Review Article

Multidisciplinary management of N2 stage III non-small cell lung cancer: opportunities and challenges for radiation oncology

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Abstract: Stage III non-small cell lung cancer (NSCLC) constitutes a heterogeneous ailment, with optimal treatment evolving. This is especially true in N2 disease, where definitive treatment is often a discussion of surgery versus definitive chemoradiotherapy (CRT). New developments in neoadjuvant and adjuvant systemic therapeutics have shifted treatment paradigms, emphasizing the importance of multidisciplinary team discussions. The recent revisions to the ninth edition of the American Joint Commission on Cancer (AJCC) staging system have prompted a realignment in nodal stage categorization, introducing refined subcategories of N2 disease (N2a and N2b), which enhance prognostic accuracy. Critical questions including defining resectability and operability, feasibility of definitive CRT for operable patients, radiotherapy in operative and non-operative disease, and advanced radiation technology for definitive CRT are needed to be considered and answered in clinical practice. The current review aims to present a comprehensive overview of radiation oncology in management of N2 stage NSCLC by summarizing key clinical trials as well as most advanced evidence, including defining resectability and operability, feasibility of definitive CRT for operable patients, radiotherapy in operative and non-operative disease, and advanced radiation technology for definitive CRT. The review summarizes the most recent evidence and insights for radiation oncologists and other specialists involved in the multidisciplinary thoracic oncology team, to provide a better understanding of the opportunities and challenges for radiotherapy in the management of N2 stage III NSCLC.

Keywords: Non-small cell lung cancer (NSCLC); N2; stage III; radiotherapy

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Introduction

Lung cancer stands as the most frequently diagnosed cancer globally, accounting for 12.4% of all cancer cases, and it is the foremost cause of cancer-related mortality, responsible for 18.7% of all cancer deaths worldwide (1). Approximately 20–35% of non-small cell lung cancer (NSCLC) cases are diagnosed as stage III, which has a 5-year overall survival (OS) of approximately 35%, according to the Surveillance, Epidemiology, and End Results database (2). Stage III NSCLC represents a diverse and complex condition, posing a clinical challenge in determining the optimal treatment approach. This dilemma is particularly true for N2 disease (3). Curative options for N2 disease include definitive chemoradiotherapy (CRT) followed by adjuvant systemic therapy, or surgical resection with various options for perioperative, neoadjuvant and adjuvant systemic therapies. The intent of this review is to define the various treatment pathways for N2 stage III NSCLC, and to highlight the importance of multidisciplinary decision-making.

Definitive treatment: surgery versus CRT

Defining resectability and operability may be the most important issue in determining management for stage III NSCLC. In cases of operable stage III NSCLC, surgical intervention may be combined with perioperative chemoimmunotherapy, with or without adjuvant radiotherapy in carefully selected patients, as tailored treatment strategies aim to improve outcomes.

Defining resectability and operability

The criteria for a complete resection were defined by the International Association for the Study of Lung Cancer (IASLC) in 2005 (4). In order to be considered complete (R0), a surgical resection must entail all of the following: free resection margins microscopically; systematic nodal dissection or lobe-specific systematic nodal dissection; no extracapsular nodal extension of the tumor and the lymph nodes sampled from the highest mediastinal station must be negative (4). So far, these criteria have not changed. However, with the introduction of more effective preoperative drug protocols, a borderline resectable disease may now turn into a completely resectable tumor. Mediastinal staging is therefore pivotal to evaluate the need for induction regimens. Given this, endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) should be employed for lymph node station mapping, considering the rate of 20 to 30% false positive at positron emission tomography/computed tomography (PET/CT) (5).

While there is no widely accepted definition for resectability, several initiatives have attempted to address this question. The American Society of Clinical Oncology (ASCO) Guideline for Management of stage III NSCLC defines some prerequisites to pursue resection in T1–2N2 NSCLC, including that R0 resection of the primary tumor and lymph nodes is deemed possible, and the 90-day mortality is expected to be under 5% (6). While it is generally agreed that N1 disease is resectable and N3 disease is unresectable, the resectability of N2 disease is a matter of debate. Some guidelines define resectability based on the number and size of nodes; European Society of Medical Oncology (ESMO) Clinical Practice Guidelines indicate that a single station N2 node is resectable, while multistation N2 disease should be considered for CRT over surgical resection (7). The Asian Thoracic Oncology Research Group (ATORG) Expert Consensus states that patients with non-bulky (<3 cm), discrete, single-level N2 nodes may be the best candidates to undergo resection as part of a multimodality approach (8). For patients whose likelihood of N2 involvement is at least moderate (such as central tumours, or those >3 cm), a thorough preoperative staging workup is necessary. These guidelines suggest pathologic confirmation of nodal disease, except in multilevel infiltrative nodal involvement, in which case upfront curative-intent surgery is not possible (9).

As N2 disease does not categorically exclude patients from surgical intervention, the use of multidisciplinary teams is vital to decision-making. Given the technical nuances of these decisions, patients should not have surgical candidacy determined by non-surgical physicians. In the case of resectable disease, recent trials suggest that patients benefit from treatment with neoadjuvant therapy rather than upfront surgery; in these cases, it was necessary to determine resectability upfront with the use of a multidisciplinary team including thoracic surgery (10-15). The recently published update by the IASLC, proposing new N2 sub-categories (N2a, involvement of single ipsilateral mediastinal or subcarinal nodal station; N2b, involvement of multiple ipsilateral mediastinal nodal stations with or without involvement of the subcarinal nodal station) may provide guidance in defining resectable disease (3). A survey by the European Organization for Research and Treatment of Cancer-Lung Cancer Group (EORTC-LCG) in 2023

introduced the concept of potentially resectable disease, including T4 tumors and the presence of non-bulky multi-station N2 involvement (16). Nevertheless, even bulky lymph nodes (i.e., larger than 3 cm in their short axis) can be resected if well capsulated, while in other cases, small lymph nodes invading surrounding structures hinder the possibility of a complete resection.

Sixty percent of all newly diagnosed cancer cases occur in patients over 65 years old (17). Operability, meaning overall fitness for a patient to undergo with surgery, depends on patient factors including age, performance status, co-morbidities, patient willingness, and social considerations. When discussing surgery, the postoperative quality of life of the patient is as important as the OS. Between 35–50% of patients screened for eligibility were excluded from recent phase III trials of neoadjuvant immunotherapy, including Checkmate 816: 268/773 (35%) not randomized; KEYNOTE 671: 567/1,367 (41%) not randomized; AEGEAN: 678/1,480 (46%) not randomized; NEOTORCH: 492/992 (50%) not randomized (10-15), highlighting the importance of such patient factors. Patients suitable for both surgical resection and radiotherapy may choose based on perceived tolerance of treatment-related side effects. Older, frailer patients might opt for surgery, considering potential noncompliance with several weeks of CRT. However, elderly patients face heightened vulnerabilities to the complications stemming from anesthesia and the rigors of extensive surgical procedures, underscoring the necessity for additional research to inform treatment decisions and choices.

Evolution of the role of surgery in N2 disease

The surgical treatment encompasses several advantages, including lymph nodes staging, when compared to sampling of tissue for histology, molecular profiling and assessment of therapeutic response. Furthermore, surgery is often preferred by patients over systemic regimens, as it is carried out in a single procedure, typically with just a few days of post-operative hospitalization. However, surgery alone is not a realistic option for patients with N2 disease; all such patients should be offered systemic therapy in the neoadjuvant, perioperative or adjuvant setting in the current standard of care.

In terms of surgical approach, a clear turning point has been the technical advancement in the field of minimally invasive surgery (MIS), including video-assisted thoracoscopic surgery (VATS) and robotic-assisted thoracic surgery (RATS). The ability to radically resect the tumour while maintaining low invasiveness reduces risk, especially when considering pre-treatment may result in side effects that reduce fitness from baseline. In light of the benefits of MIS, according to the US Agency for Healthcare Research and Quality (AHRQ) (18) data, the overall trend in lobar resections from 2009 is characterized by a steady increase of robotic procedures, a stable rate of VATS procedures and a decrease in the traditional open approach. The robot offers increased dexterity, tremor compensation, three-dimensional vision, and consequentially, better tissue manipulation, a key strength to approach post-induction cases (19). The robotic approach also provides an enhanced lymph node dissection, as demonstrated by the prospective randomized controlled study ROMAN in 2021, wherein RATS performed better than VATS in lymphadenectomy both in terms of number of hilar and mediastinal lymph nodes sampled {7 [interquartile range (IQR), 5–10] *vs.* 4 (IQR, 2–7)} and the number of nodal stations harvested [6 (IQR, 4–6) *vs.* 4 (IQR, 3–5)] (20). Furthermore, in 2018, Veronesi *et al.* published a retrospective multicenter study focusing on N2 disease. The aim was to assess the safety and feasibility of the robotic approach in locally advanced cases. More than 200 N2 cases were enrolled and data highlighted a low conversion rate for bleeding (2.7%), low 30- and 90-day mortality (1.9% and 4.0%, respectively, among all cases, 0% among the neoadjuvant cases) and a good 3-year OS (61.2%) (21).

Regardless, the role of surgery in stage IIIA N2 disease has been widely debated. In 2009, Albain *et al.* reported a randomized controlled trial, comparing surgical resection following CRT to CRT with definitive dose of radiotherapy. In the surgery arm, lobectomy was safe and potentially beneficial, however, there was high mortality observed in patients undergoing pneumonectomy (14:1 ratio between pneumonectomy and lobectomy). While numerically more patients died without progression in the surgery arm, OS was not significantly between the two treatment arms (22). The 5-year OS rates were 27.2% among the surgically treated cases and 20.3% in the radiotherapy group (22). Finally, progression-free survival (PFS) was superior in the surgical group compared to the radiotherapy group with a median of 12.8 *vs.* 10.5 months (12).

Induction treatments like neoadjuvant chemoimmunotherapy prior to surgical resection or perioperative strategy (neoadjuvant + adjuvant) are pivotal, as shown by multiple recent trials. The down-staging can potentially facilitate surgery with fewer complications.

Furthermore, the introduction of preoperative immunotherapy offers the advantage of enhanced T cell priming and increased expansion of anti-tumor T cells, along with continued T cell activity against micro-metastases after resection (10).

In the CHECKMATE 816 randomized controlled trial, patients with stage IB to IIIA [American Joint Commission on Cancer (AJCC) 7th] resectable NSCLC underwent 3 cycles of induction with nivolumab plus platinum-based chemotherapy or chemotherapy alone followed by surgery. The trial reported an improvement of the pathologic complete response (pCR) (24% *vs.* 2.2%), median event-free survival (EFS) (43.8 *vs.* 18.4 months), and 4-year OS (71% *vs.* 58%), with a stronger benefit in programmed cell death-ligand 1 (PD-L1) ≥1% NSCLC in the nivolumab + chemotherapy group (10,11). The US Food and Drug Administration (FDA) has therefore approved this strategy in resectable early-stage NSCLC, but European Medicines Agency (EMA) has restricted the approval to PD-L1 ≥1% (23,24). According to the data, patients who underwent induction treatment with immunotherapy plus chemotherapy had a higher rate of resectability (83.2% *vs.* 75.4%) and a higher rate of R0 resection (83.2% *vs.* 77.8%), with median residual viable tumor (RVT) cells in the primary tumor bed of 10% *vs.* 74% (10). Moreover, in 2021, Spicer *et al.* specifically analyzed the surgical outcome from phase III CHECKMATE 816 trial. MIS was employed in 30% and 22% of cases among patients treated with nivolumab + chemotherapy and chemotherapy alone, respectively, while conversion rates were 11% and 16% respectively (25). Lobectomy was carried out in 77% *vs.* 61% of patients and pneumonectomy in 17% and 25% of cases. Conversely, there was no increase in the median duration of surgery or length of hospitalization (26).

KEYNOTE 671 was a randomized double-blind phase III trial in which patients with resectable stage II to IIIB (AJCC 8th) NSCLC received induction treatment with either pembrolizumab plus chemotherapy followed by surgical treatment and adjuvant pembrolizumab to complete 1 year of therapy or preoperative chemotherapy plus placebo. Stage III patients represented the majority of the cases enrolled. Perioperative pembrolizumab combined with preoperative chemotherapy significantly improved EFS (54.3% *vs.* 35.4%) and OS (71.3% *vs.* 64.0%) at 36 months, as well as major pathological response (MPR) (30.2% *vs.* 11.0%) and pCR (18.1% *vs.* 4.0%) (12,13). The morbidity and mortality were overall acceptable, although postoperative 30- and 90-day mortality rates were higher in the pembrolizumab arm compared to the patients who underwent chemotherapy alone (1.8% *vs.* 0.6% and 4% *vs.* 1.6%) (12). There is clinical equipoise for neoadjuvant only versus perioperative approach, as these two techniques have not been directly compared. Furthermore, about 20% of patients in trials assessing neoadjuvant or perioperative chemo-immunotherapy do not proceed to surgery for various reasons. This has implications from both a cost point of view as well as toxicity and should be kept in mind when making treatment recommendations.

In the future, the identification of predictive markers to select patients who could benefit from adjuvant immunotherapy following neoadjuvant treatment may avoid overtreatment (27). The assessment of minimal residual disease (MRD) status by postoperative circulating tumor DNA (ctDNA) evolves as one promising marker, also correlating with the risk of recurrence (27-29).

Feasibility of definitive CRT for operable patients

Definitive CRT remains the standard of care in unresectable stage III N2 NSCLC, whereas the optimal treatment modality remains an option for patients with resectable disease. The use of CRT without surgical resection may be equally appropriate or even more suitable than resection in certain clinical scenarios, based on the results of several clinical trials (*Table 1*). The RTOG 8901 trail compared sequential chemotherapy and radiotherapy to preoperative chemotherapy and surgery in patients with N2 NSCLC, and demonstrated that treatment outcomes were similar between these arms, suggesting that surgery offered no survival benefit (30). The EORTC 08941 trial compared surgical resection versus radiotherapy, both preceded by induction chemotherapy, in unresectable stage IIIA-N2 NSCLC, and showed no difference in survival outcomes between the two modalities (31). The ESPATUE phase III trial similarly compared induction chemotherapy and CRT with or without surgery for resectable stage IIIA (N2) NSCLC. The 5-year OS and PFS rates in randomly assigned patients with resectable stage III NSCLC were excellent with both treatments (32).

Overall, while both surgical and radiation techniques advance, the debate between these two modalities persists in resectable NSCLC. These trials indicate that while radiotherapy is a suitable option, it does not necessarily surpass surgery in terms of effectiveness. While radiotherapy may lead to fewer treatment-related deaths, it is accompanied by risks of toxicity to nearby organs. The

Table 1 Selected trials of surgery *vs.* definitive CRT in operable NSCLC patients

Study	Inclusion stage	N2 diagnostic method	Intervention	Number of subjects	Progression-free survival (median months or %)	Overall survival (median months or %)	Reference
RTOG 8901	IIIA/N2, 54% bulky N2 disease	Mediastinoscopy, anterior mediastinotomy	Induction chemotherapy (cisplatin + vinblastine ± mitomycin-C) + surgery	29	–	19.4	(30)
			Induction chemotherapy (cisplatin + vinblastine + mitomycin-C) + radiotherapy (50±14 Gy)	33	–	17.4	
EORTC 08941	IIIA/N2	Mediastinoscopy	Induction chemotherapy (cisplatin or carboplatin based) + surgery ± adjuvant radiotherapy	167	9	16.4	(31)
			Induction chemotherapy (cisplatin or carboplatin based) + radiotherapy (60–62.5 Gy)	165	11.3	17.5	
ESPATUE	IIIA/N2 and IIIB	Pathologically proven	Neoadjuvant chemotherapy (cisplatin + paclitaxel) + concurrent CRT (45 Gy + cisplatin + vinorelbine) + radiotherapy (20–26 Gy)	81	35% (5 years)	40% (5 years)	(32)
			Neoadjuvant chemo (cisplatin + paclitaxel) + concurrent CRT (45 Gy + cisplatin +vinorelbine) + surgery	80	32% (5 years)	44% (5 years)	
INT 0139	IIIA/N2	Pathologically proven	Induction CRT (cisplatin + etoposide + 45 Gy radiotherapy) + surgery + adjuvant chemotherapy	216	12.8	23.6	(22)
			Induction CRT (cisplatin + etoposide + 45 Gy radiotherapy) + radiotherapy (16 Gy) + adjuvant chemotherapy	213	10.5	22.2	

CRT, chemoradiotherapy; NSCLC, non-small cell lung cancer.

streamlining of radiotherapy services, careful consideration of patient capabilities and multidisciplinary team discussions are crucial in treatment decisions. Also, it is noted that novel systemic therapies—especially immunotherapies—have tilted the balance towards surgery in patients with resectable disease, irrespective of N2 involvement, as long as R0 resection can be achieved. The dilemma is in patients with upfront borderline resectable patients if there is uncertainty regarding upfront R0 resection. Further research and clinical trials are necessary to address these questions comprehensively and should emphasize individual patient characteristics and treatment capability in decision-making.

Radiotherapy in operative disease

Neoadjuvant setting

Recent trials investigating the use of neoadjuvant or perioperative (10-15,25,33-36) immunotherapy and surgical resection have demonstrated promising results, which has introduced more options for resectable lung cancer management (*Table 2*). Specific subgroup analysis of N2 diseases patients from the AEGEAN study demonstrated the efficiency and safety of the addition of perioperative durvalumab to neoadjuvant chemotherapy (37). In these trials, 6–21% of the included patients required subsequent radiation. Potential reasons for requiring additional

Table 2 Selected trials of neoadjuvant chemoimmunotherapy and surgery ± adjuvant chemotherapy in locally advanced NSCLC

Study	Inclusion criteria	Intervention	No. of subjects	Overall survival (median or %)	Major complete response/pathological complete response (%)	Event-free survival (median months or %)	R0 resection rate	Postoperative radiotherapy	Subsequent radiotherapy	Reference
CheckMate 816	Resectable IB–IIIA (AJCC 7th)	Neoadjuvant nivolumab + platinum-based chemotherapy	179	82.7% (2 years)	NA/24.0%	31.6	83.2%	7.9%	11.2%	(10,11,25)
		Neoadjuvant platinum-based chemotherapy	179	70.6% (2 years)	NA/2.2%	20.8	77.8%	9.6%	21.2%	
KEYNOTE 671	II, IIIA, or IIIB (N2 stage)	Neoadjuvant pembrolizumab + cisplatin-based chemotherapy + adjuvant pembrolizumab	397	80.9% (2 years)	30.2%/18.1%	62.4% (2 years)	–	8.8%	–	(12,13)
		Neoadjuvant cisplatin-based chemotherapy	400	77.6% (2 years)	11.0%/4.0%	40.6% (2 years)	–	13.3%	–	
AEGEAN	II–IIIB (AJCC 8th)	Neoadjuvant durvalumab + platinum-based chemotherapy + adjuvant durvalumab	400	–	34.2%/17.2%	63.3% (2 years)	94.7%	6.4%	–	(14,37)
		Neoadjuvant platinum-based chemotherapy	402	–	14.1%/4.3%	52.4% (2 years)	91.3%		–	
NeoTorch	III	Neoadjuvant toripalimab + platinum-based chemotherapy + adjuvant toripalimab	202	87.2% (2 years)	48.5%/24.8%	64.7% (2 years)	95.8%	–	11.9%	(15)
		Neoadjuvant platinum-based chemotherapy	202	74.3% (2 years)	8.4%/1.0%	38.7% (2 years)	92.6%	–	16.3%	
NADIM	IIIA (AJCC 8th)	Neoadjuvant nivolumab + paclitaxel and carboplatin chemotherapy + adjuvant nivolumab	51	69.3% (5 years)	NA/25.5%	65.0% (5 years)	–	–	–	(29,36)
RATIONALE 315	II–IIIA (AJCC 8th)	Neoadjuvant tislelizumab + platinum-based doublet chemotherapy + adjuvant tislelizumab	226	88.6% (2 years)	NA/40.7%	68.3% (2 years)	95.3%	–	–	(33,34)
		Neoadjuvant platinum-based doublet chemotherapy	227	79.4% (2 years)	NA/5.7%	51.8% (2 years)	93.1%	–	–	
CheckMate 77T	IIA–IIIB (AJCC 8th)	Neoadjuvant nivolumab + platinum-based chemotherapy + adjuvant nivolumab	229	–	25.3%/35.4%	70.2% (1.5 years)	89.3%	–	12.2%	(35)
		Neoadjuvant platinum-based chemotherapy	232	–	4.7%/12.1%	50.0% (1.5 years)	90.4%	–	19.4%	

AJCC, American Joint Committee on Cancer; NA, not available; NSCLC, non-small cell lung cancer.

radiation include unresectable disease, or an inadequate resection. This begs the question of whether these patients who did not undergo surgery, or who had residual disease post-surgery, would have been better served with a CRT paradigm instead. The role of neoadjuvant radiotherapy for patients with N2 NSCLC is also unclear. Several trials have investigated the use of radiation in this context (*Table 3*). A randomized trial from the Swiss Group for Clinical Cancer Research (SAKK) investigated whether the addition of neoadjuvant radiotherapy improves outcomes in stage IIIA/N2 NSCLC and demonstrated that radiotherapy did not add any benefit to induction chemotherapy followed by surgery (38). Furrer *et al.* evaluated the efficacy of induction CRT (comprising cisplatin/docetaxel and 44 Gy in 22 fractions in 3 weeks) followed by surgery and compared anatomical resection with extended resection. Similar long-term survival rates were observed following extended and non-extended resection, however OS and EFS was worse with increasing pretreatment burden of N2 nodes (43). Tanaka *et al.* assessed the impact of induction CRT followed by resection and postoperative chemotherapy for patients with IIIA-N2 NSCLC, achieving an overall response rate (ORR) of 58% and 2-year PFS of 63% (39). In both of these trials, 80% of patients had an R0 resection following CRT (39,43). The potential adverse impacts of neoadjuvant CRT are a concern with using this treatment approach. These complications include pneumonia, respiratory insufficiency, atelectasis, prolonged air leak, bronchopleural fistula, bronchial stenosis, and completion pneumonectomy.

Most data available on the use of radiation in NSCLC was before the availability of neoadjuvant immunotherapy as a treatment option, however, some recent trials suggest that neoadjuvant radiation can also increase pathological response. A randomized phase 2 trial investigated the role of neoadjuvant durvalumab with or without stereotactic body radiotherapy (SBRT, 24 Gy in 3 fractions, given before the first cycle of durvalumab) in early-stage NSCLC. Treatment was well-tolerated and associated with MPR at rates of 6.7% in the durvalumab monotherapy group and 53.3% in the durvalumab plus radiotherapy group (40). The ongoing SAKK 16/18 clinical trial is delving into the potential of immune-modulatory radiotherapy as a means to amplify the efficacy of neoadjuvant PD-L1 blockade therapy, subsequent to neoadjuvant chemotherapy, in patients with resectable stage III N2 NSCLC. The preplanned interim safety analysis did not show a significant increase in treatment-related adverse events due to radiotherapy and confirmed surgical feasibility (41). Thus, the combination of neoadjuvant immunotherapy and SBRT presents a promising approach for resectable stage III N2 NSCLC, given its potential to enhance treatment response (41). Another phase II trial from Japan also assessed the impact of adding radiotherapy to neoadjuvant chemo-immunotherapy on long-term outcomes of patients with resectable stage IIIA–B N2 NSCLC, which resulted in high pathologic efficacy and feasibility (42). Exploratory analyses conducted to investigate potential variations among different radiotherapy regimens offer valuable insights into the potential contribution of immune-modulatory radiotherapy within the multifaceted treatment approach for resectable stage III N2 NSCLC.

Adjuvant setting

The European Lung ART trial and Chinese PORT-C trial compared mediastinal post-operative radiotherapy (PORT) versus no PORT in completely resected stage III NSCLC with pN2 involvement (44,45) (*Table 4*). Neither trial met their primary endpoint of improved 3-year disease-free survival (DFS) or 3-year OS. PORT significantly reduced the risk of locoregional relapse at the cost of higher cardiopulmonary toxicity and treatment-related death. While it is acknowledged that three-dimensional (3D) conformal or intensity-modulated postoperative radiotherapy (PORT) may hold the potential to diminish the risk of mediastinal relapse in select cases, it is not generally advisable to recommend this treatment modality as a universal standard for all stage III pN2 patients who have undergone complete resection. ESMO and ASCO guidelines do not recommend PORT for patients with completely resected stage III N2 NSCLC routinely (6,7). However, the complexities of managing stage III NSCLC are still highlighted, particularly regarding postoperative radiotherapy in certain clinical situations such as high risk of locoregional recurrence (46).

High-risk N2 population

The use of PORT in patients with high-risk N2 disease, which is characterized by factors such as multistation nodal involvement, subcarinal involvement for upper-lobe cancers, extracapsular extension, involvement of the highest resected lymph node, or inadequate nodal resection during surgery, may provide some benefits. However, there are several key points to consider when evaluating the potential benefits of PORT in this patient population. First, the quality of surgery is crucial, particularly the adequacy of nodal exploration. The Lung ART trial highlighted the

Table 3 Selected trials of neoadjuvant radiotherapy with systemic therapy in locally advanced NSCLC

Study	Inclusion criteria	Intervention	No. of subjects	Overall survival (median months or %)	Major complete response/pathological complete response (%)	Event-free survival/ relapse-free survival (median months or %)	R0 resection rate	Reference
SAKK	IIIA/N2	Neoadjuvant chemotherapy (cisplatin + docetaxel) + radiotherapy (44 Gy)	117	37.1	NA/16%	12.8/NA	91%	(38)
		Neoadjuvant chemotherapy (cisplatin + docetaxel)	115	26.2	NA/12%	11.6/NA	81%	
WJOG 5308L	IIIA-N2	Induction chemotherapy (carboplatin + paclitaxel) + radiotherapy (50 Gy)	40	75% (2 years)	NA/29%	NA/62% (2 years)	80%	(39)
NCT02904954	I–IIIA (AJCC 7th)	Neoadjuvant durvalumab + SBRT (24 Gy/3F)	30	–	53.3%/26.7%	–	83%	(40)
		Neoadjuvant durvalumab monotherapy	30	–	6.7%/0%	–	77%	
SAKK 16/18	IIIA–B (N2)	Neoadjuvant durvalumab + cisplatin and docetaxel chemotherapy + SBRT (40 Gy/2F, 25 Gy/5F, 24 Gy/8F)	31	–	NA/28%	–	–	(41)
SQUAT (WJOG 12119L)	Stage IIIA–B N2 (AJCC 8th)	Neoadjuvant durvalumab + paclitaxel and carboplatin chemotherapy + involved-field radiotherapy (50 Gy) + adjuvant durvalumab	31	76% (2 years)	63%/23%	43% (2 years)/NA	–	(42)

F, fractions; NA, not available; NSCLC, non-small cell lung cancer; SBRT, stereotactic body radiotherapy.

Table 4 Selected trials of adjuvant radiotherapy in operable NSCLC

Study	Inclusion criteria	PORT intervention	No. of subjects	Disease-free survival (median months)	Overall survival (%)	Locoregional recurrence-free survival (median or %)	Local relapse	Distant metastasis	Adjuvant chemotherapy	Reference
LungART	pIIIA-N2	3DCRT 89%, IMRT 11%	252	30.5	69.7% (3 years)	–	46.1%	73%	96%	(44)
		Control	249	22.8	69% (3 years)	–	25%	65%	96%	
PORT-C	pIIIA-N2	3DCRT 10.7%, IMRT 89.3%	202	22.1	78.3% (3 years)	66.5% (3 years)	–	38.4%	100%	(45)
		Control	192	18.6	82.8% (3 years)	59.7% (3 years)	–	38.1%	100%	

3DCRT, three-dimensional conformal radiotherapy; IMRT, intensity modulated radiotherapy; NSCLC, non-small cell lung cancer; PORT, post-operative radiotherapy.

importance of quality resection, the extent of mediastinal involvement, and lymph node ratio in determining DFS. Complete R0 resection rates were only achieved in 29% of patients, indicating that surgical quality is an important factor in determining the effectiveness of PORT. Second, prognostic factors for DFS in the Lung ART trial included quality of resection, extent of mediastinal involvement, and lymph node ratio. However, the impact of PORT on OS was not significant, suggesting that PORT may not provide a survival benefit in all patients with high-risk N2 disease. Third, secondary analyses of the Lung ART trial are awaited to identify specific patient subgroups that may benefit from PORT. Patients with high-risk N2 disease, particularly those with inadequate nodal resection or extensive mediastinal involvement, may be more likely to benefit from PORT. Further research and analysis are needed to better define the patient populations that would derive the most benefit from PORT in this context. Considerations for using PORT in high-risk N2 disease emphasize the importance of quality surgery and ongoing research to identify optimal treatment strategies (47).

Downstaging after neoadjuvant therapy

In patients with baseline clinically diagnosed N2 (cN2) NSCLC, the standard treatment typically involves neoadjuvant chemotherapy and immunotherapy followed by surgery. However, the role of PORT in these patients remains controversial due to a lack of randomized data. Key considerations are: (I) histological confirmation: patients should have histologically proven N2 disease to ensure accurate staging and appropriate treatment; (II) response to preoperative therapy: whether PORT is beneficial after preoperative systemic therapy, regardless of mediastinal involvement, remains unclear; (III) high relapse risk: patients with cN2 NSCLC have a high risk of relapse, especially if complete resection is not achieved. Future studies are needed to clarify the optimal treatment approach and the potential benefits of PORT in this patient population.

Incomplete (R1 or R2) resection

The insufficient number of prospective studies that concentrate on NSCLC patients experiencing incomplete resection, categorized by either R1 (microscopically confirmed positive margins) or R2 (macroscopically observable margins), constitutes a significant gap in our comprehension of the most effective management strategies for these individuals. Nevertheless, retrospective studies have suggested a potential benefit with PORT in this patient group. Recognizing the usual caveats of retrospective population-based database analyses, a US National Cancer Database found that R1 resection is associated with a lower OS rate compared to complete resection, and that there was a substantial improvement in OS among NSCLC patients with incomplete resection (48). The National Comprehensive Cancer Network (NCCN) guidelines advise administering postoperative sequential or concurrent chemotherapy and radiotherapy for R1 resection cases, and concurrent CRT for R2 resection instances (49). Considering the stage of the disease and the specific position of the positive surgical margin, the possibility of re-excision can be evaluated as a potential treatment approach. Adhering to ESMO guidelines, for patients with R1 resection, it is suggested to contemplate both PORT and adjuvant chemotherapy.

Radiotherapy dose, target areas and systematic therapy

When adjuvant radiotherapy is indicated, the clinical tumor volume (CTV) includes the bronchial stump and high-risk draining lymph node stations. Standard doses after complete resection are 50 to 54 Gy in 1.8 to 2 Gy fractions, but a boost may be administered to high-risk regions, including areas of nodal extracapsular extension or microscopic positive margins. R1 margins should receive 54–60 Gy in conventional fractionation, while R2 margins require higher doses (≥60 Gy) (49). For patients with R1 resection, both sequential and concurrent CRT are considered appropriate treatment options. For patients with R2 resection, concurrent CRT is recommended. Retrospective evidence strongly supports the delivery of PORT in NSCLC patients with incomplete resection, whether R1 or R2. Adjuvant systematic therapy (chemotherapy, immunotherapy, targeted therapies) and PORT play crucial roles in improving survival outcomes in this patient population. However, further prospective studies are needed to inform timing as well as the safety of delivery.

Radiotherapy for inoperable disease

Non-oncogene addicted tumours

Definitive CRT has been established as the backbone in the non-surgical management of locally advanced NSCLC, including N2 patients (*Table 5*). The PACIFIC and PACIFIC-6 trials have established the standard of care of adjuvant durvalumab immunotherapy after definitive or sequential CRT, respectively (50-53). These results

Table 5 Selected trials of non-surgical definitive CRT in locally advanced NSCLC

Study	Inclusion criteria	Intervention	No. of subjects	Progression-free survival (median months or %)	Overall survival (median months or %)	Reference
PACIFIC	Stage III (AJCC 7th)	Platinum-based chemotherapy + concurrently radiotherapy (54–66 Gy) + adjuvant durvalumab	473	16.8	66.3% (2 years)	(50,51)
		Platinum-based chemotherapy + concurrently radiotherapy (54–66 Gy)	236	5.6	55.6% (2 years)	
PACIFIC-6	Stage III (AJCC 8th)	Platinum-based chemotherapy + sequentially radiotherapy (54–66 Gy) + adjuvant durvalumab	117	10.9	25.0	(52)
PACIFIC-2	Unresectable, stage III	Durvalumab + platinum-based chemotherapy + concurrently radiotherapy (54–66 Gy) + adjuvant durvalumab	219	13.8	36.4	(53)
		Platinum-based chemotherapy + concurrently radiotherapy (54–66 Gy)	109	9.4	29.5	
GEMSTONE-301	Unresectable, stage III (AJCC 8th)	Platinum-based chemotherapy + concurrently or sequentially radiotherapy (54–66 Gy) + adjuvant sugemalimab	255	9.0	–	(54)
		Platinum-based chemotherapy + concurrently or sequentially radiotherapy (54–66 Gy)	126	5.8	–	
DOLPHIN	IIIA-C (AJCC 8th)	Durvalumab + radiotherapy (60 Gy)	35	25.6	–	(55)
SPIRAL-RT	Stage III	Radiotherapy (54–66 Gy) + durvalumab	33	8.9	20.8	(56)
SPRINT	Stage III or unresectable stage II (PD-L1 TPS of ≥50%)	Pembrolizumab + radiotherapy (55 Gy)	25	26	76% (2 years)	(57)

AJCC, American Joint Committee on Cancer; CRT, chemoradiotherapy; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death-ligand 1; TPS, tumor proportion score.

were recapitulated in the GEMSTONE-301 trial in China, wherein sugemalimab, an immunotherapy agent, administered following definitive concurrent or sequential CRT, can serve as an effective consolidation therapy for stage III NSCLC patients who have not experienced disease progression post-CRT (54). An exploratory analysis of the PACIFIC trial, focusing on tumour cell (TC) PD-L1 expression, revealed that durvalumab provided a PFS benefit across all subgroups examined. Notably, an OS benefit was observed in all subgroups except for those with TC PD-L1 expression of less than 1% (58). The use of radiotherapy with immunotherapy for definitive treatment of locally advanced NSCLC has also been investigated in phase II trials and has demonstrated promising results with chemo-free regimens of radioimmunotherapies (55-57).

Oncogene addicted tumours

While durvalumab is the established standard-of-care consolidation therapy following CRT for stage III unresectable NSCLC, its efficacy in patients with NSCLC carrying driver genomic alterations (dGA) is not well-characterized yet. A retrospective subgroup analysis from the PACIFIC trial indicated that patients with epidermal growth factor receptor-mutated (EGFRm) tumors exhibited similar PFS and OS outcomes when treated with durvalumab compared to placebo, suggesting that tumor biomarker status may impact clinical responses to this

immunotherapy (59). A multicentre retrospective analysis conducted in Europe and North America found that durvalumab consolidation therapy had limited activity in patients with stage III unresectable NSCLC who harbored EGFR, v-Raf murine sarcoma viral oncogene homolog B1 (BRAF) mutations or anaplastic lymphoma kinase (ALK) rearranged tumours, whereas no such limitation was observed in those with kirsten rat sarcoma viral oncogene homolog (KRAS) mutations (60). However, a meaningful survival benefit was observed with adjuvant durvalumab treatment in patients with KRAS mutations and uncommon dGA (61). The LAURA Phase III trial evaluated osimertinib versus placebo as consolidation therapy in EGFRm stage III NSCLC who received CRT, and noted a striking improvement in PFS. In this case, patients were treated with osimertinib or a placebo until progression occurred, rather than for a defined time or number of cycles. Recognizing the caveats of variable pre-treatment staging with PET imaging in this study, the improvement observed with osimertinib in the LAURA trial was both statistically significant and highly clinically meaningful (62), and argues strongly for osimertinib in this patient population.

Advanced radiation technology for definitive CRT in the new era

Dose escalation and de-escalation

Considering improved survival observed in unresectable stage III NSCLC treated with CRT, survivorship and longer-term quality of life considerations have increased importance. RTOG-0617 trial was a radiation dose-escalation trial of CRT, comparing 74 Gy versus the historical standard of 60 Gy, and the former did not result in improved outcomes was associated with potential risks (63). Heart dose was highlighted as a notable risk for cardiotoxicity in tumours with N2 disease due to the involvement of the mediastinum. Clinically relevant cardiac events were linked to heart dose and preexisting cardiac risk factors. In line with the current focus on minimizing radiation exposure to the heart in other malignancies, similar efforts should be made to reduce heart doses in stage III NSCLC patients (64). The risk of mortality stemming from cardiopulmonary radiotherapy has been modeled, which can provide guidance in mitigating cardiotoxicity (65). A reanalysis of the RTOG 0617 trial found that patients with ≥10% of the left anterior descending (LAD) coronary artery receiving 15 Gy (V15 Gy) had an increased risk of all-cause mortality, which highlighted the critical need for enhanced cardiac risk stratification and proactive risk reduction strategies, including the incorporation of cardiac substructure dose constraints into national guidelines and clinical trial protocols (66). A framework has been proposed for modeling radiation-induced cardiac disease, focusing on three key components: (I) baseline cardiovascular risk assessment; (II) cardiac substructure radiation dosimetry linked to cardiac-specific outcomes; and (III) the development of novel biomarkers (67).

Target volume delineation

Generally, PET boosting has not been adopted in broader practice. The PET-Plan trial showcased that utilizing PET for treatment planning has the potential to enhance local control in patients with locally advanced NSCLC undergoing CRT without appearing to increase toxicity. In this study, image-guided target volume reduction in this context was deemed feasible but warrants future research (68). The NRG-RTOG 1106/ECOG-ACRIN 6697 randomized phase II trial showed that mid-treatment PET-guided adaptive CRT for unresectable stage III NSCLC is feasible and safe in a multicenter cooperative setting. However, there was no significant difference in centrally reviewed locoregional progression. Grade 3+ toxicity rates were similar between arms, despite higher radiation doses in the adaptive radiotherapy group. Ultimately, radiotherapy dose escalation based on mid-course PET imaging during definitive CRT for inoperable stage III NSCLC did not improve locoregional control compared to conventional dose fractionation (69).

In broader practice, the delineation of target lymph nodes in radiation planning is largely guided by imaging. Recently, the SEISMIC trial challenged this concept, as the addition of systematic endoscopic mediastinal staging in patients with locally advanced or unresectable NSCLC demonstrated a discrepancy between biopsied nodes and PET interpretation. The consequence of endoscopic staging resulted in adjustment of the radiation field, which for PET false positives had a potential implication for toxicity reduction, and for PET false negatives, a potential for improved cancer control (70). These results require confirmation of generalizability in clinical practice beyond a smaller prospective trial, especially as there may be challenges in geographic and timely access to EBUS/endoscopic ultrasound (EUS) staging if this practice were to be adopted more widely.

Protons and heavy ions

Proton radiotherapy is a radiation technique that facilitates

rapid dose gradients across tissue/tumour targets through the principal of Bragg peak deposition of energy, wherein the deposition of radiation dose by charged particles occurs near the end of their range, which is in contrast to the physical properties of photon, which typically results in a large low-dose wash in non-target tissue (71). In one study, passive scattering proton therapy did not improve dose-volume indices for lung, however improvements were seen in dose to the heart, which could be a potential advantage for N2 disease (72). It has also been argued that in comparison to intensity-modulated radiotherapy, proton and carbon ion radiotherapy may limit the dose received by the thoracic vertebra and aorta, which could reduce severe lymphopenia that is associated with poor outcomes in patients with NSCLC (73). There are also some notable caveats of proton radiotherapy, for instance, changes in anatomy and/or target tumor response can result in an overshooting of target dose if there is a decrease in density in the beam path, resulting in a potential for increased toxicity and reduced tumour control (74). The results of the phase III RTOG 1308 randomized controlled trial comparing photon-based versus proton-based CRT for unresectable locally advanced NSCLC are awaited to best answer the role of protons in this context (75).

Conclusions

Key randomized clinical trials have provided evidence for radiotherapy in multidisciplinary management of N2 stage III NSCLC, while challenges still exist in many complex clinical scenarios. Critical questions, including defining resectability and operability, feasibility of definitive CRT for operable patients, radiotherapy in operative and non-operative disease, and advanced radiation technology for definitive CRT, need to be considered and answered in clinical practice. Our review summarizes the most recent evidence and insights for radiation oncologists and other specialists involved in the multidisciplinary thoracic oncology team, to provide a better understanding of the opportunities and challenges for radiotherapy in the management of N2 stage III NSCLC. It is certain that there have been great opportunities for radiation oncologists to collaborate with other members of multidisciplinary teams to provide the best patient-centered care.

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Footnote

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