Meta-analysis of 1205 patients from six trials undergoing sequential vs concurrent chemo-RT. Sequential treatment improved 5-year OS (15% vs 10%) and 5-year PFS (16% vs 13%) at the cost of increased esophageal toxicity (grade 3+ esophagitis 18% vs 4%). No difference in pulmonary toxicity.

- There is no proven role for induction chemo before chemo-RT, although it may be considered for bulky tumors to allow for RT planning after chemo response
  - CALGB 39801 (Vokes, JCO 2007): 366 patients with unresectable IIIA/IIIB randomized to concurrent weekly carbo-Taxol chemo + RT (66 Gy) vs induction carbo-Taxol q3 weeks × 2c → same concurrent chemo-RT. No difference in MS (12–14 months) or OS. Induction chemo increased toxicity (20% grade 3–4 neutropenia).
- There is no proven role for consolidation chemo after chemo-RT, but it is routinely given for potential micrometastatic disease if full systemic chemo doses were not delivered during RT.
- Dose escalation beyond 60 Gy with conventional fractionation has not demonstrated any clinical benefit with concurrent chemo.
  - RTOG 0617 (Bradley, Lancet Oncol 2015): 544 patients with inoperable IIIA/IIIB treated with concurrent chemo-RT carboplatin/Taxol underwent 2x2 randomization to 60 vs 74 Gy, and +/– weekly cetuximab. All patients received 2 cycles consolidation carboplatin/Taxol. Trial closed early due to interim analysis showing futility for survival endpoint. 74 Gy arm had decreased MS (20 mo vs 28 mo), nonsignificantly higher local failure (39% vs 31%), and worse grade 3+ esophagitis (43% vs 16%). Cetuximab did not improve OS but had increased toxicity. Reason for survival detriment hotly debated; possible explanations include

decreased tumor coverage in 74 Gy arm, low volume centers' lack of expertise (Eaton JNCI 2016), increased acute or late toxicity, decreased quality of life in 74 Gy arm. IMRT produced similar local control and 2-year survival but lower rates of severe pneumonitis and cardiac dose (Chun JCO 2017).

- RTOG 1106 (ongoing): Randomized phase III trial comparing standard concurrent chemo-RT to 60 Gy vs concurrent chemo with adaptive dose escalation to 66–80.4 Gy, with doses constrained by mean lung dose <20 Gy.

SUPERIOR SULCUS

- SWOG 9416/Int 0160 (Rusch 2001): phase II trial of 111 patients with T3–4N0–1 superior sulcus tumors treated with concurrent chemo-RT (45 Gy) → restaging → surgery (if no progression) → chemo × 2c. Chemo was platinum/etoposide. If progression on restaging, complete definitive chemo-RT to 63 Gy without surgery. 86% of patients had surgery. 56% had pCR or minimal microscopic residual disease. The most common site of relapse was in the brain.

PROPHYLACTIC CRANIAL RT (PCI)

- Brain is the site of failure for ~15% of early-stage patients and >15% for advanced stage patients. Three older randomized trials have investigated PCI in advanced NSCLC. PCI delayed and reduced the incidence of brain failure, but had no impact on OS. Extracranial disease was the cause of death for most patients, and may be a source of CNS re-seeding after PCI.
- RTOG 0214 (Gore JCO 2011): 356 patients with definitively treated stage IIIA/B disease randomized to prophylactic cranial RT (30 Gy/15 fractions) or observation. No difference in 1-year OS or DFS, but PCI reduced rate of brain metastasis at 1 year (8% vs 18%).

RADIATION TECHNIQUES

SIMULATION AND FIELD DESIGN

- Simulate patient supine with arms up.
- Immobilize with a wingboard, body cradle, or SBRT immobilization device (with arms up).
- 4DCT to account for respiratory motion.
- Use a 3D conformal or IMRT plan.
  - IMRT associated with decreased pneumonitis risk (Yom IJROBP 2007, Chun JCO 2017).
- Favor 6–10 MV photons over higher energies, which can cause underdosing in regions of electronic disequilibrium such as the tumor/lung interface.
- GTV: gross primary and nodal disease, including LN(s) ≥1 cm or hypermetabolic on PET scan or harboring tumor cells per mediastinoscopy.
- CTV: typically includes the GTV plus 5–10 mm margin.
  - Giraud (IJROBP 2000): 6–8 mm margin required to cover 95% of microscopic disease.
- PTV: add 5–10 mm margin to CTV depending on respiratory motion management.
- Respiratory tracking or gating systems or 4D CT planning to generate ITV may allow for decreased PTV margins.
- Comprehensive elective nodal RT generally not recommended due to low observed rates of failure in uninvolved nodes without elective treatment:
  - MSKCC (Rosenzweig JCO 2007): 524 patients with NSCLC treated with 3DCRT to only tumor and histologically or radiographically involved LN regions. No elective nodal RT. Only 6% of patients developed failure in an initially uninvolved LN region in the absence of local failure. Many patients experienced treatment failure in multiple LN regions simultaneously.
  - Yuan (AJCO 2007): 200 patients with inoperable stage III disease. Randomized to elective nodal RT to 60–64 Gy vs IFRT to 68–74%. IFRT improved 5-year local control (51% vs 36%) and decreased rate of pneumonitis (17% vs 29%).
  - At UCSF, we commonly treat involved nodal station + immediately adjacent nodal stations felt to be at highest risk for subclinical disease.

- Post-op RT:
  - If N2 and margins are negative:
    - CTV = Involved LN region ± paratracheal ± ipsilateral hilum ± subcarinal LN regions to 50.4 Gy depending on the extent of node dissection, number, bulk, and location of mediastinal disease and primary tumor; wide variations seen in Lung ART contouring study (Spoelstra IJROBP 2010).
  - If + margin: favor initial post-op chemo-RT or RT → adjuvant chemo. Limit field to area of +margin if N0–1 disease (i.e., no elective mediastinal nodal coverage).
  - If gross residual disease: recommend concurrent chemo-RT to 60–66 Gy.

DEFINITIVE RT DOSE PRESCRIPTIONS

- Stage I SBRT: Several dose/fractionation regimens have been published. At UCSF we typically give 50 Gy in 5 fractions for central/chest wall lesions, or 54 Gy in 3 fractions for peripheral lesions not abutting chest wall, with heterogeneity corrections. See NCCN guidelines for other 1–5 fraction SBRT schemes and dose constraints:
  - To account for or reduce internal motion, respiratory gating, active breath holding techniques, and/or abdominal compression may be used.
  - For planning, the GTV = CTV. ITV generated from 4DCT if real-time tumor tracking not performed. PTV = ITV + 5 mm.
  - Generally treat every other day, particularly if central lesion or abutting chest wall.
- Stage II–III
  - Primary and involved LN: 60–66 Gy at 1.8–2 Gy per fraction with chemo.
  - May consider treating up to 77.4 Gy without concurrent chemo (keep V20 ≤ 35%).
  - When chemo will not be tolerated, consider hypofractionated (e.g., 45 Gy at 3 Gy/fx) (Fig. 15.2).

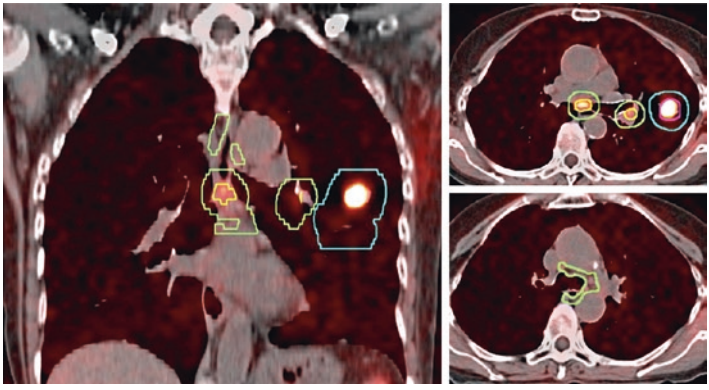

Fig. 15.2 Example contours for preoperative RT for patient with cT1N2 NSCLC with single subcarinal lymph node on PET. GTV shown in *pink* (primary) and *yellow* (nodal disease), with CTV in *blue* (primary) and *green* (nodal disease). CTVs encompass 7 mm margin on gross disease, with elective coverage of adjacent nodal regions (8: Paraesophageal, 4: Pretracheal). Prescriptions was 45 Gy in 25 fractions

NEOADJUVANT AND ADJUVANT RT DOSE PRESCRIPTIONS

- Preoperative: 45 Gy
- Postoperative:
  - If N2: 50.4 Gy
  - If ECE or +margin, boost to 54–60 Gy
  - If gross residual tumor, boost to 60–66 Gy (Fig. 15.3)

PALLIATIVE RT DOSE PRESCRIPTION

- ASTRO guideline (Rodrigues, PRO 2011): 30 Gy/10 fx or greater equivalent preferred over shorter courses (e.g., 20 Gy/5 fx, 17 Gy/2 weekly fx, 10 Gy/1 fx) for pts with good PS

DOSE LIMITATIONS

Standard Fractionation

- Spinal cord:
  - RT alone: maximum dose <50 Gy.
  - Chemo-RT: maximum dose <46 Gy at 1.8–2 Gy/fx QD or <36 Gy with bid RT.

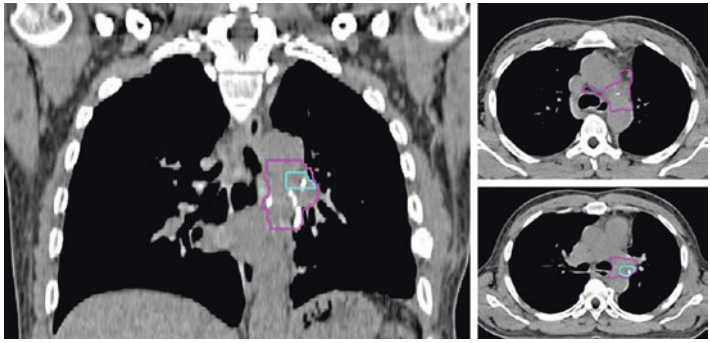

Fig. 15.3 Example contours for postoperative RT for patient with cT2aN1 NSCLC found to have single level 5 node at surgery (pT2aN2). Location of involved node shown in *blue*, with CTV shown in *purple* encompassing level 5 (AP window) and adjacent levels (4: Pretracheal, 6: Para-aortic). Prescription was 50 Gy in 25 fractions

- Lung:
  - Combined volume of both normal lungs receiving ≥20 Gy (V20): <35%.
  - Mean lung dose: <20 Gy.
  - Utility of V5 controversial, with data from RTOG 0617 suggesting a lack of prognostic value. V5 < 65% if used
  - Pneumonitis grading
    - Grade 1: asymptomatic radiographic changes.
    - Grade 2: changes requiring steroids or diuretics; dyspnea on exertion.
    - Grade 3: requires oxygen; shortness of breath at rest.
    - Grade 4: requires assisted ventilation.
    - Grade 5: death.
- Esophagus:
  - Maximum dose <105% of prescription dose
  - Mean < 34 Gy.
- Heart: V40 < 80%, V45 < 60%, V60 < 30%, Mean < 35 Gy.
- Pacemakers/internal cardiac defibrillators (ICD):
  - Increased risk of pacemaker malfunction at ~2 Gy, depending on manufacturer and model. Assess level of patient's dependence on device. Attempt to get RT tolerance specifications from manufacturer. Contour device and exclude it from radiation field. Determine actual dose with radiation dosimeter. If total dose >2 Gy, move out of field.

- Use energy <10 MV based on increased rates of malfunction with neutron-producing RT (Grant JAMA Oncol 2015).
- ICDs can be more sensitive to radiation than pacemakers. Consider deactivating ICD during RT and replace as needed with ECD (external cardiac defibrillator, temporary).
- Cardiology (electrophysiology) should evaluate and interrogate pacemaker/ICD before, weekly during RT, and immediately after RT.
- Have CPR equipment available. Monitoring of vital signs advisable during RT.
- Netherlands has published a guideline for pacemaker/ICD pts (Hurkmans, Radiation Oncology 2012)

- Brachial plexus: maximum dose <66 Gy.

SBRT

- See TG-101(Benedict Med Phys 2010) and NCCN guidelines for full constraints for 1, 3 and 5 fractions.
- Spinal cord: Dmax <18 Gy (3 fx) or <30 Gy (5 fx).
- Trachea/proximal bronchial tree: Dmax <30 Gy (3 fx) or <105% of PTV prescription (5 fx).
- Brachial Plexus: Dmax <24 Gy (3 fx) or <32 Gy (5 fx).
- Heart/pericardium: Dmax <30 Gy (3 fx) or <105% of PTV prescription (5 fx).
- Great vessels: <105% of PTV prescription (5 fx).
- Esophagus: <27 Gy (3 fx) or <105% of PTV prescription (5 fx).
- Rib: <30 Gy (3 fx).
- Skin: <24 Gy (3 fx) or 32 Gy (5 fx).

COMPLICATIONS

- Acute RT complications include fatigue, esophagitis, dermatitis, and/or cough.
- Subacute and late complications include pneumonitis, pericarditis, pulmonary fibrosis, bronchial or esophageal stricture, brachial plexopathy, rib fracture or intercostal nerve pain.
- Radiation pneumonitis occurs ~6 weeks after RT. It presents with cough, dyspnea, hypoxia, and fever. Treat symptomatic radiation pneumonitis with prednisone (1 mg/kg/d) or 60 mg/day and trimethoprim/sulfamethoxazole for PCP

prophylaxis. Often produces dramatic and quick response in symptoms, but very gradual and prolonged taper (>12 weeks) is critical for durable symptom resolution.

FOLLOW-UP

- H&P and chest CT every 3–6 months for 3 years, then annually.
- For patients after peripheral SBRT, low-dose non-contrast CT sufficient.
  - Solid mass-like component commonly seen 6–12 months after SBRT due to inflammation/scarring, easily confused for recurrence. Follow with short interval CT to assess for resolution.

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