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Clinical and research priorities for combined modality therapy in stage III NSCLC

Angela Lin^{1,2} & Andrea Bezjak^{*1,2}

Practice points

- Stage III NSCLC is a heterogeneous disease entity.
- Patient factors, such as advanced age, medical comorbidities, reduced respiratory reserve and poor performance status, contribute to the complexity of managing stage III NSCLC cases.
- Disease factors, such as bulky disease, N3 and T4 status, represent unique challenges.
- In order to improve the therapeutic ratio of treatment, one needs to either increase the benefit of treatment or reduce toxicities, or both.
- Dose escalation of radiation without increasing overall treatment time is a focus of current research.
- Understanding tumor-specific biology is important; and the addition of targeted agents or immunotherapy to radiation requires further investigation.

Stage III NSCLC comprises of a heterogeneous group of patients with regard to stage, extent of disease and prognosis. Disease presentation can often be complex in clinical practice, and the challenges are not well-defined in clinical trials or practice guidelines. In order to improve the therapeutic ratio of treatment, one needs to either increase the benefit of treatment or reduce toxicities, or both. Priorities in radiation therapy include dose escalation, imaging advances, improved target delineation, reduced planning target volume margin, intensity-modulated radiotherapy, image-guided radiotherapy, motion management and the use of cytoprotectants. Priorities in systemic therapy include the incorporation of molecularly targeted and immune-modulatory agents.

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Lung cancer is the most common cancer worldwide [1]. NSCLC accounts for approximately 85% of lung cancer diagnoses [2]. Stage III NSCLC comprises of a heterogeneous group of patients with regard to T and N classification, extent of disease and prognosis. Heterogeneity exists even within a single N classification, such as N2 disease, which includes a spectrum from occult pathological N2 discovered at the time of surgery, to biopsy proven N2, to bulky or multistation mediastinal lymphadenopathy [3]. These differing presentations of stage III NSCLC require vastly different management considerations. A multidisciplinary approach is essential for managing such cases.

Presumed stage I or II NSCLC are often managed with upfront surgery; however, some will ultimately be stage III pathologically, necessitating decisions about adjuvant treatment [4,5]. While there is a clear survival benefit of adjuvant chemotherapy in these patients [5], the role of adjuvant radiotherapy is more controversial. Phase III studies and meta-analyses of adjuvant radiotherapy

KEYWORDS

• combined modality therapy • improve therapeutic ratio • modern radiotherapy • stage III NSCLC • targeted agents

¹Radiation Medicine Program, Princess Margaret Cancer Centre, Toronto, Ontario, Canada

²Department of Radiation Oncology, University of Toronto, Toronto, Ontario, Canada

*Author for correspondence: andrea.bezjak@rmp.uhn.on.ca

in completely resected stage III NSCLC with N2 disease suggest that its addition to surgery does not impact on overall survival, but has an observed benefit in reducing local recurrence [4]. Trimodality approach utilizing neoadjuvant chemoradiation and surgical resection is well recognized for superior sulcus tumors, and is also recommended for carefully selected stage IIIA patients, for example, with single station N2 disease [6,7]. Definitive concurrent chemoradiation is recommended as a curative treatment for more advanced disease not suited to a trimodality approach [8,9]. Alternative options for patients who are not suitable for concurrent chemoradiation include radiation alone, sequential treatment with induction chemotherapy followed by radiation or surgery, or consolidative chemotherapy after radiation or surgery [8,9]. We will now review the current challenges and research priorities for combined modality therapy in stage III NSCLC.

Challenging clinical scenarios

The presentation of stage III NSCLC can be complicated and the data with which to meet these challenges is often limited in clinical trials or practice guidelines. There are a number of disease factors and patient factors that contribute to the complexity of lung cancer management.

• Disease factors

Bulky primary or nodal disease can be challenging because of increased risk of toxicity of therapy and concerns about likelihood of local control. Specifically, both radiation pneumonitis and radiation esophagitis would be expected to be more severe with large irradiated volume. N3 disease can be difficult to irradiate safely even if not bulky, due to the dispersed location of nodal involvement and the need to avoid critical organs such as spinal cord. Modern planning techniques such as intensity-modulated radiotherapy may help to ensure coverage of a complex target with more acceptable dose to normal tissues [10]. Induction chemotherapy before concurrent chemoradiation may be considered to help reduce irradiated volume to achieve a safe radical radiation plan, although clinical trials suggest poorer outcomes when concurrent therapy is preceded by induction therapy [11]. Carefully selected resectable T4N0–1 lesions may benefit from surgery in the context of multimodality approach. For instance, with improvement in surgical techniques and perioperative

care, selected T4 lesions that involve the carina, superior vena cava or one vertebral body may be managed with preoperative chemotherapy or chemoradiotherapy. Separate nodule in a different ipsilateral lobe (T4) can be a synchronous primary or satellite metastatic nodule, which may have a favorable outcome if treated aggressively with surgical resection or stereotactic radiotherapy.

• Patient factors

Lung cancer is predominately a disease of older adults [12]. Older patients with lung cancer have lower rates of receiving anticancer treatment than their younger counterparts [13,14]. That is particularly the case when the curative therapy involves surgery and/or combined modality therapy. Decisions regarding surgery or systemic therapy in older patients can be challenging. However, older patients with advanced NSCLC can derive equivalent benefit from chemotherapy compared with younger patients, and that despite some increased toxicity with platinum-based regimens, this treatment is still tolerable [15,16]. Comprehensive geriatric assessment incorporating performance status, organ function, functional and cognitive abilities to perform activities of daily living, socioeconomic and emotional situation, nutritional factors and medication profile, as opposed to chronological age alone, can aid in clinical decision-making [15].

The presence of medical comorbidities is a key factor in decision-making. Two of the major factors in the etiology of lung cancer – older age and smoking status – are also associated with a higher prevalence of comorbidities [17]. Population-based studies demonstrate that higher comorbidity burden is associated with higher lung cancer-specific mortality [18–21]. Patients with comorbidities are more likely to experience treatment toxicity, and sometimes cannot receive standard therapy. These patients are also less likely to complete planned treatment. Beyond the impact on treatment delivery, comorbidities can significantly limit expected survival thus mitigating any benefit from radical treatment [17].

Reduced respiratory reserve poses a particular challenge to treatment recommendation for stage III NSCLC. Patients with significant chronic obstructive pulmonary disease (COPD) may not be good surgical candidates due to their low cardiopulmonary reserve and increased risk

of perioperative pulmonary complications. With definitive chemoradiation, there are challenges as high-dose radiation volume leads to lung fibrosis and increased risk of radiation pneumonitis, which a patient with reduced lung reserve may not be able to tolerate. Furthermore, the presence of severe COPD often negatively impacts patients' performance status, which is closely associated with both tolerance and benefit of treatment. Idiopathic pulmonary fibrosis (IPF) is a particular challenge – it is associated with an increased risk of lung cancer and patients with IPF can experience acute exacerbation of IPF following surgical intervention, radiotherapy and chemotherapy [22,23]. More specifically, acute extended radiation pneumonitis, characterized by bilateral pulmonary ground-glass or infiltrates that extend out of the irradiated area within 30 days after completion of radiation, occurs at a much higher rate in patients with pre-existing interstitial lung disease compared with those without [24]. Input from respirologists, careful pretreatment computed tomography (CT) evaluation and clinical assessment of the patients are critical to the diagnosis of IPF, particularly to differentiate between IPF and other similar interstitial processes with less risk of worsening after treatment. Multidisciplinary collaboration is also important in determining whom to treat and how, as well as post-treatment follow-up of their lung cancer and continued management of their IPF.

Patients with poor performance status are less likely to tolerate radical treatment and have worse outcomes [25]. The optimal treatment for these patients is difficult to determine, as this cohort is often excluded from clinical trials. It may be prudent to consider the likely pathophysiology of poor performance status in a specific patient, such as tumor-related factors versus host-related factors, to individualize therapy [26]. Sometimes, poor performance status is secondary to disease-related symptoms, and radical treatment in these patients may in fact improve their performance status. Other patients may have poor performance status secondary to comorbidities that are not having a direct impact on their life expectancy, for example, severe osteoarthritis, and should deserve an opportunity to be considered for radical treatment as well. In patients whose poor performance status is truly due to concomitant diseases (e.g., smoking-related conditions, such as COPD or cardiovascular disease), alternative options may include

sequential rather than concurrent chemotherapy and radiotherapy, altered chemotherapy regimen or radiation alone [27].

Clinical & research priorities

It is important to focus on identifying clinical and research priorities for stage III NSCLC patients, since they are potentially curable and there is a clear need to improve their currently achievable outcomes. In order to improve the therapeutic ratio of treatment, one needs to either increase the benefit of treatment or reduce toxicities or both.

• More biologically effective &/or safer radiotherapy

In order to increase the benefit of radiation treatment, many attempts have been made to increase the radiation dose, as evidence from early-stage NSCLC stereotactic radiation trials as well as from the CHART trial strongly suggests that there is a dose effect [28,29]. The benefit of high radiation dose has been demonstrated in early-stage patients, as biological effective dose over 100 Gy is associated with high local control rates [30,31]. However, uniform dose escalation of tumor volumes beyond 60 Gy in standard fractionation in locally advanced patients has not shown benefit, and in fact has shown survival detriment, which may be owing to increased rates of lethal toxicities [32]. This leads to increased interest in exploring other methods of treatment intensification to improve local control and survival, such as dose escalation with altered fractionation, individualized dose escalation of tumor subvolumes, stereotactic radiotherapy boost and the addition of targeted agents and immunotherapy to radiation [33].

Accurate delineation of gross tumor volume is paramount in radiotherapy. In lung cancer, there can be large uncertainties associated with target delineation based on CT information alone. Both intra- and inter-observer variability have been demonstrated, especially at tumor-atelectasis interface and with identification of involved or suspicious lymph nodes [34]. Integration of fluorodeoxyglucose (FDG)-PET/CT information not only improves clinical staging, but also substantially improves the accuracy of target delineation [35]. However, the common practice is for patients to have a diagnostic PET/CT scan, which is used as a reference or fused with CT simulation scan to aid radiation oncologist's target delineation. There

are two significant limitations to this process: one is that the disease may have progressed in the time interval between PET/CT scan and treatment start so that relying on PET information is misleading. Indeed, MacManus and colleagues have demonstrated that 39% of patients with NSCLC progressed during the interval between the diagnostic PET/CT scan and a subsequent PET/CT scan performed at the same time as the radiation planning scan [36]. The other limitation stems from the technical challenges of using PET information obtained in the radiology department, for radiotherapy planning. Ideally, both FDG-PET and CT simulation scans should be completed simultaneously, with the same patient position and slice thickness, and with same respiratory motion management, in order to prevent common errors with image fusion [37]. Continued research will be needed to further optimize application and contouring protocols with PET/CT simulation in radiotherapy planning. A focus of current research is on exploring dose escalation of tumor subvolumes, such as parts of the tumor that have higher FDG uptake. The pretreatment volume of highest FDG-avid disease within the primary lung tumor correlates with areas of local relapse following treatment [38–40]; this provides grounds for ongoing studies that selectively boost the most FDG-avid disease within the tumor in the hope to improve local control without adding toxicities [41–43].

In addition to FDG-PET/CT, other new functional imaging biomarkers are emerging as research priorities. For example, there is increasing interest in imaging hypoxia with ^{18}F -misonidazole (FMISO) or ^{18}F -fluoroazomycin-arabinoide (FAZA)-PET. Hypoxia may serve as an important biologic determinant of clinical outcome following treatment in lung cancer; the evidence from other cancer types is convincing [44,45]. The ability to reliably measure hypoxia with noninvasive techniques opens the door to many areas of research, such as prognostication, adaptive radiotherapy with dose escalation to hypoxic areas [41–43], and the use of hypoxic cell sensitizers, such as nimorazole, in combination with radiation [46].

The aforementioned methods are a few ways to increase tumor control, by increasing dose and by improving the accuracy of radiation target. On the other hand, we can reduce normal tissue toxicity. This can be achieved in several ways: for example, by reducing planning target volume (PTV) margin to reduce exposed normal tissue volume, by increasing the precision of real-time

delivery through image-guided radiotherapy, by using patient-specific margin to account for organ motion, by reducing motion with active breathing control or respiratory gating, by using more complex planning techniques such as intensity-modulated radiotherapy or by using normal tissue protecting agents.

Technological advances have already enabled the implementation of breathing-adapted radiotherapy. The use of 4D CT and internal target volume (ITV) concepts has been routinely implemented in clinical practice, as it allows individualized margin that is tailored to patient-specific respiratory motion, which in turn allows for a small internal target volume to PTV expansion [47]. Daily cone-beam CT for image guidance further reduces PTV margin [48]. The improved accuracy decreases irradiated dose and volume of organs at risk. Adaptive management of anatomical and biological response during treatment has large potential, and is being investigated. One needs to be vigilant not to adapt to the shrinking tumor volume if there is tumor regression without considering potential negative consequences, as subclinical disease surrounding the regression may still require full treatment dose.

Another method to reduce toxicity is to use pharmacologic agents that can scavenge free-oxygen radicals as radiation cytoprotectants. The most commonly investigated and used agent is amifostine, which is thought to be preferentially active in normal cells, as the drug floods the normal tissues more quickly after administration but enters tumor cells much more slowly [49]. Its clinical use has not been widely accepted, mainly due to the concerns of possible tumor protection and loss of therapeutic gain. Meta-analyses of several published randomized trials involving patients with locally advanced NSCLC treated with radiotherapy with or without chemotherapy found that amifostine had no effect on tumor response and it decreased grade 3–4 esophagitis and pneumonitis rates [50,51]. However, more research will be required before its wide use in practice.

• Systemic therapy

The addition of chemotherapy to radiotherapy improves 2-year overall survival by 4%, which is a fairly modest gain considering the toxicities of cisplatin-based chemotherapy [52]. This leads to the search for novel approaches to improve cure rates in stage III NSCLC, including the

evaluation of targeted agents and immunotherapy in the past several years. EGFR tyrosine kinase inhibitors (TKIs) have been compared with chemotherapy as first-line therapy for patients with advanced NSCLC harboring *EGFR* mutations, and are shown to improve progression-free survival, overall response rate and disease-control rate [53]. The success of EGFR TKI monotherapy in metastatic NSCLC has led to the investigation of these agents in the earlier stages of disease, and in combination with other treatment modalities. However, early attempts at incorporating molecularly targeted agents into chemoradiation have been discouraging. For example, EGFR TKI gefitinib in the maintenance setting, after definitive chemoradiation and consolidative chemotherapy, was not shown to have any survival benefit compared with placebo in patients with stage III NSCLC [54], but the patients in this study were not selected on the basis of their molecular characteristics. A Phase II study showed that concurrent use of gefitinib with chemoradiotherapy had no apparent survival advantage in ‘good-risk’ (performance status: 0–1 and weight loss: <5%) patients with wild-type or mutated *EGFR* [55]; but these results need to be interpreted with caution given the small number of patients (n = 39). Studies showed that NSCLC cell lines harboring *EGFR* mutations exhibit significant delay in the repair of DNA double-strand breaks and increased sensitivity to ionizing radiation [56]. Given the clinical evidence

and scientific rationale of the potential benefit of EGFR TKIs, investigators continue to seek new and effective methods to integrate these agents into the standard treatment of stage III disease.

Other molecular targets such as ALK fusion proteins and *RAS* oncogene may provide new methods of radiosensitization and are worth further research [57]. Immunomodulatory agents including anti-PD-1 and anti-PD-L1 antibodies have been investigated as monotherapy in refractory and metastatic lung cancer, with impressive results of efficacy and tolerability [58,59]. This provides encouragement that similar effect is possible in stage III NSCLC, where efficacy of curative treatment can be furthered. Evidence indicates that radiation enhances T-cell activation and infiltration, and can increase the expression of PD-L1 [60]. Therefore, combining radiation with PD-1 or PD-L1 inhibitors may be beneficial. Ongoing randomized clinical trial (PACIFIC) is investigating the role of MEDI4736, an antibody to PD-L1, as consolidative therapy in patients with stage III NSCLC who have not progressed following definitive, platinum-based, concurrent chemoradiation [61]. Another Phase II single-arm study is evaluating pembrolizumab, an antibody to PD-1, as consolidative therapy after concurrent chemoradiation [62]. Combination of radiation with immune checkpoint inhibitors may have an effect on local control as well as enhance immune response on a systemic level. At the same time, we need to be cautious to follow-up on the incidence of severe

Table 1. Key ongoing clinical trials in North America that add novel agents to the standard chemoradiation treatment for unresectable or inoperable stage III NSCLC.

ClinicalTrials.gov identifier	Study design	Schema	Ref.
NCT02125461 (PACIFIC)	Randomized Phase III	Following definitive, platinum-based, concurrent CRT Arm 1: MEDI4736 Arm 2: placebo	[61]
NCT01822496	Randomized Phase II	Arm 1: erlotinib induction → CRT Arm 2: concurrent CRT (<i>EGFR</i> mutant cohort) Arm 3: crizotinib induction → CRT Arm 4: concurrent CRT (<i>ALK</i> + cohort)	[64]
NCT02343952	Phase II	CRT → pembrolizumab consolidation	[62]
NCT02412371	Phase I/II	Phase I: dose escalation of veliparib + CRT (paclitaxel/carboplatin-based chemotherapy) Phase II: before consolidation paclitaxel/carboplatin Arm 1: veliparib + CRT Arm 2: placebo + CRT	[65]
NCT01912625	Phase I	Trametinib + concurrent CRT → consolidation chemotherapy	[66]

CRT: Chemoradiotherapy.

pneumonitis in patients treated with these regimens, as pneumonitis is a rare and potentially serious immune-mediated adverse effect associated with PD-1 inhibitors [63]. When pembrolizumab was used in the refractory and metastatic NSCLC patients, the reported incidences of any grade and grades 3–5 pneumonitis were 3.8 and 2.0%, respectively [63]. **Table 1** summarizes key ongoing trials in North America that add these novel agents to the standard chemoradiotherapy for inoperable or unresectable stage III NSCLC. These areas of research are certainly promising and warrant further investigation.

Conclusion & future perspective

Stage III NSCLC is a heterogeneous entity, with great variation in clinical extent of disease. The clinical and research priorities to optimize stage III NSCLC management will require a multidisciplinary approach. In addition, one widely advocated strategy to improve cancer outcomes is the development of personalized medicine, taking into account a combination of clinical and biological factors, with treatment tailored for individual patients. In

order to achieve this, laboratory, molecular and genetic markers will be the subject of ongoing research. For example, as discussed above, EGFR and ALK-targeted agents are showing promise, and more of such advances are expected. Finally, as new therapeutic options and treatment techniques emerge, further work will be needed to determine the optimum combinations for such advances and how best they can be sequenced.

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