Lung Cancer and Other Thoracic Malignancies

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Contents

Abstract

Lung cancer is the deadliest malignancy in the United States, and much research has been dedicated over the last many decades to improve patient outcomes. Smoking cessation education, lung cancer screening, improved diagnostic and functional imaging, improved surgical and radiation techniques, multimodality therapy, and targeted biologic and immunologic therapy have all lead to earlier detection of lung cancer and improved treatment resulting in improvements in overall survival. There are still many controversies that exist within each of these many aspects in the diagnosis and treatment of lung cancer. This chapter is dedicated to the controversies that exist in the management and treatment of all aspects of lung cancer with additional discussion of the controversies regarding thymoma and malignant pleural mesothelioma.

1 Lung Cancer

Lung cancer is the second most common malignancy and the leading cause of cancer death in the United States. Lung cancer is primarily related to cigarette and other types of tobacco smoking, though secondhand smoke exposure, radon, and environmental exposures also contribute to lung cancer incidence. Fortunately, the rates of new lung cancer diagnoses and lung cancer-related deaths are decreasing as smoking has become less prevalent (A Snapshot of Lung Cancer).

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Historically, early-stage lung cancer has been treated surgically and advanced disease with concurrent radiochemotherapy. In this section, the evolution and controversies of lung cancer treatment are discussed with the emphasis on those pertaining to radiotherapy.

1.1 Non-Small Cell Lung Cancer

Non-small cell lung cancer (NSCLC) comprises 85–90% of lung cancer with adenocarcinoma and squamous cell carcinoma being the most common. The majority (~55%) of patients have metastatic disease at diagnosis and the 5-year survival of all patients with newly diagnosed NSCLC is only 17% (SEER Cancer Statistics Factsheets: Lung and Bronchus Cancer). Due to the high incidence and poor survival, there has been significant interest in screening for lung cancer. The National Lung Screening Trial evaluated patients at high risk for lung cancer (age 55–74 and ≥30 pack-year smoking history) with annual low-dose computed tomography (CT). A 20% reduction in lung cancer mortality was demonstrated with low-dose CT screening (National Lung Screening Trial Research Team et al. 2011). With lung cancer screening, earlier-stage disease and potentially curable patients can be treated prior to development of metastases. In this section, the controversies regarding the management of NSCLC will be reviewed with an emphasis on the role of radiotherapy.

1.1.1 Early-Stage NSCLC

Surgery

Early-stage NSCLC will become an increasing portion of the radiation oncologist's patient population as more institutions establish lung cancer screening programs. Early-stage NSCLC is classically treated surgically with lobectomy with hilar and mediastinal lymph node dissection. Martini et al. reported surgical results with an approximately 95% locoregional control rate with 5- and 10-year overall survival of 75% and 67%, respectively (Martini et al. 1995). However, a lobectomy can result in inferior pulmonary function preservation, and many patients with poor cardiopulmonary function will not tolerate lobectomy. Sublobar resections with either segmentectomy or wedge resections can be considered for patients with suboptimal lung function. The Lung Cancer Study Group trial investigated lobectomy vs. sublobar resection for T1 N0 NSCLC and demonstrated an improved local recurrence rate with lobectomy (6%) compared with sublobar resection (17%; $p = 0.02$) (Ginsberg and Rubinstein 1995). Furthermore, the severity of the patient's comorbidities may preclude any surgical intervention including lung-sparing surgeries such as wedge resection.

External Beam Radiotherapy

Historically, medically inoperable early-stage NSCLC patients were offered definitive external beam radiotherapy (EBRT) as primary management, but studies showed poor rates of local control (Qiao et al. 2003; Dosoretz et al. 1992; Sibley et al. 1998; Zierhut et al. 2001). Qiao et al. reviewed 18 studies of stage I NSCLC treated with EBRT alone and showed a median local recurrence rate of 40% with 5-year overall survival rate of 21% (Qiao et al. 2003). Trends of improved local control and lower intrathoracic recurrence rates were reported with increasing radiation dose, providing a rationale for dose escalation (Qiao et al. 2003; Kaskowitz et al. 1993; Kupelian et al. 1996). Although studies using dose escalation with conventionally fractionated EBRT have shown improved outcomes, the results remained far inferior to surgical intervention (Chen et al. 2006; Kong et al. 2006).

Stereotactic Body Radiation Therapy

Stereotactic body radiation therapy (SBRT) is a technique which delivers very high doses of radiation per fraction over a few number of fractions to precisely defined volumes with steep dose gradients. Patient immobilization, setup reproducibility, image guidance, and tumor motion management are critical to ensure target coverage and normal tissue sparing. SBRT was first studied for the treatment of biopsy-proven early-stage NSCLC in medically inoperable patients. An increasing amount of evidence demonstrates the

feasibility, safety, and efficacy of SBRT in this patient population (Onishi et al. 2004; Nagata et al. 2005; Fakiris et al. 2009; Lagerwaard et al. 2012). Local control rates of 80–98% have been consistently reported (Onishi et al. 2004; Nagata et al. 2005; Fakiris et al. 2009; Lagerwaard et al. 2012; Uematsu et al. 2001; Baumann et al. 2009; Timmerman et al. 2010; Timmerman et al. 2014; Ricardi et al. 2010; Verstegen et al. 2011; Bral et al. 2011; Takeda et al. 2012). Yet heterogeneous dose schedules, total dose, and dose delivery methods in these institutional studies make it difficult to standardize SBRT.

In the early work from Indiana University, Timmerman et al. treated 70 patients with early-stage (T1–T2), inoperable NSCLC with 60 Gy in three fractions for T1 tumors and 66 Gy in three fractions for T2 tumors. Primary tumor control was 95% at 2 years. With a median follow-up of 17.5 months, grade 3–5 adverse events occurred in 14 out of the 70 patients (20%) with six treatment-related deaths. Central tumor location, defined as tumors within 2 cm of the proximal bronchial tree, was a significant factor related to adverse event occurrence; freedom from severe toxicity at 2 years was 83% for peripheral lung tumors compared to 54% for central lung tumors (Timmerman et al. 2006). With longer follow-up, the 3-year local control was 88.1%, and 3-year overall survival and cancer-specific survival were 42.7% and 81.7%, respectively. The rate of grade 3–5 toxicity remained significantly higher for central lesions (27%) compared to peripheral lesions (10%) (Fakiris et al. 2009). These results established that central tumors should be approached differently than peripheral tumors. Radiation Therapy Oncology Group (RTOG) 0236 study, the first major multi-institutional Phase II SBRT study, delivered SBRT (54 Gy in three fractions) to medically inoperable patients with biopsy-proven peripheral early-stage (<5 cm) NSCLC. For the 55 evaluable patients, 3- and 5-year local control rate was 97.6% and 93.0%, respectively, and 3- and 5-year overall survival was 55.8% and 40%, respectively. Grade 3 and 4 adverse events occurred in seven patients (12.7%) and two patients (3.6%) at 3 years and 15 patients (27.3%) and two patients (3.6%) at 5 years, respectively (Timmerman et al. 2010, 2014). Though these studies used a three-fraction SBRT schedule, there are many dose-fractionation regimens that have been reported with comparable outcomes as shown in Table 1.

Though numerous schedules may be used, one method of comparing different regimens is by calculating the biologic effective dose (BED) using the linear quadratic model. Onishi et al. published a multi-institutional retrospective series of 257 lung cancer patients treated with SBRT using several dosing schedules. Patients receiving a $BED_{(\alpha/\beta=10)}$ ≥100 Gy vs. <100 Gy endured fewer local recurrences (8.1% vs. 42.9%, $p < 0.001$) and experienced significantly improved 5-year overall survival (70.8% vs. 30.2%, $p < 0.05$) (Onishi et al. 2007). A population-based study showed that there was improved overall survival for a higher BED of >150 Gy for T2 tumors but no difference for T1 tumors (Koshy et al. 2015).

The results of the initial Indiana University study showed an unacceptable level of toxicity for patients treated with 60–66 Gy in three fractions (Timmerman et al. 2006). Controversy exists whether SBRT of any dose-fractionation schedules is safe for centrally located tumors. RTOG 0813 further investigated SBRT for central tumors with a Phase I/II dose-escalation/de-escalation study starting at 50 Gy in five fractions. The study successfully escalated doses to 60 Gy in five fractions with dose-limiting toxicity in 7.2% of patients among all dose levels (Bezjak et al. 2016). Centrally located lesions can safely be treated to doses of 48–60 Gy in 4–5 fractions or 60 Gy in eight fractions based on single-institution studies (Chang et al. 2008; Stephans et al. 2009; Haasbeek et al. 2011; Mangona et al. 2015; Bradley et al. 2015a). Dose-fractionation schedules and results of SBRT for centrally located tumors are shown in Table 2.

Some additional concerns for toxicity may influence fractionation schedules. Pneumonitis, pulmonary fibrosis, and obstructive pulmonary processes are the most commonly described toxicities. The symptomatic lung toxicity rate is reported as 9.2–20.3% (Barriger et al. 2012; Matsuo et al. 2012; Baker et al. 2013). Compared

Table 1 Dose-fractionation schedules and results of prospective SBRT trials

Author (year)	Type/stage	No. of patients	Dose	Median follow-up	Local control	Overall survival
Nagata et al. (2005)	Phase I–II/stage I NSCLC	45	12 Gy × 4	30 months	1-year LC: 100% 5-year LC: 98%	1-year OS: 80% 5-year OS: 70%
Fakiris et al. (2009)	Phase II/T1–2N0M0 NSCLC	70	20 Gy × 3 for T1 tumors (n = 34) 22 Gy × 3 for T2 tumors (n = 36)	50.2 months	3-year LC: 88.1%	3-year OS: 42.7%
Baumann et al. (2009)	Phase II/stage I NSCLC	57	15 Gy × 3 to 67% IDL	35 months	3-year LC: 92%	3-year OS: 60%
Timmerman et al. – RTOG 0236 (2010, 2014)	RTOG Phase II/ T1–2N0M0 NSCLC (peripherally located)	55	18 Gy × 3	34.4 months (2010) 48.0 months (2014)	3-year LC: 97.6% 5-year LC: 93.0%	3-year OS: 55.8% 5-year OS: 40.0%
Ricardi et al. (2010)	Phase II/stage I NSCLC	62	15 Gy × 3 to 80% IDL	28 months	3-year LC: 87.8%	3-year OS: 57.1%
Bral et al. (2011)	Phase II/T1–3N0M0	40	20 Gy × 3 (peripheral) 15 Gy × 4 (central)	16 months	2-year LPFS: 84%	2-year OS: 52%
Timmerman et al. – RTOG 0618 (2013)	Phase II/T1–3N0M0 (operable)	26	18 Gy × 3	25 months	2-year LC: 92.3%	2-year OS: 84.4%
Videtic et al. – RTOG 0915 (2015)	Phase II/T1–2N0M0	84	34 Gy × 1 (n = 39) vs. 12 Gy × 4 (n = 45)	30.2 months	1-year LC: 97.0% vs. 92.7%	2-year OS: 61.3% vs. 77.7%
Chang & Senan et al. – STARS/ROSEL (2015)	Phase III/T1–2aN0M0	31	18 Gy × 3 (peripheral) 12.5 Gy × 4 (central) 12 Gy × 5 (n = 5)	40.2 months	3-year LC: 96%	3-year OS: 95%
Nagata et al. (2015)	Phase II/T1N0M0	100 inoperable 64 operable	12 Gy × 4	47 months (inoperable) 67 months (operable)	Inoperable: 3-year LC: 87.3% Operable: 3-year LC: 85.4%	Inoperable: 3-year OS: 59.9% Operable: 3-year OS: 76.5%

Table 2 Dose-fractionation schedules and results of SBRT studies for centrally located tumors

Author (year)	Type/stage	No. of patients	Dose	Median follow-up	Local control	Overall survival	Acute toxicity	Late toxicity
Chang et al. (2008)	Retrospective/T1–2N0M0 or isolated lung recurrence	27	10 Gy × 4 (n = 7) 12.5 Gy × 4 (n = 20)	17 months	LC: 100% at 17 months for 50 Gy group; 57.1% for 40 Gy group	Not reported		Grade 2 pneumonitis: 14.8% (all recurrent disease) Grade 2–3 dermatitis and chest wall pain: 11.1%
Haasbeek et al. (2011)	Retrospective/T1–3N0M0	63	7.5 Gy × 8	35 months	3-year LC: 92.6%	3-year OS: 64.3%	Grade 2 dyspnea: 3.2% Grade 2–3 chest wall pain: 3.2%	Grade 2–3 dyspnea: 6.3% Grade 2–3 chest wall pain: 4.8%
Mangona et al. (2015)	Retrospective/T1–2N0M0 or isolated local recurrence or stage IV/non-lung primary	79	12 Gy × 4 (n = 45) 12 Gy × 5 (n = 30) 10 Gy × 5 (n = 3) 11 Gy × 5 (n = 1)	17.3 months	2-year LC: 91.4%	2-year OS: 71.7%	Grade 2 radiation dermatitis: 3.4% Grade 2 fatigue: 2.5%	Grade 2 chest wall pain: 6.9% Grade 2 myositis: 3.4% Grade 2 rib fracture: 5.2% Grade 2 soft tissue fibrosis: 3.4% Grade 2–3 fatigue: 6.9% Pneumonitis: 0%
Bradley et al. (2015a)	Prospective phase II/early stage	41	11 Gy × 5	11.9 months	1-year LC: 95.4%	1-year OS: 81.2%	Grade 3 hypoxia: 2.4%	Grade 3: 3/41 Grade 4 lung atelectasis and dyspnea: 4.9% Grade 5 fatal hemoptysis: 2.4%
Bezjak et al. (2016)	Phase I/T1–2N0M0	89	10 Gy × 5– 12 Gy × 5	26.6 months	Not reported	Not reported		Grade 3–4 bradycardia, hypoxia, or pneumonitis: 12.4% Grade 5: 4.5%

to the early three-fraction regimens, more protracted courses of SBRT appear to have similar rates of lung toxicity for central and peripheral lesions (Haasbeek et al. 2011; Mangona et al. 2015). As mentioned, doses such as 50–55 Gy in five fractions are most commonly delivered for central lesions (Daly et al. 2013). Lesions that are proximate to the esophagus can lead to rare high-grade esophageal toxicity (Stephans et al. 2014; Stang et al. 2015). With a three-fraction SBRT regimen, patients with apical lung tumors had a grade 2–4 brachial plexopathy rate of up to 20%. Those patients with maximum dose to the brachial plexus ≥26 Gy experienced a significantly greater rate of brachial plexopathy (Forquer et al. 2009). Higher doses to the chest wall and adjacent rib for peripheral tumors have also resulted in increased rates of chest wall pain and rib fracture (Dunlap et al. 2010). A scenario where the tumor abuts an organ at risk, even the chest wall, warrants consideration for a more prolonged, often 5–8 fraction, course of SBRT.

Peripheral tumors have also been treated with a variety of dose-fractionation schedules. RTOG 0915 is a randomized Phase II trial which compared two dose schedules for small peripheral lung tumors – 34 Gy in one fraction vs. 48 Gy in four fractions (Videtic et al. 2015). RTOG 0915 showed that adverse events were no different for 34 Gy in one fraction vs. 48 Gy in four fractions (10.3% vs. 13.3%, respectively). Primary tumor control at 1 year was also comparable at 97.0% and 92.7%, respectively. A three-fraction SBRT regimen of 54–60 Gy is still the most commonly used dose-fractionation schedule for peripheral early-stage NSCLC though (Daly et al. 2013).

As data have matured, SBRT has gained a reputation for being a safe, nonsurgical option for early-stage lung cancer. Even medically operable patients may prefer or may be advised by their physicians to consider a nonsurgical option with SBRT. RTOG 0618 was a study of SBRT for medically operable patients with early-stage NSCLC. They showed 2-year local control of the primary tumor of 92.3%, 2-year overall survival of 65.4%, and grade ≥3 adverse event rate of 16% (Timmerman et al. 2013). Additionally, Nagata et al. reported on their population of medically operable patients with 3-year local control of 85.4%, 3-year overall survival of 76.5%, and grade 3 toxicity rate of 7.8% (Nagata et al. 2015).

Several analyses of SBRT and various forms of surgical resection have been performed. Grills et al. showed that SBRT had superior local control when compared to wedge resection though operable patients had improved overall survival with no difference in cause-specific survival. SBRT patients had greater comorbidities than the operable patients as expected (Grills et al. 2010). Hamaji et al. reported a retrospective matched pair analysis comparing video-assisted thoracoscopic surgical (VATS) lobectomy to SBRT. They reported that all survival and local control endpoints were improved with VATS lobectomy though this study was small and the SBRT dose was low (48 Gy in four fractions prescribed to the isocenter) (Hamaji et al. 2015). A meta-analysis compared surgery and SBRT studies for stage I NSCLC and found no difference in survival when adjusted for operability and age (Zheng et al. 2014).

The aforementioned prospective and comparative studies led to great interest in comparing SBRT to surgery in Phase III, randomized trials. Three randomized trials of surgery vs. SBRT have been initiated but failed to accrue. Chang and Senan et al. reported the combined results of two similarly designed studies (STARS/ROSEL). These studies randomized patients with stage I NSCLC to SBRT or lobectomy with lymph node dissection. With total accrual (from both studies) of 58 patients, local control was no different between arms, but SBRT had improved 3-year overall survival of 95% vs. 79% compared to lobectomy ($p = 0.04$) (Chang et al. 2015). There were only seven total deaths in this population though, so drawing conclusions on survival, given the combined analysis of two trials that failed to accrue, should be done with caution. Additional randomized studies are under way which will hopefully fully accrue and provide more conclusive data on this debate between surgery and SBRT for operable early-stage NSCLC patients (Moghanaki and Chang 2016).

The aforementioned major studies required histologically proven NSCLC. A subset of

patients present with clinical and radiographic evidence highly suspicious for malignancy, but pathological diagnosis cannot be obtained. The reasons for lack of tissue diagnosis may include comorbid conditions making biopsy too risky, tumor location that is not amenable to biopsy, patient refusal, biopsy was attempted but was nondiagnostic, or a biopsy-related complication occurred. In the absence of pathological diagnosis, clinical history, serial computed tomography (CT) scans, and 18-fluorodeoxyglucose positron emission tomography (18-FDG-PET) scans are capable of identifying lesions with high probability of malignancy. A meta-analysis on the accuracy of FDG-PET for detecting malignancy in solitary pulmonary lesions reported a mean sensitivity of 93.9% and mean specificity of 85.8% (Gould et al. 2001). In regions with endemic infectious granulomatous disease, PET retains its high sensitivity (92%) and positive predictive value (86%) with lower specificity (40%) (Deppen et al. 2011). Imaging findings on CT such as spiculation, ragged borders, pleural retraction, and nodule size (>1.5 cm) can be highly suggestive of malignancy. Harders et al. demonstrated the diagnosis of malignancy (vs. benignity) was five times more likely for nodules with spiculated or ragged margins and two times more likely in the presence of pleural retraction (Harders et al. 2011). In the presence of multiple CT scans, detection of growth strongly suggests malignancy (Gould et al. 2013). A validated clinical prediction model from the Mayo Clinic identified older age, current or past smoking history, and history of extrathoracic cancer as independent clinical predictors of malignancy (Swensen et al. 1997). Overall, clinical factors combined with radiographic findings can be highly predictive of malignancy, and validated clinical prediction models exist to quantify the overall probability of malignancy (Chang et al. 2008; Stephans et al. 2009). In patients where biopsy is contraindicated, these resources can guide treatment decisions. A recent decision analysis showed that the delivery of SBRT without a pathological diagnosis is justified if the likelihood of malignancy is ≥85% (Louie et al. 2014).

Currently, outcomes reported in the literature regarding the unbiopsied NSCLC patient population are limited. A retrospective analysis by Verstegen et al. included 591 stage I NSCLC patients undergoing SBRT, and 382 of these patients did not undergo biopsy prior to treatment. SBRT dose was 60 Gy in three, five, or eight fractions over 2 weeks. There were no differences in overall survival or local control rate in patients with or without pathological diagnosis (Verstegen et al. 2011). Retrospectively reporting on the Japanese population, Takeda et al. compared 58 clinically diagnosed lung cancer patients to 115 pathologically diagnosed NSCLC patients. All patients were treated with 40–50 Gy in five fractions. No significant difference for the two groups existed for 3-year local control (80% vs. 87%), regional failure-free survival (88% vs. 91%), metastasis-free survival (70% vs. 74%), progression-free survival (64% vs. 67%), cause-specific survival (74% vs. 71%), and overall survival (54% vs. 57%) rates (Takeda et al. 2012). Unlike patients in the Midwest and Southeast United States, the Dutch and Japanese populations have a very low incidence of benign granulomatous disease. A multi-institutional retrospective study by Harkenrider et al. analyzed SBRT in 34 non-pathologically diagnosed early-stage NSCLC patients from regions of endemic granulomatous disease. At a median follow-up of 16.7 months, local control was 97%, and the estimated 2-year overall survival was 85%. No acute grade ≥3 toxicities occurred, and three patients experienced late grade 3 dyspnea (8.8%) (Harkenrider et al. 2014). Recent SBRT prospective trials have incorporated unbiopsied NSCLC patients, but these studies are not from the United States (Baumann et al. 2009; Ricardi et al. 2010).

Brachytherapy

For patients undergoing surgical resection, lobectomy with lymph node dissection remains the standard of care. Since sublobar resection can result in increased rates of local failure, intraoperative brachytherapy has been studied with the goal of decreasing local recurrence rates. A pilot study from the University of Pittsburgh showed that (I-125) intraoperative brachytherapy is well

tolerated without decline in pulmonary function testing (Chen et al. 1999). They also reported their long-term series of 145 patients with a median follow-up of 38 months. They demonstrated a local failure rate of only 4.1%, and the treatment remained well tolerated (Colonias et al. 2011). They additionally compared their series of patients treated for early-stage NSCLC with sublobar resection with I-125 mesh brachytherapy to those treated with sublobar resection alone. With over 100 patients in each group, they showed that the local failure rate decreased from 18.6% to 2.0% with the addition of I-125 mesh brachytherapy (Santos et al. 2003). Birdas et al. evaluated the role of sublobar resection with brachytherapy vs. lobectomy and found local recurrence rates to be 4.8% and 3.2% ($p = 0.60$), respectively, with equivalent disease-free survival at 4 years (Birdas et al. 2006). These institutional experiences indicate that sublobar resection with brachytherapy is safe and feasible. Additionally, cancer-specific outcomes treated with sublobar resection appear to be improved with the addition of brachytherapy, and for high-risk patients, brachytherapy may be a good alternative to lobectomy.

These favorable results were subsequently tested by the American College of Surgeons Oncology Group (ACOSOG) Z4032 trial, a Phase III randomized study of high surgical risk patients with early-stage NSCLC. Patients were randomized to sublobar resection ± intraoperative brachytherapy. They found no difference in 5-year local relapse, 14.0% and 16.7% ($p = 0.59$) without and with brachytherapy, respectively. This study was powered to detect a large difference in local recurrence, so a potentially small but meaningful difference could not be detected (Fernando et al. 2014). Additionally, the local recurrence rate was lower with sublobar resection alone compared to the previous Lung Cancer Study Group trial which may be a result of increased surgeon attention to obtaining a negative surgical margin (Ginsberg and Rubinstein 1995).

The role of brachytherapy following sublobar surgical resection of early-stage NSCLC remains controversial especially given the conflicting data from ACOSOG Z4032.

1.1.2 Locally Advanced NSCLC

Stage III NSCLC is routinely treated with multimodality therapy, most commonly with concurrent radiochemotherapy (ChemoRT) for unresectable N2 and N3 disease. Surgery may be considered following neoadjuvant ChemoRT or chemotherapy alone for medically operable patients with favorable, low-volume N2 disease. Postoperative radiation therapy (PORT) may be considered for patients with positive margins or incidental mediastinal nodal involvement following surgery, though, historically, there has been much debate regarding the utility of PORT for NSCLC. In this section, the many issues and controversies regarding the management of locally advanced NSCLC will be discussed.

Definitive Radiochemotherapy

One of the earliest clinical trials within the RTOG addressed the appropriate dose for locally advanced NSCLC patients. RTOG 7301 demonstrated improved rates of intrathoracic recurrence with 60 Gy compared to 50 Gy, 40 Gy, or 40 Gy split course (Perez et al. 1980). Since then, groups have studied dose escalation with radiation therapy alone or with concurrent chemotherapy. In studies of radiation therapy alone, doses above 90 Gy were too toxic in RTOG 9311, while data from University of Michigan indicated that dose escalation improved survival (Bradley et al. 2005a; Wang et al. 2009).

The addition of chemotherapy to radiation therapy sequentially improved survival and decreased rates of distant metastases for locally advanced NSCLC (Komaki et al. 1997; Sause et al. 2000). RTOG 9410 subsequently demonstrated improved survival with concurrent ChemoRT over sequential therapy and established standard fractionation radiation therapy with concurrent platinum-based doublet chemotherapy as the standard of care. Even with these advances, median survival was still only 17 months (Curran et al. 2011). It was hoped that combining escalated doses of radiotherapy with concurrent chemotherapy would further improve patient survival. RTOG 0117 was a Phase I/II study of dose escalation to 74 Gy with concurrent chemotherapy and showed median survival of 21

months for stage III NSCLC patients (Bradley et al. 2010). Similarly, the Cancer and Leukemia Group B (CALGB) 30105 study demonstrated median survival of 24 months with 74 Gy and concurrent chemotherapy (Socinski et al. 2008).

These studies lead to RTOG 0617, a Phase III randomized study of concurrent ChemoRT with two randomizations – (1) 60 Gy vs. 74 Gy and (2) with vs. without cetuximab. Disappointingly, both randomizations yielded negative results. There was no difference in survival with the addition of cetuximab. Dose escalation to 74 Gy surprisingly resulted in significantly inferior survival compared to 60 Gy. The median survival was 28 months and 20 months for patients receiving 60 Gy and 74 Gy, respectively. There are several potential contributing factors to the inferior survival with dose escalation. There were more treatment-related deaths on the dose-escalation arm. Dose escalation was associated with inferior completion of chemotherapy, inferior target volume coverage, and increased heart dose. When only radiation plans that complied with target volume coverage were analyzed, dose escalation still had inferior survival, so poor target coverage does not explain the inferior survival. Cardiac toxicity and deaths were not specifically tracked on the study, but both V5 and V30 (percentage of the organ receiving 5 Gy and 30 Gy, respectively) of the heart predicted for patient death, so it is possible that increased dose leads to increased rate of cardiac-related deaths (Bradley et al. 2015b).

This unfortunate outcome leads to some area of controversy about the future treatment of locally advanced NSCLC. Investigators have shown that using midtreatment PET/CT to analyze response and direct dose escalation to regions of residual disease is feasible and can limit dose to normal tissues (Kong et al. 2007; Feng et al. 2009). Additionally, systemic therapy including targeted mutation-driven biologic agents for epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK)-mutated tumors may improve survival. Immunologic agents in the category of anti-PD1 or anti-PD-L1 (programmed cell death protein 1 and programmed cell death ligand 1, respectively) checkpoint-directed therapies may also prove to be beneficial. Studies with these strategies are ongoing and hopefully will help direct the future of more individualized tumor-directed therapies.

Proton therapy is also currently being studied in a randomized Phase III trial. Proton therapy has shown in institutional series to be effective and has the potential for improved toxicity profile (Hoppe et al. 2012, 2016; Oshiro et al. 2012; Nguyen et al. 2015; Harada et al. 2016). Proton therapy could be most beneficial if indeed cardiac dose predicts for patient death. The role of proton therapy for many tumor sites, including thoracic malignancies, is controversial and should ideally be performed on a clinical trial.

Trimodality Therapy

In order to improve upon the local control and survival of single- or dual-modality therapies as previously described, Phase II studies were conducted by Albain et al. through the Southwest Oncology Group (SWOG) to study two treatment regimens for locally advanced NSCLC. The first regimen was trimodality therapy consisting of neoadjuvant concurrent ChemoRT followed by surgery, and the second regimen was definitive concurrent ChemoRT followed by adjuvant chemotherapy. Overall survival was promising, though morbidity and mortality rates were challenging for patients undergoing surgery (Albain et al. 1995, 2002). Albain et al. then compared these two regimens in a randomized trial of stage IIIA/IIIB resectable NSCLC patients. The trimodality arm demonstrated improved local control and progression-free survival, with a trend toward improved overall survival at 5 years of 27% vs. 20% ($p = 0.10$). Treatment-related deaths were greater in the trimodality arm and were found to be more prevalent in patients undergoing pneumonectomy (rather than lobectomy), especially right-sided pneumonectomy. Trimodality therapy was determined to be most beneficial for patients with single-station mediastinal nodal disease and those who are most likely to undergo lobectomy (Albain et al. 2009).

A study of the National Cancer Database (NCDB) of multimodality therapy for stage IIIA

NSCLC demonstrated improved survival for patients treated with trimodality therapy with lobectomy when compared to trimodality therapy with pneumonectomy, any surgery followed by adjuvant therapy, or definitive radiochemotherapy (Koshy et al. 2013). This further supports trimodality therapy with lobectomy as the optimal treatment for resectable stage III NSCLC.

Trimodality therapy for locally advanced NSCLC epitomizes the need for highly coordinated multimodality care. Since 45 Gy as given in the aforementioned trimodality studies is insufficient for a high probability of local control, surgical resectability must be determined at the time of diagnosis. Trying to use neoadjuvant ChemoRT to convert a patient from unresectable to resectable may result in breaks in treatment and suboptimal ChemoRT doses if the patient ultimately remains unresectable. To address this issue, several institutions treat to a definitive dose of about 60 Gy with concurrent chemotherapy prior to surgery. These studies show increased mediastinal clearance and pathologic complete response rate. They have not shown marked increase in postoperative morbidity or mortality (Sonett et al. 2004; Machtay et al. 2004; Cerfolio et al. 2005, 2009; Shumway et al. 2011). A study of the NCDB reviewed low- (36–44 Gy), intermediate- (45–54 Gy), and high-dose (55–74 Gy) neoadjuvant radiotherapy. This study showed improved survival with the intermediate neoadjuvant radiotherapy dose group. Selection bias could explain why higher doses lead to inferior survival since these patients may have had bulkier disease or been at higher risk to require more extensive surgery (Sher et al. 2015).

Pless et al. reported a Phase III trial of neoadjuvant chemotherapy vs. neoadjuvant ChemoRT for stage IIIA/B NSCLC. The trial showed no difference in event-free survival (primary endpoint) or overall survival and was stopped early due to futility. About 15% in the trimodality arm did not receive radiation therapy though, and 15% in the neoadjuvant chemotherapy only arm did receive radiation therapy. With the available data at the time of study design, median event-free survival was estimated to be 18 months with trimodality therapy (Pless et al. 2015). Other large randomized studies of trimodality therapy and definitive ChemoRT report progression-free survival of about 12 months, so this study may have set a lofty goal for the trimodality arm (Curran et al. 2011; Bradley et al. 2015b; Albain et al. 2009). Debate exists, nevertheless, about whether trimodality therapy should be favored over neoadjuvant chemotherapy for stage III resectable patients.

Superior sulcus tumors may be difficult to treat surgically due to their frequent involvement of the brachial plexus, subclavian vessels, and spine. SWOG 9416 was a Phase II study of a similar trimodality therapy regimen for NSCLC of the superior sulcus. The regimen involved treating the tumor and ipsilateral supraclavicular fossa (but not the mediastinum or hila) to 45 Gy with concurrent cisplatin and etoposide chemotherapy followed by surgical resection 3–5 weeks later. With this regimen, 5-year survival was 44% for all patients and 54% for those where a complete resection could be performed (Rusch et al. 2007).

With all of the available data for clinical stage III NSCLC patients, there are three primary curative-intent approaches – trimodality therapy, definitive ChemoRT, and chemotherapy followed by surgery. Patients must obviously be operative candidates to consider a surgical option, and the choice between trimodality therapy and chemotherapy followed by surgery is primarily institution dependent. Definitive ChemoRT is optimal for patients who are poor surgical candidates due to either medical comorbidities, required surgery would leave the patient with inadequate pulmonary function, or high-volume nodal disease.

Locally Advanced with Poor Performance Status

Treatment options for patients with locally advanced NSCLC were described in the previous section. Patients who are medically unfit or unwilling to undergo one of these standard regimens may be considered for treatment with definitive therapy with sequential systemic therapy followed by radiotherapy or radiation therapy alone.

As part of the evolution of treatment of locally advanced NSCLC, chemotherapy was

investigated – first sequentially and then concurrently. Sequential chemotherapy followed by radiotherapy was shown to improve survival when compared to radiotherapy alone (Sause et al. 1995, 2000; Dillman et al. 1990, 1996). Concurrent ChemoRT subsequently was shown to improve survival compared to sequential therapy but with increased toxicity (Curran et al. 2011; Auperin et al. 2010). For patients who are unlikely to tolerate concurrent ChemoRT, sequential therapy should still be considered over radiotherapy alone.

Historically, doses of radiation therapy of 60 Gy in 30 fractions were determined to have improved overall survival compared to lower doses (Perez et al. 1980). Institutional and cooperative group studies have studied increased total dose and/or increased dose per fraction. These studies showed mixed results regarding local control but with potentially increased toxicity and have not led to subsequent randomized trials (Bradley et al. 2005a). Altered fractionation schedules such as continuous hyperfractionated accelerated radiation therapy (CHART) showed no difference when compared to standard fractionation (Saunders et al. 1999; Baumann et al. 2011). Single-institution studies have studied hypofractionated courses for patients who are not candidates for chemotherapy. A retrospective study comparing a hypofractionation regimen of 45 Gy in 15 fractions showed no difference in local control or survival when compared to standard fractionation (Amini et al. 2012a). Using advanced techniques like intensity-modulated radiation therapy (IMRT) with simultaneous integrated boost has demonstrated a reasonable toxicity profile but with failure still tending to occur in the high-dose region (Swanick et al. 2015).

Proton therapy has been used with potential for dose escalation while still maintaining a reasonable toxicity profile for unfavorable patients, even though ultimate prognosis remains poor (Oshiro et al. 2012). Proton therapy has additionally been delivered with a hypofractionated regimen of 45–60 Gy in 15 fractions which was well tolerated (Gomez et al. 2013a). There is no clear standard of care for patients with locally advanced NSCLC who are unable to receive chemotherapy, but it is reasonable to deliver doses of about 60 Gy in 2 Gy fractions or a biologically equivalent altered fractionation schedule.

Postoperative Radiation Therapy

Postoperative radiation therapy (PORT) for various pathological stages has been quite controversial over the past decades. A commonly cited study that demonstrates this controversy is the PORT meta-analysis. The PORT meta-analysis found poorer survival with PORT in patients with N0/N1 disease and no impact on survival for patients with N2 disease. This study was published in 1998 and 2005 and contained studies whose recruitment began between 1966 and 1988. Therefore, the treatment techniques routinely comprised orthovoltage or cobalt-60 with two-dimensional treatment planning (Postoperative radiotherapy in non-small-cell lung cancer: systematic review and meta-analysis of individual patient data from nine randomised controlled trials. PORT Meta-analysis Trialists Group 1998; Group PM-aT 2005).

Modern studies for resected lung cancer show a decrease in local recurrence with potential for improved overall survival with addition of PORT for patients with advanced nodal disease (Effects of postoperative mediastinal radiation on completely resected stage II and stage III epidermoid cancer of the lung. The Lung Cancer Study Group 1986; Stephens et al. 1996; Mayer et al. 1997; Feng et al. 2000; Douillard et al. 2008). Studies that comprised mostly early-stage patients showed no difference in local recurrence often with poorer survival in the group that received PORT (Van Houtte et al. 1980; Dautzenberg et al. 1999).

RTOG 9705 was a Phase II study which treated resected stage II and IIIA NSCLC with PORT and concurrent chemotherapy. The dose was 50.4 Gy in 28 fractions to the mediastinum and ipsilateral hilum, but the primary tumor bed was treated only if parietal pleura was pathologically invaded. A boost to 59.4 Gy was delivered for extracapsular extension of nodal disease and T3 disease. They reported median survival of 56.3 months with a toxicity profile which

compared favorably to historical controls. The mediastinal fields in this study were fairly large, extending from the thoracic inlet to a range of 5–8 cm inferior to the carina (Bradley et al. 2005b). The Lung Adjuvant Radiotherapy Trial (Lung ART) study is ongoing and randomizes patients to PORT vs. no PORT for completely resected N2 disease. They are also investigating smaller target volumes to treat one nodal station proximal and distal to the involved nodal station(s) (Le Pechoux et al. 2007; Spoelstra et al. 2010). A study of the NCDB reported on more modern radiation therapy from 1998 to 2006 and showed improved survival with PORT for completely resected N2 NSCLC (Corso et al. 2015). Another NCDB study showed improved survival with PORT for patients with positive surgical margins, regardless of nodal stage (Wang et al. 2015). Amini et al. reported on their institutional series of patients treated with neoadjuvant chemotherapy followed by surgery with persistent mediastinal nodal disease. With a median follow-up time of 28.1 months, the addition of PORT resulted in a locoregional failure rate of 16.4%. They also found that addition of adjuvant chemotherapy improved the distant metastasis rate and overall survival (Amini et al. 2012b).

Most of these studies describe PORT for completely resected NSCLC; however, patients with incompletely resected NSCLC have a more clear indication for PORT. The use of concurrent chemotherapy with PORT vs. sequential chemotherapy and PORT is an additional controversial topic. A study from Zhou et al. treated patients with positive surgical margins with concurrent ChemoRT to a median dose of 60 Gy. With a median follow-up time of 40 months, they reported a local recurrence rate of 19.6% (Zhou et al. 2015). Lee et al. compared their institutional experience of PORT alone to concurrent PORT with chemotherapy and showed that local control and disease-free survival were improved with the addition of concurrent chemotherapy (Lee et al. 2014). A Phase II study by Gomez et al. treated postoperative superior sulcus tumors with concurrent chemotherapy and PORT and demonstrated a 10-year locoregional control rate of 76% (Gomez et al. 2012).

The more modern series support the use of PORT for completely resected N2 or incompletely resected NSCLC of any stage. The use of more limited volume PORT will be studied as part of the current Lung ART study.

1.2 Small Cell Lung Cancer

Small cell lung cancer (SCLC) comprises 10–15% of all lung cancer diagnoses and has the predilection to be metastatic at the time of diagnosis and for brain metastases to be part of the eventual pattern of spread during the patient's treatment course. This section aims to describe the treatment and controversies regarding both limited stage (LS-) and extensive stage (ES-) SCLC.

1.2.1 Limited Stage SCLC

The history of LS-SCLC nicely progresses over time with studies showing that combined modality therapy with concurrent chemotherapy and radiation therapy followed by prophylactic cranial irradiation (PCI) should be the standard management. Studies progressed from chemotherapy or radiation therapy alone to sequential chemotherapy and radiation therapy to concurrent ChemoRT to concurrent ChemoRT followed by PCI (Radiotherapy alone or with chemotherapy in the treatment of small-cell carcinoma of the lung. Medical Research Council Lung Cancer Working Party 1979; Radiotherapy alone or with chemotherapy in the treatment of small-cell carcinoma of the lung: the results at 36 months. 2nd report to the Medical Research Council on the 2nd small-cell study 1981; Perry et al. 1987; Pignon et al. 1992; Auperin et al. 1999; Turrisi et al. 1999). However, there still remain several controversial issues in the management of LS-SCLC, especially since 5-year survival is still poor.

Radiation Dose Fractionation

Fractionation of radiation therapy is a common debate in the treatment of LS-SCLC. The first major randomized trial of radiation therapy fractionation reported by Turrisi et al. compared

45 Gy in 25 fractions of 1.8 Gy daily to 45 Gy in 30 fractions of 1.5 Gy twice daily with concurrent cisplatin/etoposide chemotherapy followed by PCI. They showed improved survival with 45 Gy delivered twice daily over 3 weeks. There was increased high-grade toxicity, primarily esophagitis, with this regimen though (Turrisi et al. 1999). This study is not truly a study of fractionation regimen but rather a dose-escalation study since the twice-daily regimen is more biologically effective. Cooperative groups initially studied other regimens though not in Phase III randomized trials. The Phase II CALGB study used 70 Gy in 35 fractions with concurrent chemotherapy and reported outcomes similar to those reported in the twice-daily arm of the Turrisi et al. study (Bogart et al. 2004). RTOG 0239 studied accelerated high-dose radiotherapy with chemotherapy delivered to a dose of 61.2 Gy over 5 weeks with 28.8 Gy in 1.8 Gy daily fractions on days 1–22. On treatment days 23–26, the same plan was delivered each morning, and an off-cord boost delivered at least 6 h later. The remainder of the plan delivered the off-cord boost twice daily to complete the course. They showed higher than expected local control and lower than expected toxicity, though survival was not superior to the twice-daily arm from the Turrisi et al. study (Komaki et al. 2012).

More recently, randomized trials began comparing once-daily vs. twice-daily radiation therapy. The CALGB/RTOG ongoing study is comparing 45 Gy in 30 twice-daily fractions to 70 Gy in 35 daily fractions. This study originally also contained the RTOG 0239 regimen as described above, but this arm was discontinued (per design of the study) due to greater toxicity when compared to 70 Gy in 35 fractions (Alliance for Clinical Trials in Oncology – CALGB 30610/RTOG 0538 – Phase III Comparison of Thoracic Radiotherapy Regimens in Patients with Limited Stage Small Cell Lung Cancer also Receiving Cisplatin or Carboplatin and Etoposide). The CONVERT trial compared the same twice-daily regimen of 45 Gy in 30 fractions to 66 Gy in 33 daily fractions. This study was reported in 2016 and showed median survivals of 30 months and 25 months ($p = 0.15$) with twice-daily and daily fractionation, respectively. Toxicity rates were also comparable except for grade 3/4 neutropenia which was increased with the twice-daily regimen (74% vs. 64%, $p = 0.03$). There were no significant differences in febrile neutropenia, esophagitis, and pneumonitis between the two regimens. This data supports the use of either regimen for the treatment of LS-SCLC (Faivre-Finn et al. 2016a, b). The results of the currently accruing CALGB/RTOG study will be important to correlate with the CONVERT study to inform on the proper radiotherapy regimen for the treatment of limited stage SCLC. The reported dose-fractionation regimens and results of ChemoRT for LS-SCLC are described in Table 3.

Elective Nodal Irradiation

Treatment fields have also been a topic of debate over the years. The Turrisi et al. study treated the tumor and the bilateral mediastinal and ipsilateral hilar lymph nodes (Turrisi et al. 1999). Other prospective studies also included elective nodal irradiation (ENI) (Bogart et al. 2004; Komaki et al. 2012). The driving force behind omission of ENI is the potential for increased toxicity associated with increased thoracic radiotherapy volumes. A study by De Ruysscher et al. reported on patients who were staged with CT only and treated with omission of ENI. They found 3 of 27 (11%) patients failed outside of the PTV, all in the ipsilateral supraclavicular fossa (De Ruysscher et al. 2006). A similar study by Colaco et al. reported on 38 patients treated without ENI again in the era of CT-only staging. They found that only 2 of 38 patients (5%) failed outside of the PTV in the elective nodal region, and both of those patients had distant metastases diagnosed concurrently (Colaco et al. 2012). When similar studies were performed in the era of PET/CT staging, isolated nodal failures occurred in <5% of cases with improved rates of esophagitis (van Loon et al. 2010; Hu et al. 2012). Han et al. compared survival and progression-free survival for patients treated with or without ENI and found no difference in outcomes. Patients who were not staged with PET/CT had inferior survival if they were treated with omission of ENI in their study (Han et al. 2012).

Table 3 Dose-fractionation schedules and outcomes for limited stage small-cell lung cancer

Author (year)	Thoracic radiotherapy dose (Gy)	Chemotherapy	Sequence	Number of patients	Median survival (months)	2-year overall survival (%)	5-year overall survival
Turrisi et al. (1999)	45 Gy (1.8 Gy daily over 25 fractions) 45 Gy (1.5 Gy BID over 30 fractions)	Cisplatin 60 mg/m^2 day 1 and etoposide 120 mg/m^2 days 1–3 q3weeks × four cycles	Concurrent ChemoRT starting on day 1, cycle 1 of chemotherapy	206 211	19 23	41% 47%	16% 26%
Bogart et al. (2004)	70 Gy (2 Gy daily over 7 weeks)	Induction topotecan 1 mg/m^2 on days 1–5 and 22–26 and paclitaxel 175 mg/m^2 on days 1 and 22 Carboplatin (AUC = 5) on days 43, 64, and 85 and etoposide 100 mg/m^2 on days 42–44, 64–66, and 85–87	RT started on day 43 – first day of carboplatin and etoposide chemotherapy	63	22.4	48%	Not reported
Komaki et al. (2012)	61.2 Gy (1.8 Gy daily on days 1–22 and then 1.8 Gy BID on days 23–33)	Cisplatin 60 mg/m^2 day 1 and etoposide 120 mg/m^2 days 1–3 q3weeks × four cycles	RT started on day 1, cycle 1 of chemotherapy	71	19	36.6%	Not reported
Faivre-Finn et al. (2016b)	45 Gy (1.5 Gy BID over 30 fractions) 66 Gy (2 Gy daily over 33 fractions)	Cisplatin 25 mg/m^2 days 1–3 or 75 mg/m^2 day 1 and etoposide 100 mg/m^2 days 1–3 × 4–6 cycles	RT started on day 22 of cycle 1 of chemotherapy	274 273	30 25	56% 51%	Not reported

In a prospective study by Bradley et al., PET upstaged 3 of 24 (12.5%) patients from limited to extensive stage, thus altering the goals of care. PET identified additional sites of nodal disease in six (25%) patients resulting in altered treatment plans (Bradley et al. 2004). PET is not only important for nodal target volume delineation but also crucial for accurate staging of distant disease.

Prophylactic Cranial Irradiation

PCI is routinely indicated for patients who have responded to concurrent ChemoRT. The Auperin et al. meta-analysis of PCI for LS-SCLC showed improved overall survival of about 5% (Auperin et al. 1999). The dose of PCI has been debated and multiple fractionation schedules have been used. Le Pechoux et al. evaluated the question of PCI dose in a randomized study of high-dose (36 Gy at 2 Gy daily or 1.5 Gy twice daily) vs. low-dose (25 Gy at 2.5 Gy daily) PCI. They showed no difference in incidence of brain metastases but showed an increase in mortality in the high-dose PCI arm (likely due to an unrelated increase in disease progression) (Le Pechoux et al. 2009). A study of the Surveillance, Epidemiology, and End Results (SEER) database limited to elderly patients (≥70 years old) maintained that PCI was an independent predictor for improved OS in patients with LS-SCLC (Eaton et al. 2013). A survey of PCI use demonstrated increasing, but still quite low, percentages of patients were receiving PCI. In 2006–2007, only 49% of patients with LS-SCLC received PCI (Komaki et al. 2013).

Hippocampal-sparing whole-brain irradiation for PCI is an area of ongoing study. The goal of hippocampal avoidance is to decrease neurocognitive deficits that are a known potential side effect of whole-brain radiotherapy. In SCLC, data suggest that brain metastases occur within the region of hippocampal avoidance in only about 5% of cases (Kundapur et al. 2015). Hippocampal avoidance PCI is currently being investigated in a randomized Phase III trial (NRG-CC003: A Randomized Phase II/III Trial of Prophylactic Cranial Irradiation with or without Hippocampal Avoidance for Small Cell Lung Cancer). PCI should routinely be offered to limited stage SCLC patients who have responded to ChemoRT. The role of hippocampal avoidance to potentially decrease neurocognitive deficits is exciting but investigational at this time.

1.2.2 Extensive Stage SCLC

ES-SCLC is primarily managed with chemotherapy, but radiation therapy has a few specific roles for these patients. At diagnosis, palliative radiation therapy may be required for the treatment of brain metastases, superior vena cava (SVC) syndrome, or obstructive respiratory symptoms. These scenarios are common given the predilection of SCLC to metastasize to the brain or for bulky thoracic disease to cause compressive symptoms.

Prophylactic Cranial Irradiation

There has been significant debate regarding the role of PCI for patients with ES-SCLC without brain metastases. This question was addressed in a European Organisation for Research and Treatment of Cancer (EORTC) Phase III randomized trial of ES-SCLC with response to chemotherapy to receive or not receive PCI. PCI significantly improved 1-year OS from 13% to 27% with addition of PCI. PCI also significantly decreased the 1-year incidence of symptomatic brain metastases from 40% to 15% ($p < 0.001$). The median survival was improved from 5.4 to 6.7 months ($p = 0.003$) with PCI which could either support or detract the value of PCI since, though statistically significant, the improvement in median survival is just over 1 month (Slotman et al. 2007). A similar Japanese study of ES-SCLC patients treated with chemotherapy randomized patients to receive PCI or observation. This study required restaging of the brain with magnetic resonance imaging (MRI) prior to PCI, which is different than the EORTC study. They showed a trend for improved median survival of 15.1 months vs. 10.1 months ($p = 0.09$) with observation and PCI, respectively, showing a potentially conflicting result to the EORTC study. They showed no difference in grade 2 toxicities in this study (Seto et al. 2014).

Any potential benefit of PCI should be balanced by potential effect on patients' quality of life (QOL). The EORTC study assessed QOL as

part of their study, and they showed that PCI decreased the health-related QOL metrics of fatigue and hair loss. Decreased functional metrics and global health status were more limited with addition of PCI (Slotman et al. 2009). The risks and benefits of PCI should be discussed with patients so they can make an informed decision.

Consolidation Radiotherapy

In an attempt to improve survival for patients with ES-SCLC, studies of dose intensification with chemotherapy were conducted. These studies showed increased toxicity with chemotherapy dose intensification without improvement in overall survival (Giaccone et al. 1993; Ihde et al. 1994; Mavroudis et al. 2001). Thoracic progression of disease in ES-SCLC is common, occurring in about 90% of patients within the first year of diagnosis, which is often life threatening (Slotman et al. 2007). In an attempt to improve survival with local therapy, Jeremic et al. studied patients with ES-SCLC treated with three cycles of cisplatin and etoposide with complete distant response and complete or partial local response. Patients were randomized to either thoracic radiation therapy (TRT) 54 Gy in 36 fractions twice daily with concurrent chemotherapy vs. chemotherapy alone. Both groups also received PCI. They showed significant improvement of median survival (17 vs. 11 months) and 5-year survival (9.1% vs. 3.7%, $p = 0.041$) with addition of TRT (Jeremic et al. 1999a). In a similar study by Slotman et al., patients who had any response to chemotherapy were randomized to PCI vs. PCI and TRT 30 Gy in ten fractions. Patients receiving TRT had a trend toward improved 1-year survival (33% vs. 28%, $p = 0.066$) with secondary analysis showing increased 2-year survival (13% vs. 3%, $p = 0.004$) (Slotman et al. 2015). A meta-analysis of TRT for ES-SCLC was performed and included these two randomized trials. They reported improved survival and progression-free survival with addition of TRT. Grade ≥3 esophageal toxicity is higher with TRT though (6.6% vs. 0%, $p < 0.001$) (Palma et al. 2015).

Further analysis of the Slotman et al. study of TRT found that patients with residual thoracic disease after chemotherapy had improved survival with addition of TRT, whereas patients with complete thoracic response to chemotherapy experienced no benefit with TRT. They conclude that TRT should be offered to patients with favorable but incomplete response to chemotherapy, and TRT should be omitted for patients with complete thoracic response (Slotman and van Tinteren 2015).

If TRT is to be given, there is no clear evidence how it should be sequenced. It reasons that if TRT is to be given, then the sequence of therapy should replicate either Phase III trial described above. In Jeremic et al., PCI was delivered after TRT which is logical since chemotherapy was given concurrently with TRT in that study (Jeremic et al. 1999a). In Slotman et al., PCI was delivered concurrently with TRT in 88% of patients and appeared to be well tolerated. This is a more convenient approach for the patient since both regimens are commonly delivered in ten fractions over 2 weeks (Slotman et al. 2015). Now with two randomized trials supporting consolidation TRT for ES-SCLC, TRT should be routinely delivered for patients with favorable, but incomplete, thoracic response to chemotherapy.

Another therapy that has been investigated in an attempt to improve survival for patients with ES-SCLC is delivery of consolidation radiation therapy to the local disease and sites of distant metastases. The role of extracranial consolidation was studied in RTOG 0937 which was a randomized Phase II study of chemotherapy followed by PCI with or without consolidation radiation to metastatic sites. Consolidation radiation delayed disease progression, but it did not improve survival (Gore et al. 2016). These data support PCI with TRT for ES-SCLC patients with a favorable but incomplete response to chemotherapy.

1.3 Recurrent Lung Cancer

Local or nodal recurrences of lung cancer are serious, but potentially salvageable, scenarios. For patients who are willing and able to pursue aggressive therapy, radiation therapy can be employed with the goal to salvage the recurrence after prior surgery or local radiotherapy.

1.3.1 Salvage Radiotherapy for Surgical Treatment Failures

Surgical resection is the standard curative-intent treatment for early stages of NSCLC and may be a component of multimodality therapy for locally advanced NSCLC. As described previously, even for T1 lesions, the Lung Cancer Study Group trial showed local recurrence rates of 6% with lobectomy and 17% with sublobar resection (Ginsberg and Rubinstein 1995). However, postoperative recurrence of NSCLC occurs in up to 45% of patients following resection. Locoregional recurrence is the first site of recurrence in 19% of surgical cases and should be treated like unresectable stage III NSCLC (Yano et al. 2014). The median overall survival for a locoregional recurrence ranges from 14 to 19 months for patients treated with salvage radiotherapy (Kagami et al. 1998; Jeremic et al. 1999b; Tada et al. 2005). In a 2005 retrospective study, Tada et al. evaluated 31 patients with recurrent NSCLC treated to a prescribed dose of 60 Gy in 30 fractions (Tada et al. 2005). A complete radiographic response was seen in 23% of the patients, and a partial response was seen in 64% of the patients. The 1-year, 2-year, and 4-year overall survival rates were 61%, 30%, and 15%, respectively (Tada et al. 2005). In a retrospective analysis of three-dimensional conformal radiotherapy for postoperative thoracic lymph node recurrence of NSCLC, the median overall survival was 37.3 months (Okami et al. 2013). In contrast, the median overall survival for patients with lymph node recurrence who received chemotherapy, an EGFR inhibitor, or supportive care was only 14.6 months. Radiotherapy, often combined with concurrent chemotherapy, can salvage surgical recurrences, and long-term survival is possible.

Salvage SBRT has also been used for postoperative locoregional recurrence in NSCLC patients. An Italian retrospective study reviewed the outcomes of 28 patients who underwent salvage SBRT for locoregional recurrence of NSCLC (Agolli et al. 2015). The prescribed doses were 23 Gy in one fraction for mediastinal nodal recurrences, 30 Gy in one fraction for peripheral or small tumors (<30 cm^3), or 45 Gy in three fractions for centrally located or large tumors (≥ 30 cm^3). Complete and partial responses were observed in 16% and 70% of patients, respectively. Local control at 1 and 2 years was 96.6% and 84.7%, respectively, and the median overall survival was 31 months (Agolli et al. 2015). Takeda et al. reported a 2-year overall survival of 76.4% in NSCLC patients treated with SBRT for isolated postoperative local recurrences (Takeda et al. 2013).

1.3.2 Salvage SBRT for Radiotherapy Treatment Failures

High-dose conventionally fractionated radiotherapy and SBRT have been used as salvage therapy for locoregional recurrences following ChemoRT or SBRT (Amini et al. 2014; De Ruysscher et al. 2014; Griffioen et al. 2014; Tetar et al. 2015). After definitive radiotherapy, the 2-year local recurrence rate is 20–44%, and in most of these cases, the recurrent tumor is not resectable (Vansteenkiste et al. 2013). With systemic therapy alone for these locoregional recurrences, median overall survival is 10–12 months (De Ruysscher et al. 2014). With re-irradiation, the median overall survival is approximately 17 months for locally recurrent NSCLC, though patients are at potentially increased risk for toxicity including radiation pneumonitis, fibrosis, and bleeding (De Ruysscher et al. 2014). In a meta-analysis of re-irradiation by De Ruysscher et al., the risk of grade 3–4 lung toxicity after re-irradiation is only 10% (De Ruysscher et al. 2014).

Salvage radiotherapy with SBRT may be the only reasonable option for potential salvage of a local failure. In patients treated with SBRT for local recurrences following conventional radiotherapy, local control ranges from 65% to 92%, and the 1-year overall survival following salvage SBRT is 59–80% (Amini et al. 2014). Hearn et al. reported on the safety of salvage SBRT for local recurrences of NSCLC after primary SBRT. Ten patients received salvage SBRT for recurrence to a dose of 50 Gy in five fractions and 60 Gy in three fractions for central and peripheral tumors, respectively. No patient experienced grade 3–5 toxicity (Hearn et al. 2014). Results of such retrospective and exploratory studies suggest that repeat SBRT is a safe and effective treatment for well-selected patients.

1.4 Palliative Radiotherapy

Palliative radiation therapy for lung cancer may be necessary to control hemoptysis, chest wall pain, superior vena cava (SVC) syndrome, or airway obstruction. Several evidence-based guidelines exist regarding the appropriate management for the palliation of intrathoracic lung cancer (Rodrigues et al. 2011, 2012a, b, 2013). The decision to offer palliative radiotherapy depends on the patient's performance status, disease status, pulmonary function, treatment volume, symptomatology, and overall prognosis. Palliative radiotherapy is generally reserved for patients presenting with or at risk for any of the aforementioned symptoms (Rodrigues et al. 2012b).

1.4.1 Pulmonary Symptoms

A standard regimen for palliation of local symptoms from lung cancer is 30 Gy in ten fractions. However, multiple radiotherapy regimens ranging from 10 Gy in one fraction to 60 Gy in 30 fractions over 6 weeks have been used to treat patients with thoracic symptoms from NSCLC (Stevens et al. 2015). Kramer et al. randomized 297 patients with inoperable stage IIIA/B or stage IV NSCLC with thoracic symptoms (excluding SVC syndrome) to either 30 Gy in ten fractions or 16 Gy in two fractions (Kramer et al. 2005). The duration of symptom improvement was significantly longer with 30 Gy in ten fractions, persisting for 22 weeks, compared to only 12 weeks with 16 Gy in two fractions. Additionally, 1-year overall survival was significantly higher with 30 Gy in ten fractions vs. 16 Gy in two fractions (19.6% vs. 10.9%, $p = 0.03$) (Kramer et al. 2005). In a study of 30 Gy in ten fractions and 10 Gy in one fraction for palliation of thoracic symptoms from lung cancer, symptomatic improvement was significantly greater in the 30 Gy in ten-fraction arm (Erridge et al. 2005). In a comparison of 10 Gy in one fraction and 20 Gy in five fractions, there was no significant difference in the palliation of thoracic symptoms from lung cancer (Bezjak et al. 2002). However, Bezjak et al. demonstrated that patients treated with a palliative regimen of 20 Gy in five fractions had significantly improved overall survival compared to those treated with 10 Gy in one fraction (Bezjak et al. 2002). Hypofractionated palliative radiotherapy schedules can be used for patients with poor performance status or those requiring a shorter treatment course due to poor prognosis (Rodrigues et al. 2011; Reinfuss et al. 2011).

Two meta-analyses showed that total dose and number of fractions did not significantly affect palliation of thoracic symptoms or overall survival in patients with NSCLC (Stevens et al. 2015; Ma et al. 2014). In a meta-analysis by Ma et al., there was no difference in palliation of cough, chest pain, or hemoptysis with higher total doses (≥30 Gy) compared to lower doses (<30 Gy). Additionally, 1 and 2-year overall survival was not significantly different between the higher and lower total radiation doses (Ma et al. 2014). A Cochrane review from 2015 indicated that the number of fractions used for palliative radiotherapy had no significant effect on 1-year overall survival in patients with either good or poor performance status. The risk of esophagitis, radiation myelopathy, and pneumonitis did not significantly differ based on the number of fractions either (Stevens et al. 2015). A meta-analysis by Fairchild et al. in 2008 showed improved 1-year overall survival in patients treated with a BED of ≥35 $Gy_{\alpha/\beta = 10}$ compared to patients treated with a lower BED. Furthermore, a palliative dose with a BED of ≥35 Gy was more likely to result in any symptomatic improvement vs. a lower BED (Fairchild et al. 2008). Several criticisms of this meta-analysis have been reported in the 2015 Cochrane review though (Stevens et al. 2015). Thus, it is possible that the reported benefits in survival and symptom improvement were due to study design rather than differences in BED.

There is no clear benefit of administering chemotherapy concurrently with radiation for the palliation of thoracic symptoms due to lung cancer (Rodrigues et al. 2011). In a Phase III study of NSCLC patients randomized to either palliative radiotherapy (20 Gy in five fractions) or the same palliative radiotherapy plus concurrent fluorouracil, there was no significant difference in overall or progression-free survival or in palliation of symptoms (Ball et al. 1997). Patients treated with radiotherapy plus fluorouracil were significantly more likely to have acute toxicity,

including nausea, vomiting, esophagitis, stomatitis, and skin reaction. It reasons to individualize dose of palliative radiotherapy to the individual patient and clinical scenario.

1.4.2 Endobronchial Brachytherapy

Endobronchial brachytherapy (EBB) has been used for the palliation of symptoms caused by lung tumors including hemoptysis, obstruction, dyspnea, and cough (Skowronek 2015). This procedure involves bronchoscopy with placement of an afterloading catheter in the airway adjacent to the tumor. There are no randomized trials to recommend EBB either alone or combined with another treatment in the routine initial palliation of symptoms secondary to lung cancer (Rodrigues et al. 2011; Rosenzweig et al. 2013). A Cochrane review from 2012 included NSCLC patients from 14 trials comparing several palliation treatment techniques including EBB, EBRT alone, EBB plus EBRT, EBB plus chemotherapy, and laser therapy. The authors demonstrated that EBRT provides more effective palliation than EBB alone and that there was no improvement in overall survival with EBB compared to EBRT or laser therapy (Reveiz et al. 2012). EBB is generally reserved for symptomatic patients with recurrent endobronchial obstructing or bleeding tumors after prior EBRT.

1.4.3 Superior Vena Cava Syndrome

SVC syndrome arises from extrinsic or intrinsic obstruction of blood flow through the superior vena cava. Symptoms of SVC syndrome include swelling of the face, neck, and upper extremity, cough, dyspnea, stridor, and altered mental status (Rice et al. 2006). While the prevalence of SVC syndrome secondary to intravascular devices has increased over the past 20 years (Cheng 2009), intrathoracic malignancies still remain the most common cause of SVC syndrome (Straka et al. 2016). NSCLC accounts for the majority of malignant causes of SVC syndrome (Straka et al. 2016; Wilson et al. 2007).

Historically, all cases of SVC syndrome were classified as an oncologic emergency requiring immediate management (Schechter 1954). Indeed, laryngeal constriction and cerebral edema secondary to SVC syndrome are life threatening and require emergent treatment (Straka et al. 2016; Sofue et al. 2013). Only about 5% of patients with SVC syndrome present with the aforementioned life-threatening conditions and require emergent treatment with a venogram and stent placement (Yu et al. 2008). Emergent radiotherapy is not a first-line treatment in life-threatening cases of SVC syndrome, as palliation is more rapid with intravascular stenting (Nicholson et al. 1997).

Most cases of SVC syndrome are relatively benign, and appropriate workup and staging can be performed (Straka et al. 2016; Wilson et al. 2007; Yu et al. 2008). Following appropriate diagnosis and staging, palliative or curative intent radiotherapy or ChemoRT is still considered the primary treatment modality for SVC syndrome. A Cochrane review meta-analysis has reported that in patients with SVC syndrome secondary to NSCLC or SCLC, chemotherapy and/or radiotherapy successfully palliates SVC compressive symptoms in the majority of cases. Insertion of an SVC stent improved symptoms in 95% of cases (Rowell and Gleeson 2001). The time to symptom relief has been reported to be 3–30 days (Straka et al. 2016).

Several fractionation regimens may be utilized for palliation of SVC syndrome including 3–4 Gy for the first 2–5 fractions followed by conventional 2 Gy fractionation to a definitive dose based on the tumor histology (Straka et al. 2016; Davenport et al. 1978; Armstrong et al. 1987; Egelmeers et al. 1996). A hypofractionated regimen of 12 Gy in two fractions has been demonstrated to induce a complete symptom alleviation in 74% of patients with SVC syndrome (Lonardi et al. 2002). Palliative hypofractionated radiotherapy and definitive ChemoRT can be used in the management of SVC syndrome based on the goals and intent of disease management.

2 Thymoma

Thymomas are rare tumors of the thymus gland with a reported incidence of 0.13–0.17 per 100,000 person-years (Engels 2010; Scorsetti

et al. 2016). The incidence of thymomas in men and women is similar, and the incidence increases with age through the eighth decade of life (Engels 2010; Scorsetti et al. 2016; Kim and Thomas 2015).

Thymomas most commonly occur in the anterior-superior mediastinum and comprise approximately 50% of all anterior mediastinal tumors (Scorsetti et al. 2016). Thymomas arise from epithelial cells in the thymus. Because the thymus is the site of T-cell maturation, thymomas are associated with multiple autoimmune syndromes including myasthenia gravis, pure red cell aplasia, hypogammaglobulinemia, and polymyositis (Scorsetti et al. 2016). Approximately 30–50% of thymoma patients have concurrent myasthenia gravis. In a retrospective study from Italy, multivariate analysis showed that myasthenia gravis in thymoma patients had no significant effect on overall survival or recurrence (Filosso et al. 2015). Patients with thymoma also have about an 8–28% increased risk of developing a secondary malignancy, most notably non-Hodgkin lymphoma (Engels and Pfeiffer 2003; Filosso et al. 2013). It is hypothesized that immune dysregulation from thymomas increases the risk of secondary malignancies (Welsh et al. 2000).

Histologic classification of thymomas is based on morphology and the lymphocyte/epithelial cell ratio with six different designations of thymomas (A, AB, B1, B2, B3, and C) as set forth by the World Health Organization (WHO) and detailed in Table 4 (Scorsetti et al. 2016). Type A thymomas are spindle cell or medullary thymomas with rare lymphocytes and no nuclear atypia. In contrast, type C lesions are heterogeneous thymic carcinomas with significant cytologic atypia, and mature lymphocytes and plasma cells present between tumor lobules. Prognosis worsens as thymomas progress from A to C histologic subtype. The 10-year overall survival for types A-B1

Table 4 Histologic classification of thymic tumors

WHO histologic classification	
Type A	
Tumor composed mainly of epithelial cells with spindle/oval shape, lacking nuclear atypia; lymphocytes are rare	Spindle cell or medullary thymoma
Type AB	
Tumor in which foci with features of type A thymoma are admixed with lymphocyte-rich areas: the segregation of two patterns can be sharp or indistinct	Mixed thymoma
Type B1	
Tumor that resembles the normal functional thymus, combining predominant areas resembling normal thymic cortex and areas resembling thymic medulla. This is a thymoma "lymphocyte predominant thymoma" and the neoplastic epithelial cells are scant, small, with little atypia	Organoid, lymphocyte rich or lymphocytic or predominantly cortical thymoma
Type B2	
Tumor in which the neoplastic epithelial component (plump cells with vesicular nuclei and conspicuous nucleoli) is scattered individually or in small clusters among immature lymphocytes	Cortical thymoma
Type B3	
Tumor composed predominantly of epithelial cells with a round or polygonal shape and exhibiting mild atypia, admixed with a minor component of immature lymphocytes	Well-differentiated thymic carcinoma or epithelial thymoma or squamoid thymoma
Type C	
Tumor exhibiting clear-cut cytologic atypia and lacking a significant number of immature interepithelial thymocytes. Mature lymphocytes and plasma cells are present in the septa between tumor lobules and in the tumor periphery. This subtype is usually indistinguishable from extrathymic carcinomas	Heterogeneous thymic carcinoma

Scorsetti et al. (2016)

thymomas is over 90% (Quintanilla-Martinez et al. 1994; Chen et al. 2002). However, for type B2, B3, and C lesions, the 5-year overall survival is 75%, 70%, and 48%, respectively (Scorsetti et al. 2016).

Staging of thymomas is based on the Masaoka system, initially proposed in 1981, with modifications in 1994 and 2011 (Masaoka et al. 1981; Koga et al. 1994; Detterbeck et al. 2011). The Masaoka staging system is shown in Table 5. Tumor stage and completeness of resection are the most important prognostic factors for thymomas (Scorsetti et al. 2016; Detterbeck and Parsons 2004). Five-year overall survival in stage I and II patients with a complete surgical resection is 90% (Scorsetti et al. 2016; Regnard et al. 1996). Stage III and IV patients with a complete surgical resection have reported 5-year overall survivals of 60% and 25%, respectively (Regnard et al. 1996). Only about 11% of thymoma patients present with stage IV disease, and 1–2% present with lymph node metastases (Scorsetti et al. 2016; Kondo and Monden 2003).

After concomitant diseases such as myasthenia gravis have been stabilized, surgery is the primary treatment for thymomas, with the goal of a complete en bloc resection. Median sternotomy is the standard approach for thymectomy (Toker

Table 5 Masaoka-Koga staging of thymomas with current modifications added by the International Thymic Malignancy Interest Group (ITMIG) indicated by the asterisk (*)

Stage	Definition
Stage I	Grossly and microscopically completely encapsulated tumor. * This includes tumors with invasion into but not through the capsule or tumors in which the capsule is missing but without invasion into surrounding tissues
Stage II	
IIa	Microscopic transcapsular invasion. * Microscopic transcapsular invasion (not grossly appreciated)
IIb	Macroscopic invasion into thymic or surrounding fatty tissue or grossly adherent to but not breaking through mediastinal pleura or pericardium * Gross visual tumor extension into normal thymus or perithymic fat surrounding the thymoma (microscopically confirmed), or * Adherence to pleura or pericardium making removal of these structures necessary during resection, with microscopic confirmation of perithymic invasion (but without microscopic extension into or through the mediastinal pleura or into the fibrous layer of the pericardium).
Stage III	Macroscopic invasion into neighboring organ (i.e. pericardium, great vessel or lung) * This includes extension of the primary tumor to any of the following tissues: * Microscopic involvement of mediastinal pleura (either partial or penetrating the elastin layer); or * Microscopic involvement of the pericardium (either partial in the fibrous layer or penetrating through to the serosal layer); or * Microscopically confirmed direct penetration into the outer elastin layer of the visceral pleura or into the lung parenchyma; or * Invasion into the phrenic or vagus nerves (microscopically confirmed, adherence alone is not sufficient); or * Invasion into or penetration through major vascular structures (microscopically confirmed); * Adherence (i.e., fibrous attachment) of the lung or adjacent organs only if there is mediastinal pleural or pericardial invasion (microscopically confirmed)
Stage IV	
IVa	Pleural or pericardial metastases * Microscopically confirmed nodules, separate from the primary tumor, involving the visceral or parietal pleural surfaces, or the pericardial or epicardial surfaces
IVb	Lymphogenous or hematogenous metastasis * Any nodal involvement (e.g., anterior mediastinal, intrathoracic, low/anterior cervical nodes, any other extrathoracic nodes) * Distant metastases (i.e., extrathoracic and outside the cervical perithymic region) or pulmonary parenchymal nodules (not a pleural implant)

Scorsetti et al. (2016)

et al. 2011). However, patients with more advanced thymomas may require more extensive resections, including sterno-thoracotomy, pleurectomy, partial or total pneumonectomy, or pericardiectomy (Scorsetti et al. 2016). The mean resectability rates for stage I, II, III, and IV thymomas are 100%, 85%, 47%, and 26%, respectively (Detterbeck and Parsons 2004). For unresectable thymomas, patients can be treated with neoadjuvant radiotherapy or chemotherapy in order to reduce tumor burden. Neoadjuvant radiotherapy has been reported to increase the rates of complete resection for stage III thymoma to 53–75% (Akaogi et al. 1996). Neoadjuvant radiotherapy is generally given concurrently with platinum-based chemotherapy. Alternatively, induction chemotherapy followed by surgery and adjuvant ChemoRT can be used in the management of thymomas (Venuta et al. 1997; Kim et al. 2004; Lucchi et al. 2005).

The role of adjuvant radiation therapy in the management of thymomas remains controversial. Because of the rarity of thymomas, there are no Phase III randomized trials that provide concrete data on the indications for radiation therapy in thymoma patients. The recurrence rate for stage I thymoma is approximately 3%, occurring at a mean interval of 10 years following surgical resection, and postoperative radiation therapy is not indicated for stage I thymomas (Scorsetti et al. 2016). Postoperative radiotherapy for stage I thymomas has no significant effect on recurrence or overall survival (Zhang et al. 1999).

Adjuvant radiotherapy is commonly administered to patients with stage III–IVA thymoma or those with an incomplete surgical resection (Scorsetti et al. 2016). This practice of delivering adjuvant radiotherapy following incomplete resection is based on small retrospective studies (Curran et al. 1988; Ciernik et al. 1994). The 1988 study by Curran et al. included 103 thymoma patients, 28 of which underwent biopsy or subtotal resection for stage III disease (Curran et al. 1988). Of these 28 patients, 20 underwent postoperative radiotherapy and 9 of 20 developed either local or distant recurrence. Ciernik et al. reported the survival rates of 31 stage III or IV thymoma patients receiving postoperative radiation therapy at doses ranging from 42 to 66 Gy, with 10-year overall survival being 57% and 8% for stage III and IV disease, respectively (Ciernik et al. 1994).

Outcomes of adjuvant radiotherapy following complete surgical resection have been reported in several studies, with mixed results. In a Japanese study, Haniuda et al. evaluated the recurrence rate of thymoma patients treated with complete tumor resection followed by adjuvant radiotherapy to 40–50 Gy. In this study, there was a significant improvement in local recurrence in patients with thymomas macroscopically adherent to the pleura that were treated with postoperative radiotherapy compared to those not treated with postoperative radiotherapy (0% vs. 36.4%, $p < 0.05$). However, postoperative radiotherapy did not significantly affect local recurrence in thymoma patients with microscopic pleural or pericardial invasion (Haniuda et al. 1996). Chen et al. showed no significant difference in disease-free survival or overall survival in stage II thymoma patients treated with or without postoperative radiotherapy. It was reported that histologic type B3 stage II thymomas have significantly worse disease-free survival compared to the other thymoma histologies (60.8% vs. 92.3% at 10 years, $p = 0.001$) (Chen et al. 2010). In a 2016 retrospective study from the Chinese Alliance for Research in Thymomas (ChART), overall survival and disease-free survival were actually worse in stage I–III thymoma patients who underwent complete resection and adjuvant radiotherapy compared to surgical resection alone. However, the ChART study showed improved overall and disease-free survival in patients with incomplete resections who received postoperative radiotherapy compared to those who were treated with surgery alone (Liu et al. 2016). In contrast to the ChART study, the meta-analysis by Zhou et al. showed improved overall survival in stage II and III thymoma patients treated with complete surgical resection and postoperative radiotherapy compared to surgery alone (Zhou et al. 2016).

Radiation doses for thymoma depend on the extent of resection. The general practice is to treat with 45–50 Gy for negative or close (<1 mm) margins, 54–60 Gy for microscopically positive

resection margins, and 60–70 Gy for gross residual disease or as definitive treatment (Komaki and Gomez 2014). Thymic carcinomas are often treated more aggressively with higher adjuvant radiation doses with or without concurrent chemotherapy (Yano et al. 1993; Ogawa et al. 2002; Hsu et al. 2002). Studies have shown adjuvant radiotherapy to improve disease-free survival with a trend toward improved overall survival (Yano et al. 1993; Hsu et al. 2002; Mao and Wu 2015).

In the neoadjuvant or definitive setting, the radiation field should cover the entire extent of disease as visualized on CT or PET imaging. In the adjuvant setting, any pretreatment scans should be fused to the CT simulation planning scan to cover the surgical bed and preoperative tumor volume. Elective nodes are generally not covered in the treatment volume. Four-dimensional CT (4D CT) should be used to improve target localization, and patients should undergo simulation in the supine position with their arms above their heads (Gomez and Komaki 2010; Gomez et al. 2011). Radiotherapy should be delivered by 3D conformal technique or IMRT to reduce the dose to the surrounding normal tissues. Because of its characteristic Bragg peak, proton beam radiation therapy can further reduce dose to normal structures. In a prospective study of 27 thymoma patients treated with proton beam therapy, no patient experienced grade ≥3 toxicity, and 3-year regional control and overall survival were 96% and 94%, respectively (Vogel et al. 2016).

Thymomas are uncommon tumors that are primarily managed surgically, though neoadjuvant or adjuvant radiotherapy can improve local control and is preferentially recommended for patients with stage III/IV tumors or those that are incompletely resected.

3 Malignant Pleural Mesothelioma

Malignant pleural mesothelioma (MPM) is a rare malignancy arising from the coelomic cavities of the body, including the pleura, peritoneum, pericardium, and tunica vaginalis (van Meerbeeck et al. 2011; Chen and Pace 2012). The vast majority of MPM occur in the pleura, with approximately 80% of MPM occurring in the visceral pleura and 20% occurring in the parietal pleura (van Meerbeeck et al. 2011; Chen and Pace 2012; Zhang et al. 2015). The median age at diagnosis is 72–74 years (Chen and Pace 2012). There are approximately 2,000–3,000 new cases of MPM in the United States annually, and about 80% of MPM patients are men (Chen and Pace 2012; Price and Ware 2009; Taioli et al. 2014). The incidence of MPM peaked in the early 1990s in the United States (Price and Ware 2009; Taioli et al. 2014). The predilection of men for MPM and the declining incidence are related to asbestos exposure and the subsequent asbestos ban.

Approximately 60% of patients with MPM present with dyspnea and chest wall pain (van Meerbeeck et al. 2011; Chen and Pace 2012; Robinson et al. 2005). Dyspnea is most commonly due to accumulation of pleural fluid in the thoracic cavity, and chest wall pain is due to invasion into the thoracic wall (van Meerbeeck et al. 2011). Patients can have phrenic nerve paralysis and concomitant impaired diaphragmatic movement (van Meerbeeck et al. 2011; Zhang et al. 2015). Other presenting symptoms include weight loss, fatigue, cough, chest wall pain, pneumothorax, and cardiac tamponade (van Meerbeeck et al. 2011; Chen and Pace 2012).

CT imaging generally reveals thickening of the pleura often with pleural plaques and calcifications (van Meerbeeck et al. 2011; Chen and Pace 2012; Zhang et al. 2015). MRI may be used preoperatively to assess for invasion into the chest wall or diaphragm (Zhang et al. 2015). Biopsy is generally performed via thoracoscopy (van Meerbeeck et al. 2011; Rodriguez 2015). The three most common histologic subtypes of MPM in the order of decreasing frequency are epithelial, biphasic, and sarcomatoid (Chen and Pace 2012; Zhang et al. 2015). Biphasic MPM consists of a combination of epithelial and sarcomatoid cells (Chen and Pace 2012).

The prognosis of MPM is dismal, with median overall survival (without treatment) ranging from 4 to 12 months (van Meerbeeck et al. 2011;

Zhang et al. 2015; Taioli et al. 2014; Flores et al. 2010). SEER data indicates a 5-year overall survival of approximately 9% (Chen and Pace 2012). MPM patients with epithelial histology have the most favorable prognosis, while patients with sarcomatoid histology have the worst prognosis (Herndon et al. 1998; Ray and Kindler 2009). Female gender, better performance status, and lower white blood cell count have been associated with improved survival (Chen and Pace 2012; Price and Ware 2009).

Optimal management of stage I–III medically operable MPM consists of either resection followed by sequential chemotherapy ± hemithoracic radiotherapy or neoadjuvant chemotherapy followed by surgical resection ± hemithoracic radiotherapy (de Perrot et al. 2009; Krug et al. 2009; Bolukbas et al. 2011; Thieke et al. 2015). Surgical resection consists of either extrapleural pneumonectomy (EPP) or pleurectomy/decortication (P/D); mediastinal nodal dissection is recommended with either procedure (Rice et al. 2011). EPP consists of removal of the involved pleura, lung, ipsilateral diaphragm, and pericardium. P/D consists of resection of the involved pleura and all gross tumor as a lung-sparing surgery. An extended P/D involves a total pleurectomy and resection of the diaphragm and pericardium. In many cases of MPM, a complete resection is not possible with either EPP or P/D (Hasani et al. 2009; Friedberg 2013). A meta-analysis by Cao et al. comparing extended P/D to EPP showed significantly lower perioperative mortality (2.9% vs. 6.8%, $p = 0.02$) and morbidity (27.9% vs. 62.0%, $p < 0.0001$) with extended P/D (Cao et al. 2014). Additionally, there was a trend toward improved median overall survival with P/D vs. EPP (13–29 months vs. 12–22 months, respectively) (Cao et al. 2014). Even among patients with early-stage MPM, there is a higher postoperative complication rate and worse long-term quality of life following EPP compared to P/D (Rena and Casadio 2012). Therefore, EPP tends to only be recommended on clinical trials and/or at specialized, high-volume surgical centers (van Zandwijk et al. 2013).

Chemotherapy alone may be recommended for patients with medically inoperable or metastatic MPM (Kelly et al. 2011; Blomberg et al. 2015). The preferred chemotherapy regimen used either alone or as a component of multimodality therapy is cisplatin/pemetrexed (Kondola et al. 2016). In a Phase III randomized trial in MPM patients who were not surgical candidates, cisplatin/pemetrexed significantly increased median survival compared to cisplatin alone (12.1 vs. 9.3 months, $p = 0.02$) (Vogelzang et al. 2003). In a multicenter randomized Phase III trial in patients with unresectable MPM, bevacizumab plus cisplatin/pemetrexed significantly improved median overall survival compared to cisplatin/pemetrexed alone (18.8 vs. 16.1 months, $p = 0.016$) (Zalcman et al. 2016).

Outside of a clinical trial, radiotherapy alone or in combination with chemotherapy is not recommended for MPM, as radiotherapy alone results in significant morbidity with no improvement in survival (McAleer et al. 2009). Historically, prophylactic radiotherapy has been administered to instrument insertion sites to prevent tumor seeding (Low et al. 1995; De Ruysscher and Slotman 2003). Boutin et al. showed significantly decreased local failure in MPM patients receiving 21 Gy in three fractions using 12.5–15 MeV electrons within 15 days of an invasive procedure compared to patients who did not receive radiotherapy (0% vs. 40%, $p < 0.001$) (Boutin et al. 1995). In contrast, a 2007 study using the same dose-fractionation regimen (with either photons or electrons) following a pleural invasive procedure showed no significant difference in local failure (O'Rourke et al. 2007). Both of the aforementioned trials were limited with small numbers of patients. In order to assess the utility of prophylactic irradiation to intervention sites, an ongoing multicenter Phase III trial in the United Kingdom plans to enroll 374 MPM patients to receive either 21 Gy in three fractions or no radiotherapy directed at instrumentation sites (Bayman et al. 2016).

Local failure after surgical resection of early MPM ranges from 30% to 60% (McAleer et al. 2009). Therefore, adjuvant radiotherapy may be administered after EPP or P/D. Several prospective studies have evaluated the outcomes of adjuvant radiotherapy following EPP (Yajnik et al.

2003; Flores et al. 2006; Pagan et al. 2006; Rea et al. 2007; Batirel et al. 2008; Tonoli et al. 2011). The recommended adjuvant dose after EPP is 45–54 Gy for negative margins or 54–60 Gy for positive margins. In a study from Memorial Sloan-Kettering Cancer Center, 54 MPM patients received adjuvant EBRT 3–5 weeks after EPP. A total dose of 54 Gy was administered via anterior and posterior fields in 30 daily fractions of 1.8 Gy with spinal cord blocks after 41.4 Gy. Liver, heart, and stomach blocks were all added, and the pleural/diaphragm dose in these blocked regions was supplemented with electrons. Median overall survival was 33.8 months for stage I and II patients and 10 months for stage III and IV patients. Radiotherapy was well tolerated, with most toxicities being of grades 1 and 2 (Rusch et al. 2001).

IMRT has also been used to deliver adjuvant radiotherapy following EPP in an effort to improve dose conformality to the target volume and decrease dose to normal structures (Chi et al. 2011). The clinical target volume (CTV) is usually defined as all surgically violated areas and clips, including the thoracic wall, diaphragm, pleural reflections, deep margin of the incision, and ipsilateral mediastinal nodes (Tonoli et al. 2011; Ahamad et al. 2003). In a study from MD Anderson Cancer Center, 86 patients who received EPP for MPM underwent adjuvant IMRT. The CTV dose was 45–50 Gy, with a boost to 55–60 Gy for areas at high risk for recurrence or positive margins. Median survival and 1-year survival were 14.6 months and 55%, respectively. There were five patients who experienced treatment-related death due to pulmonary toxicity (Gomez et al. 2013b). In an Italian study from 2011, 50 MPM patients received IMRT after EPP. The dose was 45–50 Gy in 25 fractions given to the affected hemithorax and ipsilateral mediastinum. A simultaneous integrated boost to 60 Gy was given to sites of involved margins. Three-year overall survival and disease-free survival rates were 57% and 60%, respectively (Tonoli et al. 2011). In a 2016 study of 62 MPM patients, hypofractionated IMRT of 25 Gy in five daily fractions delivered 6–8 days prior to EPP showed median overall and disease-free survivals of 51 months and 47 months, respectively (de Perrot et al. 2016). However, 39% of the patients developed grade 3 or higher complications (de Perrot et al. 2016).

More modern series report on the use of adjuvant radiotherapy following P/D and chemotherapy with reasonable results and acceptable toxicity. These studies report median survival of 23.3–28.4 months and grade ≥3 pulmonary toxicity rates of 8–20% (Rosenzweig et al. 2012; Patel et al. 2012; Chance et al. 2015). The largest study by Minatel et al. reported on 69 patients treated with either extended P/D or partial pleurectomy followed by chemotherapy and postoperative IMRT. The IMRT dose was 50 Gy in 25 fractions with a boost to 60 Gy in 30 fractions for areas at risk for residual disease. Two-year locoregional control was 65% and 64%, and overall survival was 65% and 58% with extended P/D and partial pleurectomy, respectively (Minatel et al. 2015).

Palliative radiotherapy can be used to treat chest wall pain from MPM with doses of 20–40 Gy in fractions of 4 Gy (Macleod et al. 2014; Taioli et al. 2015). Several retrospective and Phase II studies evaluating palliative radiotherapy for pain control in pleural MPM have been published (Bissett et al. 1991; Davis et al. 1994; de Graaf-Strukowska et al. 1999; El Hossieny et al. 2010; Jenkins et al. 2011). de Graaf-Strukowska et al. reported improved pain relief with a median dose of 36 Gy in 4 Gy per fraction compared to a median dose of 30 Gy in 2 Gy per fraction (de Graaf-Strukowska et al. 1999).

MPM is a devastating disease with a poor prognosis. The mainstay of treatment is surgery for resectable disease and chemotherapy for unresectable or metastatic disease. Adjuvant radiotherapy following EPP or P/D can be delivered for patients who have responded favorably to surgery and chemotherapy though it should preferably be performed on a clinical trial and/or at high-volume centers.

Conclusion

There are numerous areas of controversy regarding the treatment of lung cancer and uncommon thoracic malignancies like thymoma and MPM. Ongoing clinical trials will hopefully provide answers to several of these

controversies. Much work is still needed to develop clinical studies, novel therapeutics, and biomarker-driven therapies to improve the outcomes for our patients.

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