

Treatment of Locally Advanced Non–Small Cell Lung Cancer



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KEYWORDS

• Non–small cell lung cancer • Chemoradiation • Locally advanced disease

KEY POINTS

- Stage III non–small cell lung cancer (NSCLC) is a heterogeneous disease.
- Concurrent chemoradiation with platinum/etoposide and carboplatin/paclitaxel is the standard of care for unresectable disease.
- 60 Gy in standard fractionation remains the standard of care for radiation dose.
- Integration of novel immunotherapeutic and molecular targeted therapies is a promising area of investigation.

INTRODUCTION

Stage III NSCLC comprises the most heterogeneous group of patients and accounts for one-third of all patients diagnosed with lung cancer. Despite this heterogeneity, chemoradiation is the treatment of choice for the majority of patients. The 2-year and 5-year overall survival (OS) rates are estimated at 55% and 36%, respectively, for patients with stage IIIA disease and 34% and 19%, respectively, for patients with stage IIIB disease.¹

PATIENT EVALUATION

To accurately classify a patient within this diverse stage, a comprehensive work-up is imperative. After a thorough history and physical examination, staging focuses on the pathologic and radiographic assessment of primary and/or nodal disease and assessment of a patient's physiologic reserve and expected tolerance to planned therapies.

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Initial imaging includes a computerized tomography (CT) of the chest to delineate local and regional disease and anatomic relationship to normal thoracic structures, whole-body positron emission tomography (PET)/CT for regional and distant staging, and a brain magnetic resonance imaging (MRI) to evaluate for intracranial metastases. Pathologic disease confirmation should be obtained from the most accessible tumor site, whether primary or nodal. Primary tumors may be accessed by CT-guided fine-needle aspiration or core biopsy, surgically via video-assisted thoracoscopic surgery, or by endobronchial ultrasound-guided fine-needle aspiration for centrally located tumors adjacent to bronchus. Nodal deposits may be accessed via endobronchial ultrasound (levels 2R/2L, 4R/4L, 7, and 10R/10L), esophageal ultrasound (levels 5, 7, 8, and 9), mediastinoscopy, mediastinotomy, or video-assisted thoracoscopic surgery.

If surgical management is being considered, comprehensive pathologic mediastinal staging is recommended (Fig. 1) especially because the rates of both false-positive and false-negative PET/CT interpretations for mediastinal nodes remain high. A meta-analysis of 28 studies, including 3255 patients, identified sensitivity and specificity of 0.67 and 0.87, respectively, for PET/CT in the nodal staging of NSCLC.² Patients with bulky, multistation mediastinal adenopathy less commonly undergo comprehensive pathologic nodal staging and are managed nonsurgically. Biopsy of

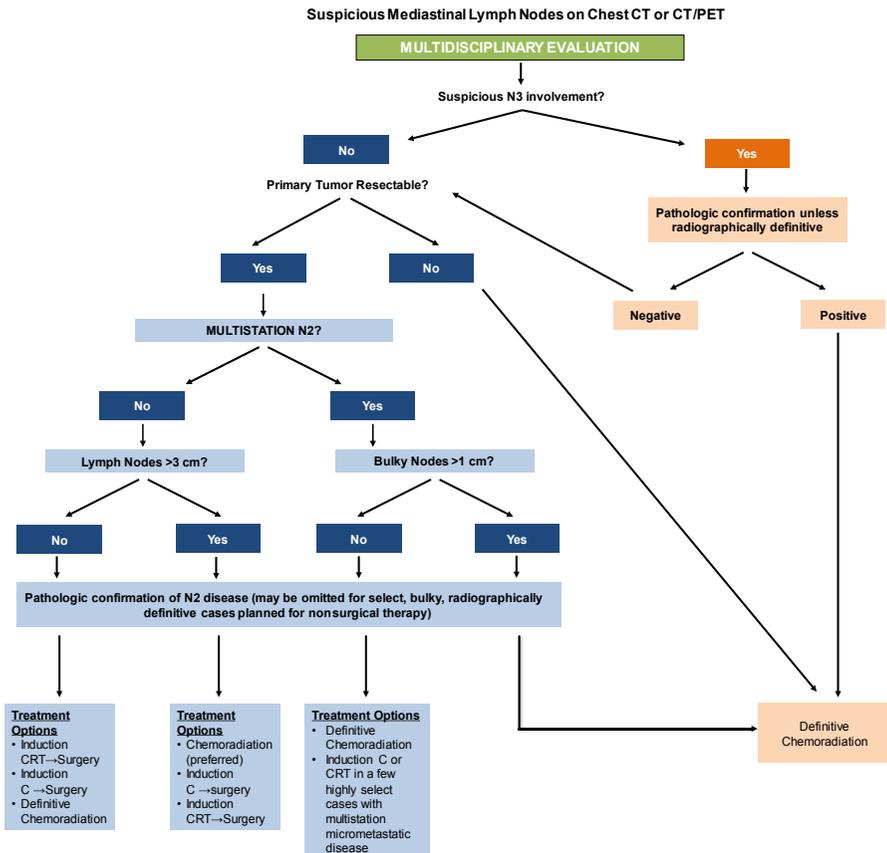


Fig. 1. Recommended evaluation and treatment strategy for patients with radiographically suspicious mediastinal nodes. C, chemotherapy; CRT, chemoradiotherapy.

radiographically borderline nodes in nonoperative patients, however, may also have an impact on radiation therapy target delineation for definitive chemoradiation.

For patients under consideration for surgical resection, assessment of performance status, pulmonary reserve, and comorbidities is crucial. Pulmonary function tests with spirometry and diffusion capacity are a standard component of a presurgical work-up and are a helpful baseline prior to nonsurgical therapy. Threshold values for resectability vary among surgeons, but an estimated postoperative forced expiratory volume in the first second of expiration or diffusing capacity of the lungs for carbon monoxide of less than 30% indicates an increased risk for complications after resection. Low-technology exercise tests, including stair climbing and shuttle walk, as well as cardiopulmonary exercise tests, are also used to determine expected operative risk.³

RESECTABLE STAGE III NON–SMALL CELL LUNG CANCER

The role of surgery in the treatment of stage III NSCLC remains controversial. A small body of evidence suggests that a subset of patients with pathologic N2 disease may benefit from surgery after induction chemoradiotherapy or chemotherapy. The most persuasive data come from a subset analysis of the North America Intergroup trial (INT0139; Radiation Therapy Oncology Group [RTOG] 9039)⁴; 429 patients were randomized to receive 2 cycles of cisplatin/etoposide (PE) concurrently with 45 Gy radiation followed by surgery or continued radiation to 61 Gy. There was no survival difference between the 2 arms but a subset analysis by the extent of surgery showed a significant survival advantage for patients undergoing lobectomy, with a median survival (MS) of 34 months after lobectomy versus 22 months for the nonsurgical arm ($P = .002$) and a 5-year OS of 36% versus 18%, respectively. Patients undergoing pneumonectomy had a nonsignificant but numerically worse outcome, with an MS of 19 months with surgery compared with 29 months without surgery and 5-year OS rates of 22% versus 24%, respectively. A higher than expected perioperative mortality in the pneumonectomy arm of 26% contributed to these results. In addition to the extent of surgical resection, retrospective analyses show that the number and size of involved nodes and nodal response to induction are important factors. Lymph node(s) greater than or equal to 1 cm on CT (clinical N2 disease), multistation involvement, or nodes greater than 3 cm portend survival decrements,⁵ and mediastinal tumor clearance with induction therapy is associated with prolonged survival.^{4,6,7} In INT0139, patients who cleared their mediastinal disease (N0) had an MS of 34.4 months compared with 26.4 months for patients with N1–N3 or unknown N status.⁴ Based on these data, it is recommended that patients undergo repeat pathologic evaluation of the mediastinum prior to definitive surgery; if disease is found, the resection should be aborted and the patient should receive or complete definitive chemoradiation.

The optimal induction regimen is unknown. A randomized phase III trial conducted by the Swiss Group for Clinical Cancer Research evaluated induction docetaxel and cisplatin versus docetaxel plus cisplatin followed by radiotherapy in resectable pathologically proved stage III N2 disease.⁸ There was no difference in event-free survival between the arms, suggesting chemotherapy alone was sufficient prior to resection. The trial had several limitations, however, including its small sample size, 11 years of accrual, sequential radiotherapy design, and lack of an OS endpoint. Several attempts to conduct randomized trials comparing the 2 approaches have failed due to poor accrual. Current guidelines allow for chemotherapy alone or chemoradiation as the induction regimen. For patients treated without neoadjuvant radiotherapy, adjuvant postoperative radiotherapy (PORT) may be considered after surgical management of N2 disease. A large meta-analysis, including 2128 patients from

9 randomized trials, identified a survival decrement to the use of PORT for N0–N1 patients with no apparent survival impact for N2 disease, although many of the analyzed trials used outdated radiation techniques, including cobalt.⁹ Subsequent population-based studies using modern radiation techniques have suggested a small OS benefit to the use of PORT for N2 disease.^{10,11} It is anticipated that the currently accruing Lung Adjuvant Radiotherapy Trial trial in Europe, in which resected N2 patients are randomized between PORT and no PORT, should provide a definitive answer to this question. All patients should be discussed at a multidisciplinary tumor board and a tailored treatment plan devised.

UNRESECTABLE STAGE III NON–SMALL CELL LUNG CANCER

A majority of patients with stage III disease are unresectable. Radiation as monotherapy cures fewer than 10% of patients.¹² Multiple studies show that patients with unresectable disease may achieve long-term survival when radiation therapy is combined with chemotherapy (Table 1). The landmark study performed by Dillman and colleagues¹³ demonstrated a 4-month improvement in MS and a doubling of long-term survivors after induction chemotherapy with cisplatin and vinblastine followed by thoracic radiation compared with radiation therapy alone. RTOG and the Eastern Cooperative Oncology Group conducted a confirmatory trial that favored the combination arm. The results were also corroborated by a French multicenter randomized study.¹⁴ Based on the positive results from these 3 trials, the addition of chemotherapy to radiotherapy became the standard of care for the management of locally advanced NSCLC.

Timing of Chemotherapy and Radiotherapy

The next set of studies investigated timing of chemotherapy and radiation (Table 2). The West Japan Thoracic Oncology Group was the first to demonstrate that concurrent compared with sequential chemoradiation significantly improved response rate and survival.¹⁵ Confirmatory trials performed by cooperative groups in France,¹⁶ the Czech Republic,¹⁸ and the United States (RTOG 9410),¹⁹ also showed a survival

Table 1
Phase III trials comparing induction chemotherapy followed by radiation therapy versus radiation therapy alone

Author, Reference	N	Treatment	Median Survival (mo)	2 y Overall Survival (%)	5 y Overall Survival (%)	P Value
Dillman et al, ¹³ 1990	78	Cisplatin-vinblastine + radiation therapy	13.8	26	19	$P = .0066$
	77	RT alone	9.7	13	7	
Sause et al, ¹⁴ 2000	149	Cisplatin-vinblastine + radiation therapy	13.2	32	8	$P = .04$
	152	RT alone	11.4	21	5	
Le Chevalier et al, ¹⁷ 1994	176	Cisplatin-vindesine-cyclophosphamide-lomustine + radiation therapy	12	21	11 ^a	$P = .08$
	177	Radiation therapy alone	10	14	5 ^a	

^a 3-Year data.

Table 2
Phase III trials comparing concurrent versus sequential chemoradiation

Author, Reference	N	Treatment	OR (%)	Median Survival (mo)	2 y Overall Survival (%)	5 y Overall Survival (%)	P Value
Furuse et al, ¹⁵ 1999	156	Concurrent	84	16.5	34.6	15.8	<i>P</i> = .03998
	158	Sequential	66.4	13.3	27.4	8.9	
Fournel et al, ¹⁶ 2005	100	Concurrent	49	16.3	39	21 ^b	<i>P</i> = .24
	101	Sequential	54	14.5	26	14 ^b	
Zatloukal et al, ¹⁸ 2004	52	Concurrent	80	16.6	34.2	18.6 ^a	<i>P</i> = .023
	50	Sequential	47	12.9	14.3	9.5 ^a	
Curran et al, ¹⁹ 2011	193	Concurrent	70	17	—	16	<i>P</i> = .46
	195	Sequential	61	14.6	—	10	

Abbreviation: OR, overall response.

^a 3-Year data.

^b 4-Year data.

benefit for the concurrent approach. A meta-analysis of concurrent versus sequential chemoradiation data from 6 randomized trials involving 1205 patients with median follow-up of 6 years demonstrated a significant survival benefit for concurrent chemoradiation (hazard ratio 0.84; 95% CI, 0.74–0.95; *P* = .004), with an absolute benefit of 5.7% at 3 years and 4.5% at 5 years.²⁰ Based on these results, concurrent therapy is considered standard for good-performance status patients. Sequential chemoradiation remains an option for patients with a marginal performance status, and poor-performance patients are typically treated with radiation alone.

Selection of Chemotherapy Regimen

All cytotoxic chemotherapy agents used to treat metastatic lung cancer exhibit radiosensitizing properties. Based on a small study evaluating PE with concurrent radiation that demonstrated a doubling of survival compared with historical data and the encouraging results with this combination in a Southwest Oncology Group (SWOG) trial in limited-stage small cell lung cancer,^{21,22} PE was chosen for subsequent phase III studies. Trials evaluating second-generation agents (taxanes, vinorelbine, gemcitabine, and irinotecan) in combination with cisplatin or carboplatin concurrently with radiation^{23–25} were also conducted. Weekly paclitaxel and carboplatin emerged as a well-tolerated and efficacious regimen. The most recent phase III randomized trial evaluating the modern regimen pemetrexed and cisplatin followed by pemetrexed consolidation versus standard chemoradiotherapy with PE in patients with nonsquamous histology was stopped early for futility (Table 3)²⁶ after randomization and treatment of 555 patients. OS for the pemetrexed and cisplatin arm was found not superior to the PE arm. As a result of these studies, concurrent weekly paclitaxel and carboplatin or cyclic PE remain the most commonly administered regimens.

Role of Induction, Consolidation, and Maintenance Systemic Therapy

Despite improvements in both MS and OS using concurrent chemoradiation, efforts to improve the still high rates of distant failure using induction or consolidation chemotherapy were undertaken (Table 4). The Cancer and Leukemia Group B 39801 randomized patients to chemoradiation alone with weekly carboplatin and paclitaxel or 2 cycles of induction carboplatin and paclitaxel followed by the identical chemoradiotherapy.²⁷ The results failed to show a benefit for induction chemotherapy. An induction approach is, however, a plausible strategy to evaluate in patients whose tumors

Trial, Reference	N	Treatment	Median Survival (mo)	95% CI	2 y Overall Survival (%)	3 y Overall Survival (%)	P Value
RTOG 0617 ³⁴	217	Standard-dose radiation therapy (60 Gy)	28.7	24.1–36.9	57.6	—	<i>P</i> = .04
	207	High-dose radiation therapy (74 Gy)	20.3	17.7–25	44.6	—	
	237	With cetuximab	25	20.2–30.5	52.3	—	<i>P</i> = .29
	228	No cetuximab	24	19.8–28.6	50.1	—	
PROCLAIM ²⁵	301	Concurrent chemoradiation with pemetrexed-cisplatin followed by consolidation pemetrexed	26.8	0.79–1.2	52	40	<i>P</i> = .831
	297	Concurrent chemoradiation with PE followed by consolidation chemotherapy	25	—	52	37	

have an epidermal growth factor receptor (EGFR) sensitizing mutation or an anaplastic lymphoma kinase (ALK) fusion given the exceptional efficacy of tyrosine kinase inhibitors in stage IV disease. The RTOG 1306 is an ongoing randomized phase II trial of induction erlotinib or crizotinib for 12 weeks followed by standard treatment using weekly paclitaxel/carboplatin or cyclic PE with radiation versus standard treatment alone.

Author/Trial	N	Treatment	Median Survival (mo)	95% CI	2 y Overall Survival (%)	3 y Overall Survival (%)	P Value
CALGB 39801 (induction)	184	Induction followed by concurrent chemoradiation	14	11–16	31	23	<i>P</i> = .3
	182	Concurrent chemoradiation	12	10–16	29	19	
Hanna (consolidation)	73	Concurrent chemoradiation followed by 3 cycles of docetaxel	21.2	—	—	27.1	<i>P</i> = .883
	74	Observation	23.2	—	—	26.1	
S0023 (maintenance)	118	Gefitinib	23	17–29	46	—	<i>P</i> = .013
	125	Placebo	35	25–40	59	—	
START (maintenance)	829	Tecemotide	25.6	22.5–29.2	51	40	<i>P</i> = .123
	410	Placebo	22.3	19.6–25.5	46	37	

The role of consolidation therapy was initially studied by SWOG. They reported an impressive 26-month MS and 3-year OS of 37% in 83 patients with stage IIIB disease after standard PE with radiation therapy followed by 3 cycles of docetaxel.²⁸ A randomized phase III trial, however, by the Hoosier Oncology Group and US Oncology Network using the identical SWOG regimen did not demonstrate a survival advantage for consolidation docetaxel.²⁹ Although there is no evidence to support consolidation chemotherapy, most physicians consider consolidation therapy if weekly radiosensitizing paclitaxel/carboplatin is used to address potential micrometastatic disease.

Building on the docetaxel consolidation backbone, SWOG undertook an evaluation of maintenance gefitinib. The S0023 trial randomized patients to gefitinib or placebo after concurrent chemoradiation with PE followed by docetaxel. Patients treated with gefitinib had inferior survival that remains unexplained but was not due to toxicity.³⁰ Another randomized study, the START (Stimulating Targeted Antigenic Response to NSCLC trial, evaluated tecemotide, a MUC1 antigen-specific immunotherapy that induces a T-cell response to MUC1, a commonly overexpressed antigen on lung cancer cells. Patients were randomized to maintenance tecemotide after concurrent or sequential chemoradiation. OS was similar in the 2 arms.³¹

Radiation Dose and Fractionation

Multiple early phase I and II nonrandomized trials suggested safety and efficacy of radiation dose escalation with thoracic radiation as monotherapy for NSCLC.³² RTOG 0117 was designed to determine the maximum tolerated radiation dose in the setting of concurrent chemotherapy.³³ A maximum tolerated dose of 74 Gy in 37 fractions was identified using 3-D conformal radiation therapy (3DCRT) with concurrent paclitaxel and carboplatin. This dose was found well tolerated with a low rate of acute and late toxicities.

This dose fractionation schedule was then tested in a phase III randomized comparison with 60 Gy in 30 fractions with concurrent carboplatin and paclitaxel, RTOG 0617 (see [Table 3](#)). After the phase II study RTOG 0324 identified an impressive median OS of 22.7 months with the addition of cetuximab,³⁴ RTOG 0617 was modified to 2 × 2 factorial design to also evaluate the addition of cetuximab to chemoradiation. An interim analysis did not reveal benefit to high-dose radiation therapy (74 Gy) and the high-dose arms were closed. The randomization to cetuximab arms continued to completion and found similar OS with or without cetuximab. Further analysis of the radiation dose comparison suggested potential harm from 74 Gy.³⁵ In light of these results, 60 Gy in standard fractionation remains the standard-of-care dose for the treatment of locally advanced NSCLC with concurrent chemotherapy.

Radiation Techniques

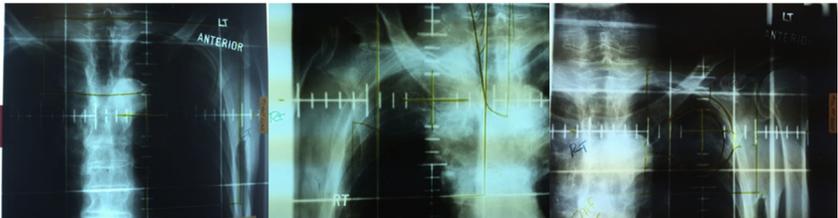
Radiotherapy techniques for locally advanced lung cancer have markedly evolved over the past 2 decades. Historically, 2-D radiation therapy was used to treat locally advanced NSCLC, using simple field arrangements based on bony anatomic landmarks on plain films. CT-based simulation has gradually replaced 2-D radiation therapy planning, allowing accurate target delineation on axial CT slices and use of 3DCRT planning with multiple conformal beams shaped to the target volume. 4-D CT, a technique in which images are acquired at each table position for a full respiratory cycle, has been widely implemented to allow accurate assessment of respiratory tumor motion. Target delineation is also enhanced by the routine use of PET/CT staging. With improved imaging, there has been a reduction in the use of elective nodal irradiation in recent years, and retrospective and population-based studies do not suggest an excess of isolated regional failures with this approach.^{36,37}

Planning techniques have transitioned from 2-D to 3-D, with more recent implementation of intensity-modulated radiotherapy (IMRT). IMRT uses inverse planning with modulated beams to conformally sculpt dose around irregular target volumes (Fig. 2). Planning studies suggest the potential for IMRT to reduce dose to critical structures, including heart, lung, and spinal cord.³⁸ Clinical data supporting its routine use for locally advanced NSCLC, however, are limited. Several retrospective studies suggest reduced rates of pneumonitis after treatment with IMRT.^{39,40} A nonrandomized, exploratory analysis from RTOG 0617 identified significantly less decline in patient-reported quality of life after treatment with IMRT compared with 3DCRT up to 1 year after completion of treatment.⁴¹ Several population-based studies have failed, however, to demonstrate a clear survival or toxicity benefit to IMRT for the treatment of NSCLC.^{42–44} There are no completed, prospective randomized trials comparing IMRT to 3DCRT for any thoracic malignancy.

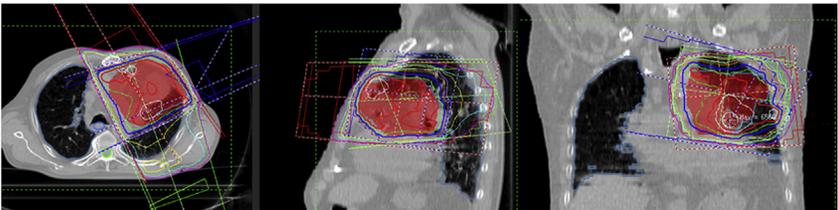
TREATMENT COMPLICATIONS

Although it is difficult to isolate the side effects from each component, chemotherapy is typically associated with cytopenias and nausea and vomiting. Radiation is associated with esophagitis, cough, pneumonitis, fatigue, dermatitis, and myelosuppression. Late toxicities from radiation include chronic lung fibrosis, esophageal strictures, cardiac toxicity, brachial plexopathy, and rarely radiation-induced myelopathy.

A



B



C

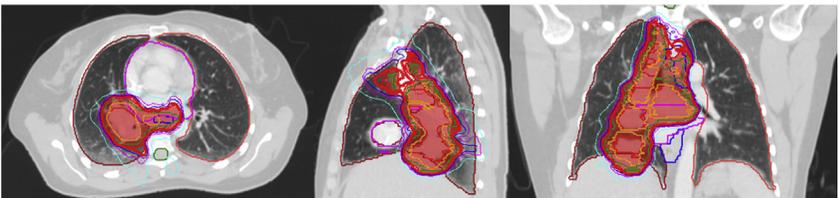


Fig. 2. The evolution of radiation planning for lung cancer. (A) 2-D simulation radiographs. (B) 3DCRT conformal plan using CT with 3 fields. (C) IMRT plan.

of the spinal cord. Overall both regimens are safe and tolerable. Chemotherapy side effects can be managed with dose reductions, dose delays, and supportive care measures. Granulocyte stimulating factors are a contraindication with concurrent therapy.

Esophagitis is typically the most prominent acute side effect observed with thoracic radiotherapy. Management is symptom directed, including antacids; topical anesthetics, such as viscous lidocaine; and narcotic and non-narcotic pain medications. Radiation pneumonitis is a common and potentially fatal subacute complication that manifests with shortness of breath, cough, and low-grade fevers. Risk factors include volume of lung receiving greater than or equal to 20 Gy (V20), the volume of lung receiving 5 Gy (V5), mean lung dose,^{45,46} the use of carboplatin/paclitaxel chemotherapy, and increasing age.⁴⁷ Symptomatic radiation pneumonitis is managed with oral prednisone over a slow taper of 4 to 8 weeks, with supplemental oxygen as necessary. Historically, limited attention was given to cardiac dosimetry during treatment because cardiac complications were believed to predominantly manifest years to decades after treatment. A secondary analysis of RTOG 0617 identified the volume of the heart receiving 5 Gy (V5) and 30 Gy (V30) as major predictors of mortality.³⁵ These results suggest cardiac dosimetry should be a significant consideration in the treatment planning process.

SURVEILLANCE

Unfortunately, a majority of patients develop distant metastases, local recurrence, or both. The current National Comprehensive Cancer Network guidelines recommend a history and physical examination and chest CT every 6 to 12 months for 2 years followed by a low-dose CT annually thereafter, noting that patients with residual imaging abnormalities after treatment may require more frequent imaging. National Comprehensive Cancer Network guidelines suggest PET/CT or brain MRI is not warranted, although PET/CT may be useful to differentiate radiation fibrosis or consolidation from malignancy identified on CT. Localized recurrences are occasionally amenable to definitive intent reirradiation, but long-term disease control is rare.⁴⁸ Whether earlier detection of local failure would increase cure rates remains speculative. Distant metastases are treated with the appropriate systemic regimen.

SUMMARY

Stage III NSCLC is the most challenging stage of lung cancer to treat due to its heterogeneous makeup. Additional factors, such as comorbidities, cardiopulmonary reserve, and performance status, add to this complexity. It is essential that stage III patients undergo multidisciplinary evaluation and treatment planning to ensure optimal therapy is selected for each patient.

Although there have not been therapeutic advances in the treatment of stage III NSCLC in recent years, there is a renewed optimism for near-term advances based on exciting new therapies to treat metastatic disease and in radiation planning and delivery. Thus, the continued evaluation of integrating novel systemic agents and defining optimal radiation doses and schedules remain the backbone of research efforts. The proved benefit of immunotherapy in stage IV lung cancer warrants evaluation in earlier stages of lung cancer. The PACIFIC study is a randomized phase III, double-blinded, international trial to evaluate the efficacy and safety of durvalumab, an antiprogrammed death ligand 1 antibody in patients with unresectable stage III NSCLC who have not progressed after definitive, platinum-based, concurrent chemoradiation. It is likely that immune checkpoint inhibitors are the first of many novel immune agents that will be evaluated in the coming years. Another interesting class of

agents being examined is DNA repair inhibitors. SWOG is conducting a phase I/II trial evaluating the addition of the poly-ADP-ribose polymerase inhibitor veliparib to concurrent chemoradiation as a potential chemosensitizer and radiosensitizer. In addition, the discovery of predictive biomarkers and imaging tools that would allow tailoring therapy is being pursued.

Despite the disappointing results from RTOG 0617, there remains substantial interest in dose escalation for locally advanced NSCLC, given the high rates of locoregional failure and associated symptom burden. Hypofractionation, the delivery of larger than the conventional 2 Gy daily fractions to achieve a higher biologic effective dose, is one area of particular interest. The currently accruing RTOG 1106 uses modest hypofractionation with 2.2 Gy fractions over the first 21 fractions, coupled with midtreatment target volume reduction and adaptive replanning, followed by a hypofractionated boost dose individualized based on normal tissue dose-volume metrics. In aggregate, current prospective trials seek to bring systemic advances realized for metastatic disease to patients with locally advanced NSCLC and to personalize local therapy based on patient and tumor-specific metrics.

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