Locally Advanced Non-small Cell Lung Cancer: The Past, Present, and Future

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Abstract: Approximately a third of patients with newly diagnosed non-small cell lung cancer (NSCLC) have locally or regionally advanced disease not amenable for surgical resection. Concurrent chemoradiation is the standard of therapy for patients with unresectable locally advanced NSCLC who have a good performance status and no significant weight loss. Prospective studies conducted over the past two decades have addressed several important questions regarding systemic therapy and thoracic radiation. They include the role of induction/consolidation chemotherapy, integration of newer chemotherapy agents with radiation and the impact of molecularly targeted agents. Improved radiation therapy techniques and precise targeting of the tumors have played a key role in this setting. Moreover, it has been shown that higher than conventional doses of thoracic radiation can be administered safely in combination with chemotherapy. This review will discuss these issues in detail and outline the strategies that need to be employed to improve the outcomes in patients with locally advanced NSCLC.

Key Words: Stage III NSCLC, Locally advanced NSCLC, Chemoradiation.

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Approximately one third of patients with non-small cell lung cancer (NSCLC) are diagnosed with locally or regionally advanced unresectable disease at presentation. Combined modality therapy with chemoradiation is the standard of care for patients with unresectable locally advanced NSCLC who have a good performance status and no significant weight loss. There is no universally agreed definition of "unresectable locally advanced NSCLC." Many physicians would consider patients with primary tumors involving major blood vessels and vertebral body or those with multistation mediastinal lymph node involvement to have unresectable locally advanced NSCLC. Prospective clinical trials conducted over the past three decades have firmly established the beneficial role of chemotherapy and radiation over radiation alone in this disease. The progress has been slow; nonetheless, the 3-year survival rate has steadily increased from less than 10% to over 25% in some trials over the past thirty years.[1] Although some of the improvement could be attributed to refined and improved staging chiefly secondary to the widespread use of fluorine-18 (F-18) dexoyglucose positron emission tomography (FDG-PET), advances in radiation therapy planning and improved delivery of chemotherapy certainly have contributed to the modest success. Disappointingly, recent studies have demonstrated no improvement in survival with the use of docetaxel consolidation therapy after concurrent chemoradiation and detrimental effect with the addition of gefitinib maintenance therapy. This conceptual review will summarize briefly the seminal studies conducted in the past two decades, address the current areas of research and explore potential avenues for future research.

PROGNOSTIC FACTORS IN PATIENTS WITH LOCALLY ADVANCED NSCLC

Locally advanced stage III NSCLC comprises a heterogeneous group even if one applies the readily available demographic and clinical features without considering the inherent and as yet poorly defined biologic characteristics.[2] These clinical characteristics include number of nodes and nodal stations involved, size of primary tumor, baseline pulmonary function, gender, presence or absence of significant weight loss, and performance status. Patients with microscopic N2 disease involving a single station or two stations have a better outcome than those with contralateral or supraclavicular lymph node (N3) involvement.[2] In a prospective study of 203 patients with locally advanced NSCLC, 10 prognostic factors including age, sex, ethnicity, smoking status, performance status, body mass index, forced expiratory volume in 1 minute (FEV1), use of baseline FDG-PET scan, stage (IIIA versus IIIB), and baseline hemoglobin were analyzed to find out the factors associated with better outcomes.[3] In a multivariate analysis, baseline hemoglobin ($\geq$12 g/dl) and FEV more than 2 L predicted favorable outcomes in patients treated with chemoradiation. Apart from known clinical characteristics, molecular aberrations very likely play an important role in determining outcomes and responses to

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chemotherapy and radiation. Global genomic studies have correlated signature patterns associated with poor outcomes in patients with resected NSCLC.[4,5] Moreover, resistance to platinum agents has been associated with expression levels of key proteins involved in DNA repair.[6,7] Although no such studies have been done exclusively in patients with unresectable locally advanced NSCLC, it is likely that such an approach could potentially identify those with inherently unfavorable biology and those who are unlikely to respond to platinum based therapy.

CHEMOTHERAPY ISSUES IN STAGE III NSCLC

Several prospective studies conducted over the past two decades have clearly demonstrated the superiority of concurrent chemoradiation over sequential chemotherapy followed by radiation in patients with locally advanced NSCLC who have a good performance status and no significant weight loss (Table 1).[1,8–14] However severe toxicities (chiefly esophageal) associated with concurrent chemoradiation are more commonly seen than with sequential chemotherapy followed by radiation. Clinical trials conducted over the past several years have addressed some important questions with regard to systemic therapy. They include the role of consolidation chemotherapy after concurrent chemoradiation, use of induction chemotherapy administered before concurrent chemoradiation, the optimal strategy for using chemotherapy (radiosenitizing low dose versus systemically active dose) in conjunction with radiation and finally the role of molecularly targeted agents in the treatment of locally advanced NSCLC.

Consolidation Chemotherapy

Because administration of docetaxel improves survival over best supportive care for patients with progressive disease after initial treatment with platinum based chemotherapy, a phase II study was conducted by the Southwest Oncology Group (SWOG) to test the efficacy of docetaxel as consolidation therapy in patients with locally advanced NSCLC after treatment with concurrent cisplatin, etoposide, and thoracic radiation.[15] This study reported an impressive median survival of 26 months and a 5-year survival of 29% in 83 patients with stage III B NSCLC. These results seemed particularly striking when compared with SWOG's historic control from a similar study (with cisplatin/etoposide consolidation) where the median survival was only 15 months and a 5-year survival of 15%.[16] A randomized study conducted by the Hoosier Oncology Group (HOG) enrolled 203 patients with locally advanced NSCLC to cisplatin, etoposide, and thoracic radiation and randomized 147 patients who completed chemoradiation to observation or three cycles of consolidation docetaxel.[17] The study was closed prematurely following a planned interim futility analysis conducted by the Data Safety Monitoring Board. The overall median survival for the entire population of 203 patients was 21 months. Addition of docetaxel did not improve overall survival (primary end point) or progression free survival. However treatment related severe toxicities (chiefly neutropenic fever and pulmonary toxicities) were predictably higher with docetaxel compared with observation alone. Consequently, docetaxel consolidation was associated with more treatment related death associated (5%) than with observation alone (0%, $p = 0.058$). A preliminary analysis of the population studied by SWOG and HOG failed to identify any clinical or demographic features that could have accounted for the disappointing results seen with docetaxel consolidation in the HOG trial (Table 2). The eligibility criteria between the SWOG and HOG studies differed significantly with regard to pulmonary function tests. However, analysis of the outcomes in the HOG

TABLE 1. Select Phase III Trials Assessing Chemoradiotherapy

Study	*n*	Therapy	Median Survival	*p*	Toxic Effects: Esophagitis (grade 3+)	Toxic Effects: Pneumonitis (grade 3+)
Furuse et al.[14]	314	(C) MVP × 2/TR	16.5 mo	0.039	4%	2%
		(S) MVP × 2 → TR	13.3 mo		4%	2%
Currran et al.[13]	400	(C) PVbl × 2/TR	17 mo	0.046	25%	4%
		(S) PVbl × 2 → TR	14.6 mo		4%	7%
Fournel et al.[12]	205	(C) PE/TR → PVr × 3	16.3 mo	NS	32%	5%
		(S) PVr × 3 → TR	14.5 mo		3%	11%
Clamon et al.[11]	283	(C) PVbl × 2 → Cb/TR	13.4 mo	NS	12%	4%
		(S) PVbl × 2 → TR	13.5 mo		4%	8%
Huber et al.[10]	214[a]	(C) TCb × 2 → TCb/TR	18.7 mo	NS	13%	0%
		(S) TCb × 2 → TR	14.1 mo		6%	0%
Zatloukal et al.[9]	102	(C) PVr × 1 → PVr/TR	16.6 mo	0.023	18%	4%
		(S) PVr × 4 → TR	12.9 mo		4%	2%
Gervais et al.[8]	163[b]	(C) PVr × 2 → Cb/TR	14 mo	NS	4%	—
		(S) PVr × 2 → TR	11 mo		3.5%	—

[a] Patients randomized after induction chemotherapy.
[b] Primary endpoint local control at 1-yr.
TR, thoracic radiotherapy; C, concurrent therapy; S, sequential therapy; MVP, cisplatin/vindesine/mitomycin; PVbl, cisplatin/vinblastine; PVr, cisplatin/vinorelbine; Cb, carboplatin; PE, cisplatin/etoposide; TCb, paclitaxel/carboplatin.

TABLE 2. Consolidation Therapy with Docetaxel

Study	SWOG 9504[15]	HOG 01–24[17]	SWOG 0023[19]
No. of patients	83	203	571
Median age	60 (34–80)	63	61 (20–83)
Proportion of women	27%	34%	31%
FEV-1 ≥2	100%	47%	73%
RT dose	61 Gy	59.4 Gy	61 Gy
Febrile neutropenia (G3/4)			
During chemodRT	NR	10%	5%
During consolidation	9%	11%	5%
Esophagitis (G3/4)			
During chemo-RT	17%	17%	14%
Pneumonitis (G3/4)	7%	8%	—
Treatment related death	5%	5%	6%
Median survival (mo)	26 mo	21.1 mo[a]	19[b]

[a] Median survival with observation vs. docetaxel consolidation, 24.1 and 21.5 mos, respectively ($p = 0.940$).
[b] Median and overall survival includes patients who received gefitinib or placebo.

study based on the pulmonary function test criteria did not reveal survival differences between those who had lower FEV1 (≤2 L) or higher FEV1. Based on the results of the HOG study, use of consolidation chemotherapy is not a current evidence-based standard of care. At the same time it remains counterintuitive that the optimal number of cycles in stage IV NSCLC is currently defined as 4, whereas in stage III disease only two cycles given during radiotherapy provide maximum therapeutic effect.

Induction Therapy

CALGB conducted a phase III study (CALGB 39801) that randomized 366 patients with locally advanced NSCLC to concurrent chemotherapy (low dose paclitaxel and carboplatin weekly) with thoracic radiation or the same regimen administered after two cycles of induction chemotherapy (paclitaxel and carboplatin for two cycles in systemically active doses).[18] Addition of induction chemotherapy to concurrent chemoradiation did not improve survival ($p = 0.3$). Outcomes were poor in both the groups with median overall survival of only 12 months without induction therapy and 14 months with induction therapy. Addition of induction chemotherapy did not improve the outcomes. Similar results were observed in a prospective study that randomized 134 patients with locally advanced NSCLC to induction therapy (with two cycles of gemcitabine and cisplatin) followed by concurrent chemoradiation (weekly paclitaxel and cisplatin) or concurrent chemoradiation alone with weekly paclitaxel and cisplatin.[19] The median overall survival with induction followed by concurrent chemoradiation was 12.6 months (95% CI: 8.6–16.7 months) and with concurrent chemoradiation alone was 18.2 months (95% CI: 11.7–24.8 months, $p = 0.18$). Based on these two studies that directly addressed the issue of induction therapy, we do not recommend the use of induction chemotherapy before concurrent chemoradiation in routine clinical practice.

The CALGB 39801 study brought to the forefront the issue of the optimal strategy for chemotherapy (systemically active doses of chemotherapy or the so called "low dose") to be used in conjunction with radiation therapy. An argument for systemically active doses of chemotherapy can be made as the majority of the relapses in patients with locally advanced NSCLC occur at distant sites presumably because of the presence of micrometastatic disease at presentation. Furthermore, it is worth reflecting that progress made in the treatment of locally advanced esophageal cancer and limited stage small cell lung cancer have been achieved through the use of systemically active doses of chemotherapy in conjunction with radiation. Some of the best results in the treatment of locally advanced NSCLC have been reported when chemotherapy was administered in doses that could be considered to be systemically active.[15,17,20,21] Administration of systemically active doses has the potential to eradicate micrometastatic disease that is almost universally present in stage III NSCLC. Although no prospective randomized studies have compared so called "low dose" chemotherapy with "full dose" chemotherapy with thoracic radiation to the best of our knowledge, in general, median overall survival reported with the latter strategy has consistently exceeded 17 months. Future attempts should be made to optimize systemic therapy that can be safely administered in conjunction with thoracic radiation therapy.

The Locally Advanced Multimodality Protocol (LAMP) compared sequential chemotherapy followed by radiation with two experimental regimens, one that employed induction chemotherapy followed by concurrent chemoradiation (induction regimen) and another, concurrent chemoradiation followed by consolidation chemotherapy (given at systemically active doses) with the same doublet chemotherapy (consolidation regimen).[22] Chemotherapy in this study consisted of paclitaxel and carboplatin. The median survival of the consolidation regimen was 16.3 months compared with 13 months with the sequential approach (control group) and 12.7 with the induction approach. Concurrent chemoradiation followed by consolidation was associated with a greater incidence of severe toxicities than the other two approaches. This randomized phase II study was not adequately powered to answer which of the two experimental regimens was superior to the (then) control regimen of sequential chemotherapy followed by radiation. Notably, the LAMP study did not compare concurrent chemoradiation followed by consolidation with concurrent chemoradiation alone.

RADIATION THERAPY OPTIMIZATION IN STAGE III NSCLC

Therapeutic gains in the treatment of locally advanced NSCLC have been generally attributed to the integration of systemic chemotherapy with thoracic radiotherapy. For example, 4 of 24 phase III North American Cooperative Group Trials conducted between 1970 and 1998 demonstrated a benefit for the experimental arm, and all studied the addition of cisplatin based chemotherapy to thoracic radiotherapy.[23] That said, the last decade and a half has brought major advances in the technology available for tumor imaging,

radiotherapy treatment planning and the delivery of thoracic radiotherapy. Coupled with an evolving philosophy of target determination, these changes have resulted in several single arm trials assessing intensive thoracic radiotherapy doses, and phase III trials comparing thoracic radiotherapy regimens have recently been initiated. As technology continues to rapidly evolve, it will be critical to demonstrate that integration of these efforts into routine practice results in an improved therapeutic ratio, either by improving tumor control or reducing the toxic effects of therapy.

Dose

Although thoracic radiotherapy is recognized as an integral component therapy in locally advanced NSCLC, there is no established (e.g., level 1 evidence) standard thoracic radiotherapy regimen. A phase III trial initiated by the Radiation Therapy Oncology Group (RTOG) in the 1970s, RTOG 73-01, is often cited as the seminal work assessing thoracic radiotherapy dose regimens for locally advanced NSCLC.[24] This trial randomized patients to receive continuous daily fractionation thoracic radiotherapy to a total dose of 40, 50, or 60 Gy, or to receive 40 Gy in 4 Gy fractions with a planned 2-week interruption. The group receiving 60 Gy continuous daily fractionation experienced the best short-term survival, although the 5-year survival, approximately 5%, was equally poor in all cohorts. Although 60 Gy conventionally fractionated thoracic radiotherapy has been accepted as standard of care, the relevance of this trial to current practice is further muddied by the use of radiotherapy fields and techniques that are no longer considered acceptable. Moreover, careful assessment following standard thoracic radiotherapy demonstrates residual local tumor in more than 80% of cases.[25]

Several dose escalation trials have been conducted since the introduction of conformal three-dimensional radiotherapy (3D-chemoradiotherapy) planning. The 3D-chemoradiotherapy era allows for increased confidence in treatment planning through more accurate definition of tumor volumes and normal tissues as well as improved tools for visualizing dose distributions surrounding these structures. Initial 3D-chemoradiotherapy trials aimed to increase dose by adding fractions of conventional thoracic radiotherapy. Trials from Memorial Sloan Kettering Cancer Center, Washington University, the University of Michigan and the University of Chicago demonstrated that modest dose escalation, in the range of 70 Gy, could be safely achieved.[26–28] A larger prospective phase I dose escalation trial conducted at the University of Michigan assigned patients into dose escalation "bins" based on the volume of irradiated lung.[29] Target volumes included the primary tumor and lymph nodes more than 1 cm on computed tomography (CT). Sixty-nine patients had stage III NSCLC and 28 stage I/II NSCLC. Approximately 25% of patients received neoadjuvant chemotherapy. The maximum-tolerated dose was only established for the largest bin, at 65.1 Gy, whereas dose escalation as high as 102.9 Gy was achievable for limited lung volumes. The median survival for patients with stage III or locally recurrent disease was 16 months, with 3-year survival of 14%.[30] A multi-institutional phase I/II three-dimensional radiation therapy dose escalation trial including 177 patients has been reported by the RTOG.[31] Neoadjuvant chemotherapy was allowed. Similar to the Michigan trial, patients were stratified at escalating radiation dose levels according to the calculated risk of pneumonitis. The percentage of total lung volume receiving in excess of 20 Gy (V20) was used to determine group assignments. The maximum tolerated dose was 83.8 Gy for patients with V20 of less than 25% and 77.4 Gy for those with V20 of 25 to 36%. Accrual to a third arm treating larger lung volumes was unsuccessful. Local control at 2 years ranged from 50 to 78%, and median overall survival ranged from approximately 12 to 16 months (estimated from survival curve) in stage III disease.

Given the impact of phase III trials demonstrating the superiority of combined modality therapy for stage III NSCLC, recent studies have assessed high dose thoracic radiotherapy delivered concurrent with chemotherapy (Table 3).[13] Rosenman reported a phase I/II trial from the University of North Carolina. Sixty-two stage III NSCLC patients were treated with two cycles of induction carboplatin/paclitaxel chemotherapy followed by concurrent weekly carboplatin/paclitaxel with radiation doses escalated from 60 to 74 Gy with conformal three-dimensional planning.[32] The median survival and 3-year survival rates were 24 months and 38%, respectively. Toxicity was modest. The results of a confirmatory phase II trial cooperative group study assessing 74 Gy conformal thoracic radiotherapy, CALGB 30105, were recently reported and once again an encouraging median survival of 24 months was observed for patients receiving concurrent (plus induction) carboplatin and paclitaxel.[33] CALGB 30105 also included a treatment arm assessing gemcitabine/carboplatin induction chemotherapy and twice-weekly gemcitabine during thoracic radiotherapy which was closed early because of excessive pulmonary toxicity. Contemporaneous phase I thoracic radiotherapy dose escalation trials from the RTOG and North Central Cancer Treatment Group (NCCTG) evaluated conformal thoracic radiotherapy concurrent with carboplatin and paclitaxel.[34,35] The maximum tolerated dose from each trial was 74 Gy in 2 Gy fractions. A phase III Intergroup Study (RTOG 0617/NCCTG N0628/CALGB 30609) comparing thoracic radiotherapy dose (60 Gy versus 74 Gy) has now been activated to help define the impact of radiotherapy dose in the context of concurrent chemotherapy.[36] In the meantime, the appropriate thoracic radiotherapy dose remains unclear, as witnessed in part by the range of thoracic radiotherapy doses employed in North American cooperative group Studies. An assessment of thoracic radiotherapy dose across protocols is confounded by the use of varying selection criteria, chemotherapy regimens, and schedules and timing/sequencing of thoracic radiotherapy as shown in Table 4.[13,15,17,18,20,37]

Fractionation

An alternative approach to enhancing outcomes through thoracic radiotherapy modulation is to increase the biologic intensity of therapy by accelerating the time to complete treatment, often by delivering multiple daily treatments. It is worth noting that several randomized trials have demonstrated no benefit for hyperfractionated radiotherapy if

TABLE 3. North American Cooperative Group Studies of Chemotherapy Concurrent with High Dose (≥70 Gy) Thoracic Radiotherapy

Study	*n*	TR Dose (dose per fraction)	Concurrent Chemotherapy	Additional Chemotherapy	Median Survival	Acute Toxic Effects
CALGB 30105[32] (phase II)	37	74 Gy (2 Gy)	Carboplatin + Paclitaxel	Carboplatin + Paclitaxel (induction)	24 mo	3% grade 5 17% grade 3 + esophagitis 14% grade 3 + pulmonary
	23[a]	74 Gy (2 Gy)	Gemcitabine	Carboplatin + Gemcitabine (induction)	12.5 mo	8% grade 5 36% grade 3 + esophagitis 37% grade 3 + pulmonary
RTOG 0117[33] (phase I/II)	~45[b]	74 Gy (2 Gy)[b]	Carboplatin + Paclitaxel	Optional (adjuvant)	Recently completed accrual	Recently completed accrual
NCCTG[34] (phase I)	13	70–78 Gy (2 Gy)	Carboplatin + Paclitaxel	Carboplatin + Paclitaxel (adjuvant)	NS	No grade 5 toxic events Maximum tolerated dose = 74 Gy
CALGB 30407[72] (phase II)	~100	70 Gy (2 Gy)	Pemetrexed + Carboplatin	Pemetrexed (adjuvant)	Recently completed accrual	No data available at the present time

[a] Arm closed early because of toxic events.
[b] Phase II cohort.
TR, thoracic radiotherapy; NS, not specified.

TABLE 4. Variation in Standard TR Dose in Phase III Cooperative Group Studies for Locally Advanced NSCLC

Study	*n*	TR Dose (dose per fraction)	Concurrent Chemotherapy	Additional Chemotherapy	Overall Survival	
					Median	2-yr
RTOG 9410[13]	201	63 Gy (1.8 Gy)	Cisplatin + Vinblastine	—	17.1 mo	37%
CALGB39801[18]	184	66 Gy (2.0 Gy)	Carboplatin + Paclitaxel	Carboplatin + Paclitaxel (induction)	14 mo	31%[a]
HOG LUN01-24[17]	203	59.4 Gy (1.8 Gy)	Cisplatin + Etoposide	With or without Docetaxel (adjuvant)	21.1 mo	~42%[b]
ECOG 2597[36]	59[c]	64 Gy (2.0 Gy)	—	Carboplatin + Paclitaxel (induction)	14.9 mo	24%
SWOG 0023[19]	571	61 Gy (1.8 Gy × 2 → 2.0 Gy × 6)	Cisplatin + Etoposide	Docetaxel with or without Gefitinib (adjuvant)	19 mo	42%

[a] Eligibility includes patients with more than 5% weight loss.
[b] Estimated from survival curve.
[c] Only includes patients randomized to standard TR after completing induction chemotherapy.

the treatment course is not accelerated.[13,38,39] Experimental and clinical experience suggest that accelerating the radiotherapy course may lead to improved tumor control, perhaps by allowing less opportunity for tumor repopulation during treatment, and retrospective evidence suggests a detrimental effect of prolonging the time to complete thoracic radiotherapy delivery in NSCLC.[40] Accelerating the treatment course has resulted in improved clinical outcomes in both locally advanced NSCLC and limited small cell lung cancer.[41,42] The United Kingdom trial of continuous hyperfractionated accelerated radiotherapy (CHART), 54 Gy in 36 fractions of 1.5 Gy over 12 consecutive days, demonstrated improved survival for CHART compared with conventional thoracic radiotherapy.[43] Acute dysphagia was more frequent with CHART compared with conventional radiotherapy, but no other differences in toxicity were noted. The Eastern Cooperative Oncology Group attempted to test an "Americanized" version of CHART, which eliminated therapy during weekends (HART). This phase 3 trial, which randomized patients to standard thoracic radiotherapy or HART after completing two cycles of carboplatin and paclitaxel chemotherapy, closed early because of slow accrual. Median survival was 20.3 months for HART compared with 14.9 months with standard thoracic radiotherapy, but the difference did not reach statistical significance.[37] Nevertheless, the results in the HART cohort compare favorably to trials of simultaneous chemoradiotherapy and again point to the promise of thoracic radiotherapy dose intensity.

Few trials have documented the safety of hypofractionated radiotherapy given simultaneously with chemotherapy for locally advanced NSCLC. Target volumes may be too large to allow sufficient protection of surrounding normal structures (e.g., lung and esophagus) despite the use of conformal techniques. RTOG L0117 was initiated with the goal of establishing the maximum tolerated dose of radiotherapy, in terms of Gy per fraction that can be delivered using 3D-chemoradiotherapy and concurrent paclitaxel and carboplatin chemotherapy. Despite the requirement for strict normal tissue limits (e.g., total lung V20 <30%), the initial schedule, 75.25 Gy in 2.15 Gy per fractions, was not acceptable because of dose limiting pneumonitis.[35] Whether newer treatment techniques, including intensity modulated radiotherapy (IMRT), helical tomotherapy, or stereotactic body radiotherapy can result in safe hypofractionation in stage III disease is under investigation.[44]

Treatment Planning and Target Determination

Conformal radiotherapy planning is now routinely integrated into clinical practice throughout the United States.[45] Even in the absence of dose escalation, 3D-chemoradiotherapy has the potential to widen the therapeutic window by reducing normal tissue toxicity and by ensuring the CT-based planning volume is appropriately dosed. For instance, quality assurance reviews in the era of 2D planning demonstrate geographic tumor miss in approximately one fifth of patients.[46] Although interobserver variability is common in defining the target volumes used in conformal planning for lung cancer, the risk of actually missing gross tumor should be minimal if 3D tools are applied appropriately. 3D-chemoradiotherapy technology has allowed markedly increased doses for NSCLC, but prospective trials have generally included select patients, and treatment dose has often been tailored to the individual's calculated risk of toxicity. Further confounding the interpretation of prospective 3D dose escalation trials is the incorporation of tissue heterogeneity corrections in some, but not all, trials. There is now general agreement among the North American cooperative groups that heterogeneity corrections will be routinely employed in future studies. Implementation of IMRT may allow for improved thoracic radiotherapy dose conformality with improved tumor coverage and better protection of normal structures.[47,48] The complexity of administering IMRT in the thorax, given the sharp dose fall-off coupled with issues of tissue heterogeneity and tumor motion, needs to be emphasized. The National Cancer Institute only recently allowed IMRT in North American cooperative groups lung cancer studies, and IMRT may only be used after stringent institutional credentialing including documenting the institution's ability to control respiratory motion to a maximum excursion of 1.0 cm.

The philosophy regarding appropriate target volumes in locally advanced NSCLC has evolved, particularly in regard to the inclusion of clinically uninvolved draining hilar and mediastinal lymph nodes. The major drawback of elective nodal irradiation (ENI) is the incorporation of larger lung volumes in the radiotherapy field, which may limit thoracic radiotherapy intensification, and the pros and cons of ENI have been widely debated.[49,50] Although most of prospective trials have included ENI, recent dose escalation studies from the RTOG and NCCTG have not included ENI.[34,35] Interestingly, the University of North Carolina thoracic radiotherapy dose escalation study mandated ENI, although CALGB 30105 allowed treatment of limited clinically uninvolved lymph nodes.[32,33] Omission of ENI has not been associated with a substantial risk of isolated regional nodal failure. Rosenzweig et al. reported the Memorial Sloan-Kettering 3D-chemoradiotherapy experience for 171 patients with stage I–IIIB NSCLC.[51] ENI was not given, although 122 of 171 patients had lymph node staging through mediastinoscopy or thoracotomy. Overall, only 11 patients (6.4%) with elective nodal failure were identified, including 1% ipsilateral supraclavicular, 3% contralateral supraclavicular, 4% ipsilateral inferior mediastinal, and 1% contralateral inferior mediastinal failure rates. Reports from additional 3D-chemoradiotherapy trials confirm the low risk of isolated failures in untreated nodal regions[52,53] and a published analysis of 1705 patients treated on RTOG NSCLC trials failed to support the use of ENI.[54] In this study, the adequacy of ipsilateral hilar coverage correlated with in-field progression but did not influence survival. Coverage in the mediastinum, ipsilateral supraclavicular area and contralateral hilum did not correlate with tumor progression or survival. The preliminary results of a randomized prospective study from China, comparing involved-field thoracic radiotherapy with or without ENI, were recently reported.[55] Pulmonary toxicity was observed more frequently in patients treated with ENI (39% versus 17%), while 3-year overall survival favored the group treated with involved-field thoracic radiotherapy alone (19.2% versus 27.3%).

The integration of functional imaging with FDG-PET for radiotherapy treatment planning is an important advance that will further mitigate the potential impact of ENI in locally advanced NSCLC. PET imaging may also refine radiotherapy target volumes by displaying the extent of "active" disease, including differentiating tumor from postobstructive atelectasis. Moreover, FDG-PET can help select patients who are not appropriate candidates for radical thoracic radiotherapy. In an Australian trial including 100 patients with clinical stage III NSCLC, 24% of patients were upstaged following FDG-PET imaging.[56] In another study of 30 patients with locally advanced NSCLC, only 23 were still considered candidates for radical therapy.[57] FDG-avid nodes, which were not apparently involved by CT criteria, were observed in 5 of these 23 patients. Moreover, FDG-PET information led to a change in target definition in as many as three-quarters of all cases, although this varied heavily according to the treating physician. In a prospective study from Washington University, FDG-PET findings altered the American Joint Committee on Cancer TNM stage in 8 of 26 patients undergoing evaluation for definitive radiotherapy.[58] PET altered the radiotherapy target volumes in greater than half of patients planned with 3D-chemoradiotherapy. An ongoing multicenter prospective study, RTOG 0515, has a primary objective of determining the impact of PET/CT fusion for each patient by comparing gross tumor volume

contours and 3D-chemoradiotherapy treatment plans using two separate data sets (PET/CT and CT only).

Reproducibility of patient positioning is mandatory to maximize the therapeutic index. Immobilization is generally provided through the use of custom molded foam cradles, vacuum-locked bags, or thermoplastic sheets. Once the patient is appropriately immobilized, efforts can focus on accounting for internal tumor motion. Tumor movement during respiration may be substantial in the cranial-caudal, anterior-posterior and lateral direction, leading to inadequate tumor coverage.[59,60] Classically, the radiation field has been extended based upon observation under fluoroscopic imaging, but technology now is available to perform four-dimensional CT (4D-CT) scans, which account for several defined phases of breathing. 4D-CT scans allow determination of tumor motion for determining the internal target volume, and also can be used in concert with respiratory gating systems that can be programmed to activate the linear accelerator (beam-on) only during specific predefined phases of the respiratory cycle.[61] Other strategies to account for tumor motion include the use of modified breathing techniques and the placement of abdominal compression devices to diminish the amplitude of the respiratory cycle.[62,63] Some of these techniques may be cumbersome for patients with pulmonary dysfunction, and can markedly increase total treatment time. More advanced solutions, including true 4-D solutions that can accurately track tumor motion and adapt with real-time changes in the radiation field, are currently under investigation.[64] The recent introduction of image-guided radiotherapy (IGRT) is a major advance that facilitates treatment accuracy by obtaining either a (cone-beam) CT scan or kV images of the region of interest before each radiotherapy treatment.[65] IGRT images are then compared with appropriate reference images to assure proper positioning and the treatment couch is automatically shifted to the proper position. IGRT allows internal set-up parameters to be established rather than traditional reliance on external (e.g., skin) markings and is particularly beneficial in patients where treatment set-up uncertainty based on skin marking can result in suboptimal treatment administration. Cone-beam CT may also facilitate adaptive radiotherapy planning to account for changes in tumor size and shape during therapy.

MOLECULARLY TARGETED THERAPY

In this era of molecularly targeted therapy, there is a natural interest in studying such agents in combination with chemoradiation in NSCLC. Two specific pathways have been studied extensively in NSCLC, the epidermal growth factor receptor (EGFR) pathway and the vascular endothelial growth factor (VEGF) pathway. More than 70% of NSCLC express EGFR by immunohistochemistry.[66] In the United States approximately 10% of NSCLC have activating mutations in the EGFR tyrosine kinase domain. The majority of patients with activating mutations achieve dramatic and durable responses with EGFR TK inhibitors such as gefitinib or erlotinib.[66] Even in unselected patients with advanced NSCLC progressing after a platinum based therapy, erlotinib improves survival compared with placebo.[67] Moreover activation of the EGFR pathway occurs in tumors in response to radiation. Preclinical studies have demonstrated consistent synergistic interaction between radiation therapy and EGFR inhibitors in producing cytotoxicity.[68] Inhibition of this pathway by cetuximab during radiation therapy improves survival when compared with radiation alone in unresectable locally advanced squamous carcinoma of the head and neck.[69] Thus potentially two approaches can be studied, one to study EGFR inhibitors in combination with radiation therapy (exploiting a synergistic interaction) and another to study EGFR inhibitors after chemoradiation to eradicate residual micrometastatic disease.

The CALGB 30106 study stratified patients with locally advanced unresectable NSCLC into 2 groups: stratum 1 (performance status of 2 or performance status 0 or 1 with poor risk) or stratum 2 (performance status 0 or 1).[70] All patients enrolled in this study received two cycles of chemotherapy with paclitaxel (200 mg/m^2) and carboplatin (AUC-6) along with gefitinib before thoracic radiation. Patients in stratum 1 received gefitinib and thoracic radiation and patients in stratum 2 received paclitaxel (50 mg/m^2 weekly) and carboplatin (AUC-2) along with gefitinib once a day during radiation therapy. This study enrolled 59 eligible patients (stratum 1, 20 patients and stratum 2, 39 patients) and reported no serious acute infield toxicities with gefitinib and radiation therapy. Although the median survival for poor risk patients (stratum 1) was a surprising 19 months (95% CI: 5.6–21.2 months), the median survival for the good risk patients (stratum 2) was a disappointing 12 months (95% CI: 8.5–18.6 months). This study clearly demonstrated the feasibility of administration of gefitinib in combination with radiation or chemoradiation. A smaller phase I study from Australia demonstrated feasibility of this combination with radiation as well. However, the overall results of CALGB 30106 were disappointing particularly in the good risk group. The smaller number of patients studied in the poor risk group makes it difficult to draw any firm conclusions, and the CALGB is planning a follow-up study that will assess the EGFR inhibitor erlotinib concurrent with radiotherapy in poor risk patients. However, the failure to demonstrate survival improvement with gefitinib in advanced NSCLC and its subsequent withdrawal from the market have dampened further enthusiasm to study this specific agent in the setting of locally advanced NSCLC.

The role of gefitinib as a maintenance therapy after chemotherapy and radiation and consolidation docetaxel was studied by the SWOG investigators. SWOG 0023 randomized patients with locally advanced NSCLC to receive placebo or gefitinib after completing chemoradiation with cisplatin, etoposide and radiation followed by docetaxel consolidation therapy.[20] Median overall survival for the entire study was an encouraging 19 months but the overall survival was strikingly superior in placebo group compared with the group that received gefitinib with a median survival from randomization of 35 versus 23 months respectively ($p < 0.01$). The treatment related toxicities were similar in both the groups. Of 118 patients assigned to gefitinib after chemoradiation and consolidation docetaxel, 71 patients died during

the study period (60%), most of the deaths (86%) related to progressive disease. On the other hand, only 54 of 125 (43%) assigned to placebo died during the study period. The reasons for the excessive disease related mortality in patients treated with maintenance gefitinib is unknown presently. Therefore, EGFR TK inhibitors should not be used in the maintenance setting after chemoradiation outside the context of a carefully planned clinical trial in patients with locally advanced NSCLC.

Addition of cetuximab (an antibody to EGFR) to radiation improves survival in patients with locally advanced squamous cell cancer of the head and neck compared with radiation alone.[69] Preclinical studies have suggested up-regulation of EGFR in response to radiation injury and a synergistic interaction between cetuximab and radiation.[68] Recent phase II trials conducted by RTOG and CALGB have included an assessment of cetuximab concurrent with chemoradiotherapy in stage III NSCLC, and preliminary results of these studies should be available in the near future.[71,72]

Angiogenesis is a critical component of malignancy. VEGF plays a crucial role in tumor angiogenesis.[73] Bevacizumab, a monoclonal antibody to VEGF has been approved for use in advanced NSCLC in combination with paclitaxel and carboplatin. A phase II study of carboplatin, irinotecan, thoracic radiation, and bevacizumab in patients with limited stage small cell lung cancer was closed prematurely following three deaths related to bevacizumab with at least two patients with confirmed and one presumed to have developed tracheoesophageal fistula.[74] These observations once again emphasize the need for carefully planned and conducted studies first to demonstrate the safety and feasibility before proceeding with larger studies and routine clinical use.

THE PROBLEM OF BRAIN METASTASIS

Brain metastasis is a major cause of morbidity and mortality in patients with locally advanced NSCLC. Approximately one third of NSCLC patients develop brain metastasis, including nearly two thirds of patients who have a systemic relapse. Moreover, brain as the sole of site of relapse occurs in approximately 20% of patients. An increasing recognition of the importance of brain metastasis has paralleled improved outcomes for patients receiving aggressive multimodality therapy. Intrathoracic tumor control has improved with routine use of concurrent chemoradiotherapy and the addition of surgery in select stage III patients. Likewise, systemic chemotherapy seems to reduce the appearance of distant relapse, but initial brain relapse rates have been increasing.[75,76] For example, the brain was a major site of relapse in the landmark phase III trials, from the RTOG and the West Japan Cancer Group, that demonstrated improved survival for patients receiving concurrent radiation and chemotherapy for stage III NSCLC compared with sequential therapy.[14] Moreover, patients receiving concurrent therapy in the West Japan Cancer Group trial patients were at greater risk of developing brain metastasis (19% versus 9%) as the site of first relapse (likely relating to a reduced risk of tumor failure in the lung and draining lymph nodes).

Attempts have been made to address the problem of brain metastasis in locally advanced NSCLC in the past. Four randomized phase III trials were conducted in the 1970s and 1980s to assess the role of prophylactic cranial irradiation (PCI) in locally advanced NSCLC.[77–80] Although the incidence of brain metastases was reduced in the PCI arm in most studies, there was no evidence that PCI improved overall survival. In fact, a trial conducted by SWOG suggested poorer overall survival inpatients assigned to receive PCI. Few conclusions can be drawn from these studies given that the methods of clinical staging and treatment employed are obsolete by current standards coupled with the poor survival for locally advanced NSCLC treated at the time. A modern European study comparing tri-modality therapy with bi-modality therapy (surgery and postoperative radiotherapy) for operable stage III NSCLC employed PCI on the tri-modality arm (preoperative chemotherapy followed by chemoradiotherapy and surgery). A recently updated report demonstrated reduced brain metastases for patients receiving PCI, 9% versus 27% at 5 years, although the trial was prematurely closed because of slow accrual. The above data led in part to a renewed interest in evaluating the role of PCI in locally advanced NSCLC, and a large phase III study was undertaken by the RTOG. RTOG 0214 randomized locally advanced NSCLC patients to either PCI or observation following definitive systemic and local therapy. Unfortunately, the trial was closed in summer 2007 because of not meeting it accrual goals. Thus, there is insufficient evidence to recommend PCI outside of a clinical study.

COMPLICATIONS OF THERAPY

The 3D-chemoradiotherapy era has facilitated an assessment of dose-volume relationships with regard to thoracic radiotherapy induced toxicity. Early reports of pulmonary toxicity related to patients treated with radiotherapy alone (Fig. 1). A systematic review of the literature found that an ideal dose-volume parameter predicting pulmonary toxicity has not been identified,[81] although the most widely used measures are the volume of total lung receiving at least 20 Gy (e.g., V20) and the mean lung dose.[31,82,83] Other metrics have also been used and it is likely that multiple physical and biologic factors are important in predicting the risk of pul-

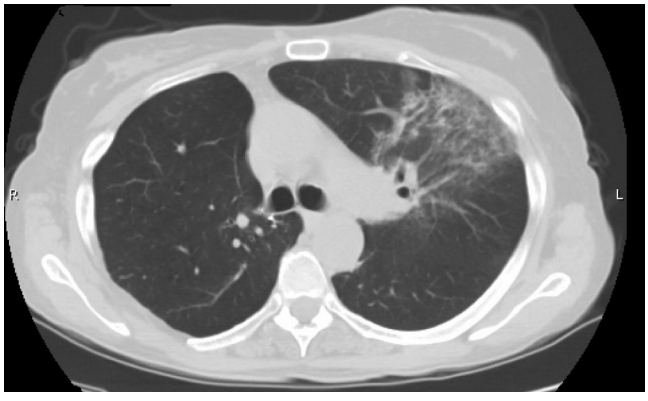

FIGURE 1. Lung fibrosis after radiation.

monary toxicity. Barriers to accurately describing the relationship between treatment and its resultant toxicity include the usage of imperfect metrics and the inaccurate reporting of toxic effects. This may be particularly relevant for patients with underlying pulmonary toxicity, where it may be difficult to determine whether a functional decline is attributable to the effects of therapy. The dose-volume relationship may also be affected by the integration of systemic chemotherapy, and the sequencing of therapies may significantly impact the toxic effects of therapy. For example, in the LAMP study, patients receiving immediate concurrent thoracic radiotherapy and chemotherapy had a higher rate (16%) of grade 3+ pulmonary toxicity than patients treated with alternate sequencing.[22] Nevertheless, most current prospective combined modality trials have adopted V20 as a treatment planning parameter and limit the V20 to a maximum 30 to 40% of the total lung volume, although obviously a more restrictive V20 could lead to selection of a more favorable patient population. CALGB 30105 did not include V20 as a planning parameter and a post hoc evaluation showed a correlation between grade 3 to 5 pulmonary toxicity and V20 more than 38%, which was most pronounced in patients with poor baseline pulmonary function.[33] Transforming growth factor beta (TGF-beta) is the most widely studied biologic predictor of radiation induced pulmonary toxicity and has been implicated in the development of fibrosis after exposure to chemotherapy or radiation. Investigators have observed a correlation between changes in TGF-beta during therapy and the development of late toxicity in lung cancer and other malignancies.[84,85] Interestingly, two recent reports suggest that inhibition of TGF-beta in the preclinical setting can reduce the appearance of radiation induced lung toxicity, and it remains to be seen whether this work will successfully translate to the clinic.[86,87]

Treatment induced esophageal toxicity is generally the major clinically relevant acute toxicity of thoracic radiotherapy. The implementation of conformal techniques may impact esophageal toxicity by markedly reducing the volume of esophagus irradiated, particularly for patients without extensive mediastinal adenopathy. The risk of radiation induced acute esophageal toxicity varies markedly according to fractionation and the integration of chemotherapy. Dosimetric parameters that may correlate with esophageal toxicity include the length of esophagus treated to more than 40 to 50 Gy, the volume of esophagus receiving more than 50 Gy, and the treated esophageal circumference.[29,88–90] The RTOG conducted a randomized trial to test the ability of amifostine to reduce esophagitis in patients receiving hyperfractionated radiotherapy and concurrent paclitaxel and carboplatin chemotherapy.[91] The rate of grade 3 esophagitis did not differ between the arms, 34% versus 30%, although subjective swallowing function was better with the addition of amifostine. Amifostine was associated with higher rates of acute nausea, vomiting, cardiovascular toxicity, and infection or febrile neutropenia. Unfortunately, design flaws, particularly the decision to administer amifostine in conjunction with only 40% of thoracic radiotherapy fractions, preclude a definitive assessment of the use of amifostine in a setting of combined therapy.

FUTURE DIRECTIONS

Several strategies are currently being evaluated to improve the survival in patients with locally advanced NSCLC (www.clinicaltrials.gov.). Based on the observations that pemetrexed and carboplatin can be administered in systemically active doses in combination with thoracic radiation, several phase II studies have been developed to study the role of pemetrexed in this setting.[92] A phase III study is being planned to study this agent in locally advanced NSCLC. The role of high dose thoracic radiation in the treatment in locally advanced NSCLC is being addressed by the ongoing RTOG-Intergroup study. The role of FDG PET in assessing the response to chemoradiation is the subject of an ongoing clinical trial led jointly by the American College of Radiologic Imaging Network and RTOG. Several small phase I and II studies are exploring the feasibility and safety of adding novel molecularly targeted drugs to chemoradiation in locally advanced NSCLC. With careful patient selection, improved radiotherapy techniques, better supportive care and novel systemic therapy, the outcomes of patients with locally advanced NSCLC are likely to improve in the coming decades.

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