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REVIEW

Therapeutic management options for stage III non-small cell lung cancer

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Abstract

Lung cancer is the leading cause of cancer death worldwide. Majority of newly diagnosed lung cancers are non-small cell lung cancer (NSCLC), of which up to half are considered locally advanced at the time of diagnosis. Patients with locally advanced stage III NSCLC consists of a heterogeneous population, making management for these patients complex. Surgery has long been the preferred local treatment for patients with resectable disease. For select patients, multi-modality therapy involving systemic and radiation therapies in addition to surgery improves treatment outcomes compared to surgery alone. For patients with unresectable disease, concurrent chemoradiation is the preferred treatment. More recently, research into different chemotherapy agents, targeted therapies, radiation fractionation schedules, intensity-modulated radiotherapy, and proton therapy have shown promise to improve treatment outcomes and quality of life. The array of treatment approaches for locally advanced NSCLC is large and constantly evolving. An updated review of past and current literature for the roles of surgery, chemotherapeutic agents, radiation therapy, and targeted therapy for stage III NSCLC patients are presented.

Key words: Non-small cell lung cancer; Chemo-radiotherapy; Multi-modality; Targeted therapy; Dose-escalation

Core tip: Locally advanced non-small cell lung cancer consists of a heterogeneous population making management challenging. Multiple strategies are being developed to maximize survival and disease control. The role of surgery is being re-evaluated given new insight into the efficacy chemotherapy and radiation. Multi-modality therapy is playing an increasingly important role for both resectable and unresectable stage III patients. Chemoradiation plays a large role in the management of inoperable or unresectable patients. Third generation

chemotherapy and other targeted therapies are being incorporated into chemoradiation. Radiation dose-escalation, alternative fractionation schedules, intensity-modulated radiotherapy, and proton therapy are evaluated to improve outcomes from chemoradiation.

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INTRODUCTION

Lung cancer is the leading cause of cancer death in the United States and worldwide. In 2016, approximately 224390 Americans are estimated to be newly diagnosed with lung cancer, and 158080 will die from this disease[1]. About 80% of lung cancer cases are non-small cell lung cancer (NSCLC), of which up to half are locally advanced at the time of diagnosis[2]. According to guidelines, locally advanced NSCLC is often defined as the 7th edition AJCC staging classification stage III NSCLC[3,4].

Stage IIIA and IIIB are two subsets within this classification, and the distinction is made because prognosis, treatment options, and long-term outcomes differ from one another. Furthermore, stage IIIA disease must be differentiated as resectable or unresectable at time of diagnosis. Stage IIIA (T1-3 N2, T3-T4 N1, T4 N0) disease involves hilar or mediastinal lymph nodes limited to the ipsilateral mediastinum, and a subset of these patients are amenable to surgery[3,4]. However, Stage IIIB (T1-4 N3, or T4 N2) involves lymph node metastasis in the contralateral thorax or supraclavicular fossa and/or an unresectable primary tumor, making patients with this disease not ideal candidates for surgical resection[3,4]. With such a heterogeneous population, a multi-modality approach involving surgery, radiation, and systemic agents is most commonly employed. A standard treatment option for unresectable or inoperable stage IIIA and stage IIIB disease is concurrent chemoradiation, while management of IIIA is more complex and controversial[5]. Treatment options for IIIA disease includes surgery with neoadjuvant or adjuvant chemotherapy, radiation, or both; as well as definitive chemoradiation[3,5,6]. Long-term outcomes are poor, with baseline 5-year overall survival (OS) of 15%-35% for stage IIIA and 5%-10% for stage IIIB[7]. The appropriate combination, timing, and sequence of individual treatment components in order to improve outcomes are under active research for both disease subsets. The aim of this review is to provide an overview of current and future treatment options for the management of locally advanced NSCLC.

MANAGEMENT OPTIONS FOR RESECTABLE STAGE IIIA NSCLC

Surgery

Up to 30%-50% of stage III NSCLC are locally advanced and inoperable at time of diagnosis[2,8]. Accurate pre-operative staging, particularly of mediastinal lymph nodes, is imperative as it dictates further management. Lymph node evaluation techniques include endobronchial ultrasound, endoscopic ultrasound-guided biopsy, cervical mediastinoscopy, or transthoracic needle aspiration. Positron emission tomography/computed tomography (PET/CT) scans have improved the accuracy of lymph node staging by improved detection of subclinical micro- and macro-metastases[9]. For patients who are deemed to have resectable disease, surgery plays an important role in their treatment. Generally, those with limited mediastinal lymphadenopathy are considered potentially more favorable candidates for resection than those with multistation or bulky mediastinal involvement, as it is associated with a higher rate of micro-metastasis. However, there are no specific guidelines to determine to what extent lung tumors should be considered "resectable"[6]. In fact, data have shown that a substantial proportion of stage IIIA-N2 patients who were considered resectable ultimately had an R1, 2 resection[10].

Pre- and post-operative chemotherapy

While surgery is an important aspect in the management for resectable stage IIIA patients, surgery alone continues to have poor outcomes, and as many as 30%-70% of resected patients experience recurrence or death[11,12]. The addition of post-operative chemotherapy has been extensively studied, and shown to improve treatment outcomes in patients with locally advanced disease[13-15]. In an analysis by the NSCLC Meta-analysis Collaborative Group[13] in which a meta-analyses totaling 34 trials and 8447 patients were evaluated, adjuvant chemotherapy was shown to have an absolute 5-year overall survival benefit of 4%, increasing OS rate from 60% to 64%, for patients with stage I-III disease. More specifically, a 5% absolute improvement in 5-year survival for stage III disease was observed, increasing 5-year OS rates from 30% to 35%. Other recent studies[14,15] have shown similar results, in which post-operative chemotherapy increased median survival from 45 mo from surgery alone to 54 mo[14]. These studies also demonstrated adjuvant chemotherapy increased 5-year progression free survival (PFS) by approximately 5%[14,15]. Because post-operative chemotherapy has been shown to significantly improve treatment outcomes, it is the standard of care for resectable locally advanced disease[3].

While surgical resection followed by chemotherapy is commonly employed, induction chemotherapy followed by surgical resection has also been studied[7,16-19]. Indu-

ction chemotherapy has the potential to eradicate micrometastases prior to resection, reduce tumor size, and increase the likelihood of resection. However, a concern with induction chemotherapy would be to delay a potentially curative surgery due to disease progression or declining health of the patient. The same NSCLC Meta-analysis Collaborative Group recently summarized the findings of 15 randomized controlled trials totaling 2385 patients on the effects of administering chemotherapy prior to surgical resection for patients with stage IB-IIIA disease[16]. In this analysis, pre-operative chemotherapy increased 5-year survival from 20% to 25%. Similar to adjuvant chemotherapy, induction chemotherapy also reduced relative risk of death by 13%. Five-year PFS improved from 30% to 36% with induction chemotherapy, and the time to distant recurrence also improved by 10% at 5-year. Results from older studies have shown that induction chemotherapy improved median survival from 11 mo to anywhere between 22 to 64 mo[17-19]. The NSCLC Meta-analysis Collaborative Group did not note a difference in complete resection rates between surgery *vs* preoperative chemotherapy with surgery, suggesting that the delay for induction chemotherapy does not significantly reduce chances of a potentially curative resection[16].

There does not seem to be a difference in survival or recurrence between adjuvant and induction chemotherapy. In a phase III trial, Felip *et al*[20] randomized 624 stage IA to IIIA patients to surgery alone, three cycles of preoperative carboplatin-paclitaxel followed by surgery, or surgery followed by three cycles of adjuvant carboplatin-paclitaxel. There was no difference in 5-year OS or PFS rates between induction and adjuvant chemotherapy regimens compared to surgery alone, though there was a non-significant trend towards longer PFS in the preoperative arm. Given that pre- and post-operative chemotherapy yields similar outcomes, induction chemotherapy could be reserved for patients with larger, more advanced tumors or those unable to tolerate chemotherapy while recovering after surgery[16]. Adjuvant chemotherapy could be utilized for patients with better prognosis and earlier disease stages[16].

Post-operative radiotherapy

Despite having complete resection and adjuvant chemotherapy, up to 40% of resectable stage IIIA patients experience local tumor recurrence[21,22]. In order to improve local tumor control and survival, post-operative radiotherapy (PORT) has long been utilized to intensify local therapy. Yet the ideal candidate for PORT has been controversial with conflicting results from different trials and series. Historical randomized control trials demonstrated that PORT significantly reduced local recurrence without any impact on overall survival[23-25]. One trial demonstrated a detrimental effect of PORT on survival compared to surgery alone, in which 5-year OS rates were 30% and 43% respectively[23]. The PORT Meta-analysis[26] demonstrated that PORT had an adverse effect on survival by increasing the relative risk of death by 21%, translating to a 7% reduction in 2-year OS from 55% to 48%. Subgroup analysis indicated a detriment in OS for patients with stage I/II N0-1 due to excess of toxicity from PORT. However, PORT for stage III-N2 disease trended toward, but did not reach, a significant survival benefit, suggesting a need for further investigation. A significant flaw of the PORT Meta-analysis was the inclusion of historical series with patients treatments utilizing antiquated techniques that were potentially more toxic than modern radiation delivery with image guidance, respiratory motion assessment, and higher dose conformality.

A recent retrospective analysis of the SEER database analyzing 7465 stage II-III patients receiving PORT following lobectomy or pneumonectomy demonstrated that PORT significantly increased survival for patients with N2 disease and associated with worse survival for N0-1 disease[27]. Among N2 patients, PORT improved 5-year OS from 20% to 27% (HR = 0.85), while reducing 5-year OS by 10% (HR = 1.2) and 4% (HR = 1.1) among N0 and N1 patients respectively[27]. The survival benefit for N2 disease was not observed until 2.5 years after PORT, while the lack of benefit for N0-1 disease was evident within one year of receiving PORT. A similar population-based series from the National Cancer Database also demonstrated an improvement in median OS from 45 mo with PORT *vs* 41 mo without PORT[28]. These results were consistent with a separate subset analysis from the Adjuvant Navelbine International Trialists Association trial[29]. In this trial 850 patients were randomized to adjuvant cisplatin and vinorelbine or observation following complete resection. The decision to provide PORT was left to the discretion of the participating institutions but was suggested for patients with node-positive disease. PORT was delivered to 232 patients. Median survival (MS) improved after PORT among patients with N2 disease receiving either adjuvant chemotherapy (from 23.8 to 47.4 mo) or observation (from 12.7 to 22.7 mo) following surgical resection. This analysis also confirmed that PORT reduced local recurrence regardless of nodal status. However, patients that received PORT and adjuvant chemotherapy with stage N1 disease experienced worse MS compared with chemotherapy alone (46.6 mo *vs* 96.6 mo) and 5-year OS (40% *vs* 56.3%), respectively. This study suggests that PORT may be influenced by the use of adjuvant therapy and extent of nodal involvement.

Since the PORT Meta-analysis, further prospective trials for PORT have drastically declined. However, this series may not be as relevant today since cobalt-60 sources and older treatment delivery systems were used for patient treatment[27]. Today's technology has significantly improved radiation delivery. There is a need for updated PORT studies using modern techniques since more conformal radiotherapy could improve local control while reducing cardiac and pulmonary toxicities observed in PORT Meta-analysis[30,31]. The LungART trial is a large European Phase III multi-institutional

prospective study of PORT using modern staging and treatment planning among N2 patients who have undergone complete resection. This trial is currently being conducted, and results are highly anticipated[32].

Post-operative radiotherapy and concurrent chemotherapy

The benefits of post-operative concurrent chemoradiation continue to be under debate. The Intergroup 0115 (ECOG 3590, RTOG 9501)[33] was a trial of 488 stage II-IIIA patients randomized to PORT alone or with four cycles of cisplatin and etoposide. A total of 50.4 Gy was delivered in 28 daily fractions to both groups. After median follow-up time of 44 mo, no survival benefit of concurrent chemoradiotherapy was observed. MS was not different in the post-operative chemoradiation group (38 mo) *vs* those in PORT group (39 mo) with a relative likelihood of survival to be 0.93. Intrathoracic disease recurrences within the irradiated field were 12% and 13%, respectively and was not significantly different. Compared to these results, the RTOG 9705 trial[34] found more favorable OS and PFS benefit with the addition of adjuvant chemotherapy to PORT. However, this was a phase II non-randomized study. In this trial, 88 stage II-III NSCLC patients received concurrent radiotherapy at 50.4 Gy in 28 daily fractions, carboplatin, and paclitaxel with a MS of 56.3 mo. The 3-year OS and PFS rates in this study were 61% and 50% respectively, while intrathoracic recurrence rate was similar to that observed in INT 0115 at 15%. To date, there remains no evidence supporting concurrent delivery of adjuvant chemotherapy with PORT.

Neoadjuvant radiation and multi-modality therapy

Thus far, treatment strategies incorporating surgical resection have demonstrated the best local control for operable NSCLC, and outcomes may be improved by managing distant metastases by induction or adjuvant therapy. However, OS and local control remains low. In an attempt to further improve resectability, local regional control, and survival for select patients with potentially resectable disease, combinations involving all three treatment modalities have been studied. An international multi-centered European trial[35] sought to compare the benefits of neoadjuvant chemoradiation or neoadjuvant chemotherapy alone prior to undergoing surgical resection randomized. Patients with stage IIIA-N2 disease were randomized to neoadjuvant regimens of 3 cycles of cisplatin and docetaxel followed by radiation to 44 Gy in 22 fractions over 3 wk or chemotherapy alone. Regimens in both study groups were well tolerated, as 91% of patients completed all three cycles of neoadjuvant chemotherapy and 7% experienced radiation-induced grade 3 or higher dysphagia. The primary endpoint of event-free survival was not significantly different between both groups. Those in the neoadjuvant chemoradiation group had median PFS of 12.8 mo compared to patients in neoadjuvant chemotherapy group with a median PFS of 11.6 mo (HR = 1.1). MS for both groups were 37.1 and 26.2 mo respectively (HR = 1), and also not different from one another. The proportion of patients with pathological complete response or nodal downstaging were 61% and 44% in neoadjuvant chemoradiation and chemotherapy group respectively, which was significantly different. While preoperative chemoradiation did not improve survival, it did significantly increase the proportion of patients with mediastinal downstaging and histopathological response. Such improvement in tumor response could improve local control and even survival for carefully selected patients, and neoadjuvant chemoradiation should be further evaluated.

Given that preoperative chemotherapy improves survival for resectable stage IIIA patients, a phase III trial[36] evaluated whether adding preoperative chemoradiation in addition to induction chemotherapy could improve treatment outcomes. This trial randomized 524 stage IIIA/B (N2/3) patients to receive either induction chemotherapy and chemoradiation (intervention) or induction chemotherapy alone (control) prior to surgical resection and PORT. The toxicity and perioperative morbidity were similar between both arms. Pneumonectomies were performed at a rate of 35% in both arms. Hematological toxicities (10% *vs* 0.5%, $P < 0.0001$) and Grade 3 or higher esophagitis (19% *vs* 4%, $P < 0.0001$) were more frequent in the intervention group, whereas Grade 3 or higher pneumonitis was more common in the control group (1% *vs* 7%, $P = 0.0006$). A significantly higher proportion of patients receiving neoadjuvant chemoradiation (46%) experienced mediastinal downstaging compared to those receiving induction chemotherapy alone (29%) ($P = 0.02$). Sixty percent of patients receiving neoadjuvant radiation achieved > 90% tumor regression compared to 20% of patients among the induction chemotherapy group ($P < 0.0001$). While response rates were significantly improved by chemoradiation, neoadjuvant chemoradiation did not improve the primary endpoint for PFS for the entire cohort. Secondary endpoints for OS, rate of disease progression, or site of first progression were also similar for all patients. Five-year PFS between intervention and control groups were 16% and 14%, respectively (HR = 0.99), and 5-year OS were 21% and 18% (HR = 1) respectively. However, subset analysis did demonstrate improved PFS (HR = 1.58, $P = 0.043$) and OS (HR = 2.07, $P = 0.03$) in patients undergoing a complete resection with successful downstaging of the mediastinum from N2-3 to N0-1 following induction radiation compared to patients with incomplete resections. These data suggest that survival outcomes may improve with mediastinal clearance and downstaging prior to surgery, and neoadjuvant chemoradiation should be considered as a treatment option for patients with potentially resectable stage III disease.

Randomized phase III trials have not yet successfully demonstrated a survival advantage of induction chemotherapy or chemoradiation prior to surgery over

definitive chemoradiation. EORTC 08941[37] reported comparable MS and 5-year OS for stage IIIA-N2 initially unresectable patients receiving induction platinum-based chemotherapy and randomized to either surgery or radiation therapy. Disease was considered unresectable if there was any N2 disease for non-squamous histology or lymph node spread beyond levels 4R or levels 5/6 for right or left squamous primaries, respectively. Treatment-related mortality was greater perioperatively (4%) compared to one death (0.6%) following radiation pneumonitis. This study suggested that surgical resection may not improve treatment outcomes compared to definitive radiotherapy. Within the context that radiotherapy leads to lower morbidity and mortality compared to surgery, definitive chemoradiation is a reasonable treatment option for patients with stage IIIA-N2 disease. However, several criticisms with this study have been made including that only 50% of patients randomized to the surgery arm received radical resection, and 40% of surgical arm patients received PORT. The chemoradiation regimen used is not an accepted standard, making extrapolation of this trial to current practice challenging. An intergroup trial, INT 0139[38] tested the benefits of trimodality with sequential cisplatin/etoposide with 45 Gy of radiation prior to surgical resection compared to concurrent chemoradiation alone. After a median follow-up of 22.5 mo, 5-year OS and MS were not improved with the induction chemoradiation. Five-year PFS was significantly higher under the intervention arm (22.4%) compared to chemoradiation arm (11.1%) (P = 0.017), which was not observed from EORTC 08941[37]. However, relatively high treatment-related deaths were observed in the trimodality arm (7.9%) compared to definitive chemoradiation arm (2.1%). No benefit of surgery was observed in patients who received pneumonectomies, likely due to an increased rate of death without progression. While induction chemoradiation may have improved 5-year PFS, a survival benefit was not observed. Such results could have been confounded by the higher perioperative mortality observed in the intervention arm, particularly among pneumonectomy patients. A subgroup analysis showed that median survival was significantly improved with induction chemoradiation prior to lobectomies (P = 0.002). In addition, 5-year OS rates were significantly better (P < 0.0001) among those with pathologic stage N0 (41%) and N1-3 (24%) at time of thoracotomy compared with those who did not receive surgery (8%). These subgroup analyses suggest that a survival advantage of trimodality over definitive chemoradiation may be demonstrated in carefully selected candidates.

To minimize perioperative mortality that was observed in INT 0139, surgeons in the RTOG 0229 trial[39] were required to demonstrate expertise in performing surgery following chemoradiation. RTOG 0229 was a multi-institutional phase II trial that followed 57 stage III-N2/3 patients receiving neoadjuvant chemoradiation of carboplatin, paclitaxel, and 50.4 Gy to the mediastinum with 10.8 Gy boost to gross disease followed by surgical resection. An impressive rate of 63% of patients achieved mediastinal disease clearance while residual disease remained in 16% of patients. The primary endpoint of improving mediastinal disease from 50% to 70% with a power of 80% was achieved. One-year OS and PFS were 77% and 52%. Fourteen percent of patients in RTOG 0229 experienced Grade 3 postoperative pulmonary complications. It is important to note that this was not increased compared with other trials of chemoradiation alone. The rate of pneumonectomies was much lower in this trial (5%) compared to INT 0139 (34%). Moreover, rate of perioperative morbidity was 3% (1 patient) which compared favorably to the relatively high rate of morbidity observed in INT 0139 (7.9%). The ability of neoadjuvant chemoradiation to sterilize mediastinal nodal disease was confirmed by this study, and thus should be considered as an option for multi-modality therapy for select patients. Lobectomy should be the preferred surgical management, and surgery should be performed by a thoracic surgeon skilled in this specific approach.

A recent trial[40] studied the outcomes of surgery *vs* definitive chemoradiation boost following both neoadjuvant chemotherapy and chemoradiation. This was a phase III multi-centered randomized control trial for stage IIIA-N2 and select IIIB patients receiving three cycles of cisplatin/paclitaxel as well as induction cisplatin/vinorelbine, and accelerated radiotherapy of 45 Gy in twice daily 1.5 Gy fractions. Patients were reassessed for resectability, and randomized to either receive chemoradiation boost to 65-71 Gy in arm A or surgery in arm B. Grade 3 or higher toxicities were acceptable and balanced between both groups. After median follow-up of 78 mo, 5-year OS was 40% in arm A and 44% in arm B, while 5-year PFS rates were 35% and 32% in arms A and B, respectively. No significant differences were found for either OS or PFS between the two groups, thus making either strategies acceptable for resectable stage IIIA, and select inoperable IIIA or IIIB patients.

Multi-modality management is efficacious for select stage IIIB patients as well. Because induction radiation and chemotherapy improves mediastinal downstaging and pathological response, tumor resectability has proven to increase among stage IIIB patients in several phase II trials[41-45]. 3-year OS rates have approached to 60%[44], and resectability rates increased up to 80%[43]. Table 1 summarizes trials for multi-modality therapy for stage IIIA/B patients.

MANAGEMENT OPTIONS FOR STAGE IIIB AND UNRESECTABLE/INOPERABLE STAGE IIIA NSCLC

Chemoradiation

Definitive chemoradiation remains a standard of care in the management of stage IIIB disease or IIIA patients

Table 1 Prospective trials of multi-modality therapy for resectable stage III non-small-cell lung cancer

Ref.	Phase	Study design	Chemo regimen	RT	Number of patients	Stage	Median f/u (mo)	OS	Median OS (mo)	PFS	Median PFS (mo)	Response rate
Pless *et al*[35] (2015)		Induction chemoRT + surgery *vs* induction chemo + surgery	Cisplatin/ docetaxel	44 Gy in 2 Gy fxns over 3 wk	232	IIIA (N2)	52.4		37.1 *vs* 26.2		12.8 *vs* 11.6 (P = 0.67)	ORR: 61% *vs* 44%
Thomas *et al*[36] (2008)	3	Induction chemo + induction chemoRT + surgery *vs* induction chemo + surgery	Induction: Cisplatin/ etoposide ChemoRT: Carboplatin/ vinorelbine	45 Gy in 1.5 Gy fxns (twice daily)	524	III A/B (N2/3)		5-yr, 21% *vs* 18% (P = 0.97)	15.7 mo *vs* 17.6 mo	5-yr, 16% *vs* 14% (P = 0.87)	9.5 *vs* 10	CR: 60% *vs* 20% (P < 0.0001) Mediastinal downstaging: 46% *vs* 29% (P < 0.02)
EORTC 08941 Van Meerbeeck *et al*[37] (2007)	3	Induction chemo + surgery *vs* chemoRT	Platinum-based	60-62.5 Gy in 1.95-2.05 Gy daily fxns	332	IIIA (N2)	> 72	5-yr, 15.7% *vs* 14% (P = 0.6)	16.4 *vs* 17.5 (P = 0.6)	2-yr, 27% *vs* 24% (P = 0.6)	9 *vs* 11.3 (P = 0.6)	
INT 0139 Albain *et al*[38] (2009)	3	Induction chemoRT + surgery *vs* chemoRT	Cisplatin/ etoposide	45 Gy boost to 61 Gy if definitive chemoRT	396	IIIA (N2)	22.5	5-yr, 27.2% *vs* 20.3% (P = 0.10)	23.6 *vs* 22.2 (P = 0.24)	5-yr, 22.4% *vs* 11.1% (P = 0.017)	12.8 *vs* 10.5 (P = 0.017)	
RTOG 0229 Suntharalingam *et al*[39] (2010)	2	Induction chemoRT + surgery	Carboplatin/ paclitaxel	50.4 Gy + 10.8 Gy to gross disease	60	III A/B (N2/3)		1-yr, 77%	26.6	1-yr, 52%	13.1	Improved mediastinal sterilization 50% to 70% met
ESPATUE Eberhardt *et al*[40] (2015)	3	Induction chemotherapy + induction chemoRT + RT boost *vs* Induction chemotherapy + induction chemoRT + surgery	Induction chemo: Cisplatin/ paclitaxel Induction chemoRT: Cisplatin/ vinorelbine	45 Gy in 1.5 Gy twice daily fxns Definitive chemoRT: Boost to 65-71 Gy	246	III A/B (N2/N3)	78	5-yr, 40% *vs* 44% (P = 0.34)		5-yr PFS, 35% *vs* 32% (P = 0.75)		
Eberhardt *et al*[40] (2015)	3	Induction chemo + induction chemoRT + surgery *vs* induction chemo + definitive chemoRT	Induction: Cisplatin/ paclitaxel ChemoRT: cisplatin/ vinorelbine	45 Gy in 1.5 Gy fxns (twice daily)	246	IIIA (N2), select IIIB (N3)	78	5-yr, 40% *vs* 44%		5-yr, 35% *vs* 32%		

CR: Complete response; ORR: Overall response rate; OS: Overall survival; RT: Radiotherapy; PFS: Progression free survival.

with unresectable or inoperable disease[3]. Radiation provides local therapy for inoperable tumors, and chemotherapy not only reduces or prevents micrometastatic spread of the disease, but also acts as a radiosensitizer to increase the therapeutic index of radiation therapy. Chemotherapy plays a critical role in the management for advanced NSCLC, and when given with radiation, the combination improves survival over supportive care or radiation therapy alone[46-49]. Standard radiation is typically 60-66 Gy in 2Gy daily fractions over 6 wk, as established by RTOG 7301 trial[50], and platinum-based doublet chemotherapy is typically used with standard radiation[3].

Sequential vs concurrent chemoradiation

Concurrent chemoradiation has proven to be superior to sequential chemoradiation, and is now considered standard of care. RTOG 9410[51] was a pivotal trial esta-

blishing the superiority of concurrent chemoradiation. This trial randomized 610 inoperable stage II-III NSCLC patients into one of three groups: Sequential cisplatin/vinblastine and conventionally fractionated radiation to 63 Gy (arm 1), concurrent chemotherapy and radiation to 63 Gy (arm 2), or concurrent chemotherapy with accelerated hyperfractionation of 69.6 Gy in twice daily 1.2 Gy fractions over 6 wk (arm 3). Five-year OS rates among the three groups were 10%, 16%, and 13% respectively, and was significantly higher in the standard chemoradiation arm compared to arm 3 (P = 0.046), but not against arm 1 (P = 0.46). MS was 17 mo in arm 2 while it was 14 mo in arm 1. Furthermore, the response rate in arm 2 was 70% and statistically significantly higher compared to sequential chemoradiation (P < 0.05). While acute Grade 3 or higher non-hematologic toxicity rates, particularly severe acute esophagitis, were higher with concurrent therapy, late toxic effects were ultimately similar in concurrent or sequential therapies.

Since RTOG 9410, the superiority of concurrent over sequential chemoradiation has been confirmed by several other studies, including a meta-analysis evaluating seven randomized controlled trials[52]. Concurrent chemoradiation improved OS by an absolute benefit of 4.5% after 5-years, increasing 5-year OS rate from 10.6% to 15.1% (HR = 0.84)[52]. Moreover, locoregional progression decreased by an absolute rate of 6.1% at 5 years, lowering the rate from 35% to 28.9% after concurrent chemoradiation. While concurrent chemoradiation provides better locoregional control, it does not lower distant disease progression compared to sequential chemoradiation (HR = 1.04). Concurrent chemoradiation, however, is associated with higher rates of Grade 3 or higher esophageal toxicity, and can reach up to 18%. The higher toxicity rates were thought to be clinically acceptable and manageable. Induction or consolidation chemotherapy in addition to chemoradiation was not necessary, as it has not been shown to improve 2-year OS or MS[53-56]. However, it could be considered for patients with bulkier tumors whose gross disease could not be treated with radiation without leading to radiation-induced toxicity[57]. Concurrent chemoradiation is better suitable for patients with minimal co-morbidities, favorable performance statuses, and minimal weight loss[53,58]. Patients who are unable to tolerate concurrent chemoradiation should still receive sequential regimens since it still incurs some benefit over radiotherapy alone by increasing 5-year OS from 5% to 10%[59-62].

Current and future directions with chemotherapy regimens for chemoradiation

Chemoradiation therapy is complex, and the agents needed to achieve the best disease control and survival are unknown. The most commonly used regimens are cisplatin/etoposide or carboplatin/paclitaxel. Cisplatin-based regimens have demonstrated to provide better outcomes compared to carboplatin-based regimens[63-65]. In a phase II randomized trial[63] comparing outcomes from 60 Gy thoracic radiation combined with either cisplatin/etoposide (PE) *vs* carboplatin/paclitaxel (PC), OS was significantly better in the PE arm. Three-year OS was 33.1% in the PE arm, but only 13% in the PC arm (P = 0.04). In a meta-analysis from individual patient data[65], cisplatin achieved significantly higher objective response rate of 30% compared to 24% from carboplatin (P < 0.001) among nine trials using platinum-based agents in first-line treatments. While cisplatin-based chemotherapy was more efficacious, it has also led to increased toxicity, especially Grade 3/4 neutropenia[15,63,65].

An individual patient data meta-analysis[65] also observed patients with non-squamous tumors experienced significantly higher mortality when treated with carboplatin and third-generation chemotherapy (HR = 1.12). However, a small number of studies have reported equivalent outcomes with carboplatin as with cisplatin[66,67]. An analysis of over 1842 patients from Veterans Health Administration data demonstrated PC having similar survival as PE. In fact, PE was associated with more hospitalizations, outpatient visits, acute kidney disease, and esophagitis/mucositis compared to PC[66]. However, the results from this trial should be interpreted with caution since 98% of patients were men, and approximately 50% of tumors was squamous cell histology *vs* approximately 20% adenocarcinoma. This was not representative of true population of stage III NSCLC[51,68,69]. Therefore, carboplatin may be more beneficial for men presenting with squamous NSCLC[70]. Liew *et al*[67] also found PC to have similar survival outcomes *vs* PE, with MS to be 20.7 and 13.7 mo with PC and PE, respectively. Relapse free survival was also comparable, and median PFS was 12 mo with PC *vs* 11.5 mo with PE. PC cause significantly less hematological toxicities compared to PE. Therefore, carboplatin therapy may also be more beneficial for older patients and those with multiple co-morbidities.

Third generation chemotherapy agents are increasingly being incorporated into the management of stage III NSCLC patients (Table 2). Their use has not been shown to improve treatment outcomes compared to "older" generation agents like cisplatin/etoposide. A retrospective review[5] compared PE, PC, and cisplatin/docetaxel (PD), and found that MS from PD was not significantly better compared to PE or PC. Median survivals were 27, 36, and 23 mo respectively. Median PFS were 21, 10, and 15 mo in PE, PC, and PD arms respectively, and was significantly better under PE arm (P = 0.01). PE not only has better treatment outcomes, but also had better objective response rates compared to PD or PC. Additionally, WTOG 0105 trial[71] was a phase III study directly comparing second to third generation regimens in the setting of concurrent chemoradiation for inoperable stage III NSCLC. In this study, patients were randomized to receive MVP, carboplatin/irinotecan, or PC along with 60 Gy of concurrent radiation for 6

Table 2 Chemotherapy agents for non-small-cell lung cancer by generation

Generation	Agents	Effect on survival for stages II-III
First	Methotrexate Cyclophosphamide Vincristine Doxorubicin	No effect
Second	Cisplatin, cisplatin-based combinations Ifosfamide Mitomycin Vindesine Vinblastine Etoposide	Combination with radiation superior to radiation alone Concurrent superior than sequential chemotherapy and radiation
Third	Paclitaxel, paclitaxel-based combinations Docetaxel Gemcitabine Vinorelbine Irinotecan Topotecan	Expected to be superior to second generation agents given with radiation

wk. Five-year OS rates for the three arms were 17.5%, 17.8%, and 19.8% respectively. Thus third generation agents did not significantly improve survival; however, it was also not inferior to second generation agents. While third generation agents may be non-inferior to second generation agents, more treatment interruptions were observed with patients receiving carboplatin/irinotecan compared to other chemotherapy groups. Other studies that have chosen to focus on understanding the efficacy of other single-agent third generation chemotherapy such as vinorelbine have findings that agree with prior phase III trials[72,73]. While third generation agents are equivocal to second generation agents regarding survival and response rates, these agents should still be further investigated, even though they do not add benefit to survival or response rates.

Pemetrexed is a new multi-targeted anti-folate chemotherapy agent commonly used with cisplatin in first-line, second-line, and maintenance therapies for non-squamous NSCLC[55,74,75]. Several phase II studies demonstrated that pemetrexed can be safely administered with either cisplatin or carboplatin, yielding a median survival ranging from 18.7 to 34 mo, and esophageal and pulmonary toxicities reaching no higher than 16% and 23% respectively[76-78]. Better outcomes among non-squamous tumor histologies were observed[76-78]. The PROCLAIM trial[79] was a phase III trial comparing concurrent chemoradiation using cisplatin/pemetrexed *vs* PE among non-squamous NSCLC. Although enrollment ended early due to futility, 598 patients were ultimately randomized. MS were 26.8 mo in the pemetrexed arm and 25 mo in etoposide arm (HR = 0.98), which were similar to those observed in phase II trials. PFS was also not significantly different between pemetrexed over etoposide regimens, but trended in favor of pemetrexed. Median PFS were 11.4 and 9.8 in pemetrexed and etoposide arms respectively (HR = 0.86). Moreover, pemetrexed yielded a mildly higher response rate (35.9%) compared to etoposide (33%). Pemetrexed had significantly lower Grade 3 or higher adverse effects compared to PE (P = 0.01), including neutropenia, febrile neutropenia, and thrombocytopenia.

Targeted therapy

Treatment response varies greatly among individuals, and the heterogeneity of tumor biology is expansive. Few driving mutations that may be exploited by therapy have been discovered. Incorporation of therapies targeted to these driver mutations has not yet been successful and remains under investigation. EGFR and ELM4-ALK mutations are likely candidates for targeted therapy in definitive treatment. EGFR inhibitors include monoclonal antibodies targeting the extracellular domain of EGFR, while tyrosine kinase inhibitors (TKI) target the intracellular domain of EGFR and also act as radiosensitizers.

Early studies with cetuximab have shown some promise. The FLEX trial[80] was an international open-labeled phase III trial that compared the efficacy of cetuximab plus chemotherapy with chemotherapy alone among EGFR-positive NSCLC patients. Patients who were given cetuximab in addition to chemotherapy survived significantly longer than those receiving chemotherapy alone (P = 0.04). MS was 11.3 and 10.1 mo respectively (HR = 0.871). The main toxicity associated with cetuximab was an acne-like rash, and 10% of patients on cetuximab experienced severity of grade 3. The RTOG 0324 phase II trial[81] evaluated whether cetuximab given in conjunction with chemoradiation would provide any benefit for unresectable stage III patients. Through this single-arm trial, MS was 22.7 mo and 2-year OS is 49.3%, which was higher than previous reports at the time[51,56]. With such promising results, RTOG 0617 phase III trial[82] evaluated the use of cetuximab with standard and high-dose chemoradiotherapy. MS among patients receiving cetuximab was 25 mo and 24 mo who did not receive cetuximab (HR = 1.07). Moreover, the addition of cetuximab was associated with significantly higher rate of toxicities (P < 0.0001). Grade 3 or higher toxicity rates were 86% with cetuximab and 70% without. Therefore, the addition of cetuximab to concurrent chemoradiation or consolidation treatment did not provide any survival benefit while increasing treatment-related toxicities.

In contrast, TKIs like gefitinib and erlotinib play a larger role in the management of locally advanced NSCLC. Gefitinib is reserved for patients with disease refractory to standard chemotherapy. When used as a first-line or maintenance agent, it has not shown to improve survival[83-85]. INTACT trials randomized unresectable locally advanced to metastatic, chemotherapy-naïve patients to receiving gefitinib with platinum-doublet chemotherapy or platinum-doublet therapy alone. The addition of gefitinib with chemotherapy as first line

treatment did not improve MS, time to progression, or response rates. In SWOG S0023[85], MS with gefitinib maintenance following concurrent chemoradiation with PE decreased to 23 mo compared to 35 mo from placebo (P = 0.013). The decreased survival is primarily due to disease progression rather than treatment toxicity, as toxic death rate was not different from placebo. It is important to notice that these trials enrolled patients with and without EGFR mutations. Perhaps selectively treating patients only with EGFR mutations with gefitinib may lead to different outcomes.

Erlotinib is often used for patients with locally advanced and metastatic disease. The TRIBUTE study[86] randomized 1059 stage ⅢB and Ⅳ NSCLC to either erlotinib or placebo in combination with six cycles of PC. While there was no benefit with the addition of erlotinib to OS and time to disease progression, there was a survival benefit among patients who never smoked. MS with erlotinib increased to 22 mo compared to 10 mo with just PC alone. In a secondary analysis, patients specifically with EGFR mutations were associated with better response rates (P < 0.05) and a trend toward improved time to disease progression (P = 0.092)[87]. However, OS remained similar with the addition of erlotinib among this subset of patients (P = 0.96).

The IPASS trial[88] was a phase Ⅲ trial randomizing stage ⅢB and Ⅳ pulmonary adenocarcinoma patients in East Asia and who were nonsmokers or light smokers to receive either gefitinib alone or carboplatin/paclitaxel as first line therapy. The primary endpoint for non-inferior PFS was met, and surpassed. Gefitinib resulted in 12-mo PFS rate of 24.9% compared to 6.7% achieved with carboplatin and paclitaxel. For patients specifically with EGFR mutations, PFS survival was significantly longer from gefitinib therapy (P < 0.001). A similar phase Ⅲ trial[89] for European NSCLC patients with EGFR mutations randomized patients to receiving erlotinib alone or standard chemotherapy (cisplatin with either docetaxel or gemcitabine), and demonstrated that erlotinib significantly improved median PFS. Thus, TKIs are now considered first-line therapeutic options for patients harboring EGFR mutations.

Crizotinib is an oral small-molecule tyrosine kinase inhibitor against the product of the EML4-ALK fusion gene. For patients who harbor this mutation, crizotinib can be used as a first-line treatment. As a first line therapy, PROFILE-1014 phase Ⅲ trial[90] demonstrated that locally advanced or metastatic ALK-positive NSCLC patients experience longer progression free survival (10.9 mo) compared to cisplatin/pemetrexed therapy (7 mo) (P < 0.001), and improved overall response rate of 74% *vs* 45%, respectively (P < 0.001). However, 1-year survivals between the two groups were not significantly different. Similar findings were found when crizotinib was used as a second-line agent among patients who received prior platinum-based chemotherapy treatment[91]. Unfortunately, acquired resistance to crizotinib can occur, and manifests after a median period of 7-11 mo[90,91]. In this situation, a more potent agent, ceritinib, can be used to treat ALK-positive NSCLC patients refractory to chemotherapy and crizotinib. ASCEND-2 is a single-arm phase Ⅱ trial that demonstrated a durable response for these patients[92]. The majority of patients enrolled in this study also had brain metastases. Whole body overall response rate was 38.6%, with median duration of response of 9.7 mo and median PFS of 5.7 mo. Similarly, ASCEND-4 and 5 trials are two phase Ⅲ randomized control trials designed to compare progression free survival of ceritinib with or without chemotherapy in chemo-naïve or previously treated patients with stage ⅢB and Ⅳ NSCLC. Based upon their success in patients with metastatic disease, a role for erlotinib and crizotinib are being investigated in the potentially curative setting. RTOG 1306 is a phase Ⅱ in which patients with Stage Ⅲ NSCLC with susceptible mutations are randomized to standard chemoradiation alone or with the addition of erlotinib or crizotinib.

Besides EGFR and EML4-ALK inhibitors, other molecular targets are being explored to use in conjunction with chemoradiation for unresectable stage Ⅲ patients. Bevacizumab is one such anti-angiogenic therapy that could have synergistic effects with radiation[93,94]. Phase Ⅲ trials have shown promising results with higher response rates, and longer OS and PFS. However, the high rate of grade 3 or worse esophagitis including formation of trachea-esophageal fistula makes this agent less likely to be used with chemoradiation[95]. Nivolumab, a PD-1 immune checkpoint inhibitor antibody, is garnering attention. Two recent randomized, international phase Ⅲ trials demonstrated that Nivolumab prolonged 1-year OS, 1-year PFS, and response rates compared to docetaxel for patients whose disease had progressed during or after platinum-doublet chemotherapy for both squamous and non-squamous histologies[96,97]. With such promising results, perhaps immunotherapy will play an increasing role in the management of locally advanced NSCLC patients in the future.

Current and future directions with radiation for chemoradiation

Definitive radiotherapy alone continues to yield poor outcomes for stage Ⅲ patients. MS continues to range from 10 to 26 mo[6,98,99], with a 5-year survival rate of less than 25%[98,100,101]. Such low outcomes are related to the failure to eradicate local disease as well as development of distant metastasis. Several ways to improve local control and survival include dose escalation and altered fractionation schedules.

Increasing dose intensity has been shown to improve local control and survival in early studies. A retrospective analysis[102] of 7 prospective RTOG trials demonstrated that the higher biological effective dose (BED) of radiotherapy was associated with better outcomes in locally advanced NSCLC. Phase Ⅰ and Ⅱ dose escalation studies[103-105] using conformal radiation demonstrated that conformal thoracic radiation up to 74 Gy was fea-

sible and tolerable, and led to encouraging survival and response rates with acceptable toxicity levels. A modified phase I/II trial[103] randomized 62 unresectable stage III NSCLC patients to one of four cohorts where radiation dose was escalated from 60 to 74 Gy. No dose-limiting toxicity was observed from any cohorts, making 74 Gy the maximum tolerated dose (MTD). The most common toxicity was esophagitis, and approximately 8% of patients experienced grade 3/4 esophagitis. Overall response rate was 52%, and MS of 26 mo. Three-year OS rate was 40% and 3-year PFS was 29%. RTOG 0117 trial[104] confirmed that MTD was 74 Gy with 3D-CRT, since doses beyond 74 Gy incurred high pulmonary toxicity levels. Delivering 74 Gy concurrently with PC led to encouraging response rate of 66.6% and 1-year OS of 66.7%. MS was 24.3 mo, surpassing the study's predefined MS benchmark of 18 mo which was chosen to be the best that was achieved by CALGB. Despite such encouraging early results, results from the intergroup phase III RTOG 0617 trial[82] did not recommend use of 74 Gy as OS was significantly worse than the standard dose of 60 Gy. MS was 20.3 mo after delivery of 74 Gy compared to 28.7 mo from standard dose (HR = 1.38, P = 0.004). The rate of severe esophagitis was significantly worse at 21% in high dose group *vs* 7% in standard dose group (P <0.0001). Constraints for heart dose were not mandated, and heart doses were significantly higher among patients receiving high dose radiation, and this likely contributed to a survival detriment in those patients.

Accelerated hyperfractionation (hyperFRT) is a way to deliver a higher dose of radiation over the same time period as one would with conventional fractionation schedules. To do so, a lower dose per fraction is delivered more frequently, typically twice a day. The benefits of hyperFRT schedule were evaluated by various trials, in which early reports were rather mixed. RTOG 8311[106] was a phase I trial of radiation dose escalation. Patients were randomized to receive total doses of total doses of 60.0 Gy, 64.8 Gy, 69.6 Gy, 74.4 Gy or 79.2 Gy delivered in 1.2 Gy twice daily fractions five days a week. Survival did not improve at doses beyond 69.4 Gy. At this dose, MS was 13 mo and 2-year OS was 29%, which was significantly better than lower radiation doses tested (P = 0.02). With an optimal dose set for hyperFRT, the phase III RTOG 8808 trial[107] compared outcomes of conventional fractionation plus induction cisplatin/vinblastine (arm 1), hyperFRT at 69.4 Gy in 1.2 Gy fractions (arm 2), and conventional fractionation RT alone (arm 3). While survival from arm 2 was better compared to arm 3, it was not significantly better than arm 1[107]. Five-year OS rates were 8%, 6%, and 5% respectively, with MS rates of 13.2, 12, and 11.4 mo respectively. RTOG 9410[51] study echoed similar findings as RTOG 8808. This study compared sequential cisplatin/vinblastine and conventional RT (arm 1), concurrent cisplatin/vinblastine and conventional RT (arm 2), and concurrent cisplatin/etoposide with hyperFRT (arm 3). Conventional fractionation was 63 Gy in 1.8 Gy fractions over 7 wk), and hyperFRT delivered 69.6 Gy in 1.2 Gy twice daily fractions. Five-year OS were 10%, 16% and 13% respectively, and significantly better in arm 2 (P = 0.046). MS were 14.6, 17 and 15.6 mo, respectively. Between the two concurrent chemoradiation treatments, overall response rates were similar between arms 2 (70%) and 3 (65%), respectively. Grade 3 or higher toxicities were observed in 45% of patients receiving hyperFRT, though was not significantly different from arm 2. Incorporation of hyperFRT into multi-modality therapy has also been tested. Pöttgen *et al*[108] retrospectively compared outcomes of neoadjuvant chemotherapy and hyperFRT (45 Gy in 1.5 Gy twice daily fractions) *vs* conventional RT (46 Gy in 2 Gy daily fractions). While complete response rates were higher in neoadjuvant concurrent chemotherapy and hyperFRT compared to the control group using conventional RT (P < 0.006), the use of hyperFRT was not associated with improved survival.

Continuous hyperfractionated accelerated radiotherapy (CHART) delivers less than 1.8-2 Gy per fraction in an accelerated course to allow for less normal tissue injury per fraction and inter-fraction normal tissue repair. Despite that total dose of radiation and dose per fraction delivered are lower compared to conventional fractionation schemes, it is hypothesized that delivering greater radiation dose per unit of treatment time outpaces tumor cell repopulation which could improve treatment outcomes[109-111]. Standard CHART delivers 54 Gy in 1.5 Gy fractions three times per day for 12 consecutive days. A randomized control trial[112] comparing the efficacy of CHART to conventional fractionation, which delivered 60 Gy in daily 2Gy fractions, showed that CHART significantly improved 2-year OS by 9%, increasing it from 20% to 29% (HR = 0.76, P = 0.004). This finding translated to a 22% overall reduction in relative risk of death. The largest benefit of CHART was observed within patients with squamous NSCLC, where 2-year survival improved by 14%, increasing the survival rate from 19% to 33%. Adverse effects were higher in patients receiving CHART compared to conventional fractionation schemes within the first three mo of therapy. Severe dysphagia in particular was seen in 19% and 3% of patients, respectively. Overall, acute and late toxicities were not different between groups. CHARTWEL was a modification of CHART in that treatments were not given during weekends. A phase III trial[113] randomized 460 patients to either CHARTWEL or conventional fractionation. Five-year OS were 11% and 7% from CHARTWEL and conventional RT, and were not significantly different from each other. Local control rates were found to improve after CHARTWEL among patients with higher T or N staging (P = 0.006) or after receiving neoadjuvant chemotherapy (P = 0.019). Acute dysphagia and radiation-induced pneumonitis were frequent among CHARTWEL patients. Therefore, unlike CHART, CHARTWEL did not exhibit a survival benefit. Results from CHARTWEL was a proof-of-concept that

delivering lower total dose can be compensated by shorter treatment time, and that time is an important factor for the management of unresectable locally advanced NSCLC patients. The addition of neoadjuvant chemotherapy to CHART did not significantly improve survival or response rates[114,115], but was associated with less toxicity compared to standard fractionated concurrent chemoradiation and therefore could still be an option for locally advanced patients. In a recent small phase I trial[100], escalating total delivered dose from 54 Gy to 64.8 Gy in the setting of CHART was feasible and did not exhibit dose-limiting toxicities. MS was 24 mo across all dose cohorts, and Grade 3 or worse adverse effects were found in 6 of 18 patients. Thus, CHART potentially enhances survival and response outcomes compared to conventional fractionation radiation. Table 3 summarizes key prospective trials evaluating hyperFRT fractionation schedules over conventional fractionation radiotherapy.

A meta-analysis of studies comparing hyperfractionated to conventional radiation[8] determined that hyperFRT ultimately has significant survival benefit despite mixed results from earlier trials. HyperFRT increased 5-year OS by 2.5% (P = 0.009) over conventional fractionation and decreased the risk of death by 12% (P = 0.02). However, hyperFRT did not significantly improve PFS, and was associated with higher toxicities compared to conventionally fractionated radiotherapy. While hyperFRT regimens may be superior to conventionally fractionated radiotherapy, the cost of greater toxicity, particularly severe esophagitis, and logistics of treating patients multiple times per day has prevented its wider adoption in a clinical setting.

Hypofractionation (hypoFRT) delivers a higher dose per fraction compared to conventional fractionation schedules. The overall delivered dose is lower than conventional fractionation schemes, but tumor repopulation may be outpaced with greater tumor cell kill per fraction. HypoFRT is potentially able to deliver higher biologically equivalent dose to provide better local control[102,109]. Hypofractionation also offers advantages of less total fractions and less machine time per patient. In a pilot study[116] of 59 stage IIIA/B patients treated with 75 Gy in 28 daily fractions (2.68 Gy/fraction) over 5.5 wk, patients had a MS of 10 mo, and a 3- and 5-year OS of 18% and 4%, respectively. Only three of 59 patients experienced severe late complications from therapy, suggesting that hypoFRT is an acceptable and tolerable regimen. A randomized control trial[117] compared conventional RT (60 Gy in 2 Gy fractions over 6 wk) to hypoFRT (60 Gy in 5Gy weekly fractions for 12 wk). One- and two-year OS were 49% and 23% in the conventional RT arm, and 59% and 29% in hypoFRT arm respectively. These survival rates were not statistically significantly different from each other, but agree with previous reports. Local failure and response rates from hypoFRT were similar to conventional RT as well, thus suggesting hypoFRT is as efficacious as conventional RT but not superior. The EORTC 08972-22973 trial[61] tested the efficacies of sequential gemcitabine/cisplatin *vs* hypoFRT or concurrent cisplatin and hypoFRT therapies. While the trial was underpowered to detect any significant difference, OS and toxicity rates favorably trended towards concurrent arm of the trial. Two-year OS rates for patients treated with sequential chemoradiation is 34% while those in concurrent chemoradiation arm is 39% survival rate. MS for the sequential and concurrent arms are 16.2 and 16.5 mo respectively. The SOCCAR phase II trial[101] also tested sequential *vs* concurrent cisplatin/vinorelbine with hypoFRT. The primary endpoint of this trial was treatment-related mortality, which occurred in 2.9% and 1.7% of patients on concurrent and sequential arms, respectively. The rate of Grade 3 or worse esophagitis was similar between the two arms, as were 2-year OS, median survival, 1-year PFS rates, and median PFS. This trial demonstrated that hypoFRT given with full dose chemotherapy has similar outcomes to previous trials and had a low, acceptable treatment-related mortality rate. Table 4 summarizes key prospective trials evaluating hypoFRT fractionation schedules for NSCLC treatment.

Intensity modulated radiotherapy (IMRT) delivers radiation using inverse computer planning to determine multiple intensity levels across varying beam shapes, which has allowed for improved homogenous and conformal dose distributions for complex target volumes while sparing critical adjacent structures. While there is a hypothetical advantage of reducing toxicity by reducing dose to normal tissue compared to 3D-CRT, there has been no prospective evidence to guide when to use IMRT for select NSCLC patients. There have been concerns with using IMRT which have limited its adoption. It can expose a larger volume of lungs to low-dose radiation, which is often associated with pneumonitis[118]. Additionally, there are uncertainties regarding the delivery of radiation related to multi-leaf collimator movement and respiratory-related tumor motion[119]. These concerns lack convincing evidentiary support. There have been several retrospective institutional studies reporting improvements in overall dosimetry and rates of toxicity with IMRT. Notably, a review of 151 NSCLC patients treated from MD Anderson Cancer Center compared rates of treatment-related pneumonitis among patients treated with 3D-CRT *vs* IMRT[118]. While patients treated with IMRT had more advanced disease, debilitated performance status, and larger median gross tumor volume, rates of Grade 3 or higher treatment-related pneumonitis at 1-year was 8%, compared to 32% observed for patients treated with 3D-CRT (P = 0.002). IMRT also significantly reduced V20 doses compared to 3D-CRT (P < 0.001). RTOG 0617[82] included patients treated with IMRT. Planned secondary analyses for survival outcomes, toxicities, and quality of life from RTOG 0617 trial were done. IMRT had comparable OS and PFS to 3D-CRT[120]. However, IMRT was associated with significantly higher lung V5, while having lower lung V20 (P = 0.08) and heart doses at V5,

Table 3 Prospective trials for hyperfractionated radiation schedules for non-small-cell lung cancer treatment

Ref.	Phase	Study design	Chemo regimen	RT	No. of patients	Stage	Median f/u (mo)	OS	Median OS (mo)	Response rate	Toxicity
RTOG 83-11 Cox *et al*[106] (1990)	1 and 2	Randomized 1 of 5 dose groups: 60, 64.8, 69.6, 74.4, 79.2 Gy	None	Dose delivered in 1.2 Gy twice daily fxns	848	III	N/A	2-yr, 29% (69.6 Gy arm)	13 (69.6 Gy arm)		Risk for severe/ life-threatening pneumonitis- 2.6% (60 Gy), 5.7% (64.8 Gy), 5.7% (69.6 Gy), 8.1% (74.4 Gy)
RTOG 8808/ ECOG 4588 Sause *et al*[107] (2000)	3	Conv. RT + chemo *vs* hyperFRT *vs* conv. RT	Cisplatin/ vinblastin	Conv RT: 60 Gy in 2 Gy daily fxns HyperFRT: 69.6 Gy in 1.2 Gy twice daily fxns	458	II-IIIB, unresectable	> 60	5-yr, 8%, 6%, 5%	13.2, 12, 11.4		6 G4+ RT-related toxic events-4 of them in hyperFRT arm
RTOG 9410 Curran *et al*[51] (2010)	3	Sequential chemoRT (conv., arm 1) *vs* concurrent chemoRT (conv., arm 2) *vs* concurrent chemoRT (hyperFRT, arm 3)	Cisplatin/ vinblastine (arms 1 and 2) Cisplatin/ etoposide (arm 3)	Conv: 63 Gy in 1.8 daily fxns HyperFRT: 69.6 Gy in 1.2 Gy twice daily fxns	610	II-III, inoperable	132	5-yr, 10%, 16%, 13%)	14.6, 17, 15.6	ORR- 61%, 70%, 65%	G3+ acute esophagitis- 4%, 22%, 45% No difference in G5 toxicities
Saunders *et al*[112] (1999)		CHART *vs* conv. RT	None	Conv RT: 60 Gy in 2 Gy daily fxns HyperFRT: 54 Gy in 1.5, 3 x daily fxns, for consecutive days	563	III	> 48	2-yr, 29% *vs* 20% (P = 0.004) 2-yr, 33% *vs* 19% if SCC			Severe dysphagia, 19% *vs* 3%
ARO 97-1 Baumann *et al*[113] (2011)		CHARTWEL *vs* conv. RT	None	Conv RT: 66 Gy in 2 Gy fxns for 6.5 wk CHARTWEL: 60 Gy in 1.5, 3 x daily fxns for 2.5 wk	460	I-IIIB	40.8	2-yr, 31% *vs* 32% 3-yr, 22% *vs* 18% 5-yr, 11% *vs* 7%			Higher incidence of acute dysphagia with CHARTWEL
INCH trial Hatton *et al*[114] (2011)		Induction chemo + CHART *vs* CHART alone	Cisplatin/ vinorelbine	54 Gy in 1.5 Gy fxns (3 x daily) for 12 consecutive days	46	I-III, inoperable	33		25 *vs* 17		G3/4 adverse effects 65% *vs* 57%
ECOG 2597 Belani *et al*[115] (2005)	3	Induction chemo + conv. RT *vs* induction chemo + CHART	Carboplatin/ paclitaxel	Conventional RT: 64 Gy in2 Gy fxns (daily) 57.6 Gy in 1.6 Gy fxns (3 x daily) for 15 d	141	IIIA/B, inoperable	> 36	2-yr, 24% *vs* 44% 3-yr, 14% *vs* 34%	14.9 *vs* 20.3	ORR, 22% *vs* 25%	Acute esophagitis 16% *vs* 25% G3/4 acute pulmonary toxicity observed in conventional RT arm
Hatton *et al*[100] (2016)	1	Randomized 1 of 4 dose groups: 54, 57.6, 61.2, 64.8 Gy	None	Each dose group delivered in 1.8 Gy, 2-6 fxns daily	18	IIIA/B	21	2-yr, 49% (entire cohort)	24 (entire cohort)	ORR, 61% (entire cohort) CR, 28% (entire cohort)	G3/4 adverse effects in 6 of 18 patients No dose-limiting toxicities

SCC: Squamous cell carcinoma; OS: Overall survival; RT: Radiotherapy.

V20, and V40. V20 was ultimately predictive of grade 3 pneumonitis. Rate of Grade 3 or higher pneumonitis was 2 fold lower among patients treated with IMRT (3.5%) *vs* 3D-CRT (7.9%) despite that patients with IMRT

Table 4 Prospective trials for hypofractionation radiation schedules for non-small-cell lung cancer treatment

Ref.	Phase	Study design	Chemo regimen	RT	No. of patients	Stage	Median f/u (mo)	OS	Median OS (mo)	Response rate	Toxicity
RTOG 8312 Graham *et al*[116] (1995)	Pilot	HypoFRT	None	75 Gy in 2.68 fxns daily for 5.5 wk	59	IIIA/B		1-yr, 41% 2-yr, 25% 3-yr, 18% 5-yr, 4%	10		Most common was G1/2 pulmonary fibrosis and pneumonitits
Slawson *et al*[117] (1990)		Conv. RT *vs* HypoFRT		Conv. RT: 60 Gy in 2 Gy fxns (daily) HypoFRT: 60 Gy in 5Gy fxn (weekly)	150	Locally advanced, unresectable	36	1-yr, 49% *vs* 59% 2-yr, 23% *vs* 29%		CR, 17% *vs* 26%	No difference for later reactions
EORTC 08972-22973 Belderbos *et al*[61] (2007)	3	Sequential *vs* concurrent chemo + hypoFRT	Gemcitabine/ cisplatin	66 Gy in 2.75 Gy fxns in 32 d	158	I-IIIB, Inoperable	39	2-yr, 34% *vs* 39% 3-yr, 22% *vs* 34%	16.2 *vs* 16.5		G3 hematological toxicity higher in sequential arm (30% *vs* 6%) Esophagitis more common in concurrent arm (5% *vs* 14%)
SOCCAR Maguire *et al*[101] (2014)	2	Sequential *vs* concurrent chemo + hypoFRT	Cisplatin/ vinorelbine	55 Gy in 2.75 Gy fxns over 4 wk	130	III, inoperable	N/A	2-yr, 46% *vs* 50%	18.3 *vs* 24.3		G3+ esophagitis 8.5% *vs* 8.8% Tx-related mortality, 1.7% *vs* 2.9%
Liu *et al*[126] (2013)		Concurrent chemo + HypoFRT dose escalation	Carboplatin/ vinorelbine	60-75 Gy in 3 Gy fxns for 5 wk	26	IIIA/B, unresectable	11.5	1-yr, 60.9%	13	CR, 26.9% Partial, 53.8% Stable, 19.2% ORR, 80.8%	Acute esophagitis, 88.5% (G3 = 15.4%) Pneumonitits, 42.3% (G3 = 77%)
Lin *et al*[127] (2013)	1	Concurrent chemo + hypoFRT dose escalation	Carboplatin/ vinorelbine	60-72 Gy in 3Gy fxns for 5 wk	13	IIIA/B, unresectable	10			CR, 23.1% Partial, 15.4% Stable, 15.4% ORR, 84.6%	4 instances dose-limiting toxicities, all occurring in 72 Gy arm
Kim *et al*[128] (2013)		Concurrent chemo + hypoFRT IMRT dose escalation	Cisplatin/ vinorelbine	48 Gy in 2.4 Gy fxns with boosts of 16.8 Gy/7, 20 Gy/7, or 22.7 Gy/7	12	II-IIIB, unresectable	22	1-yr, 58.3%	12.7	CR, 75% Partial, 33% Stable, 25%	No G3 acute or late radiation-toxicities

HypoFRT: Hypofractionation; IMRT: Intensity-modulated radiotherapy; CR: Complete response.

had more advanced stage disease and larger PTV to lung ratios compared to those treated with 3D-CRT[120]. Quality of life at 12 mo was significantly higher for patients treated with IMRT than those with 3D-CRT[121]. In an attempt to identify patients who may derive a survival benefit from IMRT over 3D-CRT, Jegadeesh *et al*[119] used the National Cancer Data Base to analyze stage III NSCLC treated with chemoradiation for curative intent. This analysis suggested that patients with T3 and T4 disease are associated with improved median survival (17.2 and 14.6 mo respectively) and 5-year OS (19.9% *vs* 13.4% respectively). T stage and treatment time was significantly associated on multivariate and propensity-matched cohort analysis. With such promising results,

a prospective randomized trial comparing IMRT and 3D-CRT for NSCLC is needed.

Proton therapy for the treatment of NSCLC is under active research. Protons have characteristic energy "Bragg peaks", which limit exit dose into adjacent tissues[122]. This unique feature could reduce the irradiated volume of normal tissues, such as the heart, normal lungs, esophagus, and spinal cord, relative to photon dose distributions. This may limit toxicity to allow improved tolerance of relatively higher doses than photon radiation. Proton therapy from single-institution reports have delivered 74 cobalt gray equivalent (CGE) with concurrent chemotherapy for locally advanced NSCLC. In various small trials and single-institution reports, MS typically ranged from 26.7 to 30.4 mo[99,123,124], which was longer compared to that achieved in RTOG 0117 trial which delivered 74 CGE with conventional photon RT. Local recurrences range from 5.5% to as high as 40%[99,124,125], and development of distant metastases is still difficult to control as up to 45% of patients experience distant progression[123,124]. Toxicity rates were expectedly lower compared to those experienced at 74 Gy with conventional photon RT from RTOG 0117 trial[124]. Results of RTOG 1308, a phase III randomized trial comparing overall survival outcomes after photon *vs* proton chemoradiation for inoperable stage II-IIIB NSCLC patients, is anticipated.

CONCLUSION

Locally advanced stage III NSCLC continues to be a deadly disease, and consists of a heterogeneous patient population. Generally, treatment requires combined modalities that address local disease control, with surgery or radiation, and control of systemic spread with chemotherapy. Several combinations and various sequences of systemic and local therapies have been investigated with similar or conflicting outcomes making determination of the optimal management for these patients challenging. Multiple strategies have been developed in order to maximize survival through improved disease control through treatment intensification; however, disease progression treatment-related toxicities continue to limit survival. For patients with resectable disease, surgery offers highest rates of local control. With new awareness of chemotherapy and radiation, the role of surgery as well as disease staging are being evaluated. Multi-modality therapy is playing an increasingly important role for both resectable and unresectable stage III patients. Concurrent chemoradiation remains the standard of care in the management of inoperable or unresectable patients. In an effort to maintain or improve outcomes with less toxic effects, 3rd generation chemotherapy agents have been studied and incorporated into treatment. Targeted therapy, immunotherapy, and other non-cytotoxic drug therapies are also being investigated, and may play a greater role in the future. While dose escalation with conventional RT has not proven to improve treatment outcomes, alternative fractionation, particularly hypofractionation, may play a larger role in future management. IMRT and proton radiotherapy provides an opportunity to provide higher radiation doses with less toxicity. Future work will be needed to exploit biological tumor differences and integrate advancements in radiation technology.

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