Review Article

Incorporating Surgery in treatment of Stage IIIA – N2 Non-Small Cell Lung Cancer.

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ABSTRACT

Stage IIIA-N2 Non-small cell lung cancer includes heterogenous group of patients with a poor 5-year survival ranging from 13% to 36% with surgery alone. Various randomized controlled trials established the role of multimodality treatment either including or excluding surgical resection. In a select group of non-bulky/ single station N2 disease, the better results have been achieved with induction chemotherapy or chemo-radiotherapy followed by surgery.

Keywords: neoadjuvant treatment; non-small cell lung cancer; surgery; IIIA (N2)

Introduction

Lung cancer is the most common cancer diagnosed worldwide and the leading cause of cancer-related deaths.[1] Non-small cell lung cancer (NSCLC) accounts for 85% to 90% of lung cancer casesand one third of patients with NSCLC have stage III disease at diagnosis.[2-3] Stage III is further subdivided in IIIA, IIIB and IIIC. Stage IIIA includes N0, N1 and N2 according to the nodal involvement. The management of IIIA (N0-N1), IIIB and IIIC is less debatable, but the optimal treatment of stage IIIA- N2 patients remains controversial due to a high degree of heterogeneity.

Surgical resection of the primary tumor and regional lymph nodes tends to be the most effective local therapy. Nevertheless, the reported 5-year survival after surgical resection alone in IIIA-N2 NSCLC is poor, ranging from 13% to 36%.[4] As postoperative locoregional microscopic residuals and microscopic metastases are the major causes of recurrence after complete resection[5], stage IIIA-N2 NSCLC has potential features of a systemic disease, thus systemic approaches for local and systemic control are preferred. Although there is a general consensus on the need for multimodality treatments in most patients with locally advanced NSCLC 6, the optimal treatment for N2 disease remains debatable.

For potentially resectable stage IIIA-N2 NSCLC, induction therapy (also known as neoadjuvant therapy) followed by surgery is recommended approach. Induction therapy includes chemotherapy alone, sequential chemoradiation, concurrent chemoradiation and concurrent chemoradiation after chemotherapy. For stage IIIA-N2 NSCLC, several studies have shown that induction chemotherapy followed by surgery improved survival, compared with surgery alone.[3,7,8] Similarly, induction by concurrent chemoradiotherapy followed by surgery resulted in 5-year survival rates of 30% to 40%, appearing superior to surgery alone.[9-11] However, a consensus has not been reached on which induction therapy should be administrated to stage IIIA-N2 patients - 50% of the National Comprehensive Cancer Network (NCCN) member institutions choose induction chemoradiotherapy, while another 50% choose induction chemotherapy.[12]

There were several meta-analyses looking at this issue. In a meta-analysis by Yao et al, comparing induction chemoradiation (CTRT) followed by surgery versus induction chemotherapy (CT) followed by surgery did not show difference in overall survival (OS) and progression free survival (PFS). The study consisted of 4 randomized controlled trails (RCT) with a total number of 461 patients.[13] Similarly,in a meta-analysis by Liang et

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al, 18 RCTs with 13 types of treatment modalities were studied. The meta-analysis showed best OS results with fewer treatment-related deaths in neoadjuvant chemotherapy followed by surgery and adjuvant chemotherapy or radiotherapy arms.[14]

In clinical practice, it is important to recognise situations where the patient can be offered multiple treatment options. The aim of this study is to review existing evidences and guidelines for the role of surgery for IIIA-N2 NSCLC.

Clinical Definition of ST IIIA-N2 NSCLC

NSCLC is currently staged by the eighth edition TNM staging system (Fig 1.).[7]

Stage IIIA – N2 includes T1-2N2M0. "N2" is a broad terminology stating positive mediastinal nodes. It can be further divided into various subgroups depending upon the nodal burden:

1. Occult N2 (not diagnosed before surgery)
2. Single zone – single station
3. Single zone – multiple stations
4. Multiple zones.

A simpler definition would be non-bulky (single station node of diameter < 3 cm and without invasion into trachea or major vessels) and bulky nodes.[15]

Fig 1. TNM 8th edition.

AJCC 8th				
	No	N1	N2	N3
T1a • 1 cm	IA1	IIB	IIIA	IIIB
T1C • > 1-2 cm	IA2			
T1C • > 2-3 cm	IA3			
T2 • invades main bronchus without carina • Partial or total atelectasis/ pneumontis T2a • > 3-4 cm T2b • >4-5 cm	IB IIA			
T3 • > 5-7 cm	IIB	IIIA	IIIB	IIIC
T4 • > 7 cm • Or any size with invasion of diaphragm, mediastinum, heart, great, vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina	IIIA			

Pathologic Definition of Stage IIIA-N2 NSCLC

Despite adequate preoperative mediastinal staging for clinical early-stage patients, 4.5% of patients are found to have pathologic stage III disease due to mediastinal nodal metastasis detected intraoperatively (incidental/unforeseen N2).[16,17] The American Joint Committee on Cancer (AJCC), Union for International Cancer Control (UICC), and International Association for the Study of Lung Cancer (IASLC) recommend that at least six lymph nodes/stations should be removed or sampled; three of these nodes/stations should be mediastinal, including the subcarinal nodes, and three should be hilar-intrapulmonary lymph nodes/stations for proper pathologic nodal staging.[18] Either systematic nodal dissection or lobe-specific mediastinal nodal sampling should be done to detect incidental N2 dis- ease.[19,20] Patients with microscopic N2 disease represent a subgroup with better prognosis compared to macroscopic disease.[21]

Diagnostic Tools

PET-CT

PET-CT provides highly accurate anatomical and metabolic data in a single imaging study. As a result, PET-CT is now a standard tool for the diagnosis and staging of lung cancer, as well as for re-staging patients with recurrent disease. Moreover, PET-CT is also used to guide treatment, assess treatment response, and for prognostic purposes.[22,12,23,24] For the diagnosis of mediastinal lymph node disease, the sensitivity and specificity of 18 F-FDG PET-CT are approximately 62–72% and 89–94%, respectively.[25-27]Moreover, The molecular information obtained with 18F-FDG PET/ CT allows us to discriminate atelectasis from tumor-related obstructive pneumonitis, allowing for more accurate delineation of the radiotherapy target volume.[28,29]

Invasive mediastinal staging:

Pathological verification of mediastinal nodes is must in suspected or detected by PET-CT nodal involvement before initiating the treatment. There are various ways for obtaining the tissue from mediastinal nodes.

Endobronchial Ultrasound (EBUS)/ Endoscopic ultrasound (EUS):

Endosonography (EBUS-TBNA and/or EUS-FNA) has been proposed as the initial imaging modality for mediastinal staging and diagnostic confirmation instead of surgical techniques.[30,31] The use of these endosonographic techniques, either alone or in combination, is equivalent to surgical techniques, with a sensitivity, negative predictive value (NPV), and diagnostic accuracy of approximately 90%, a high specificity (nearly 100%), and a low complication rate.[32-35] The combined use of EBUS-TBNA and EUS-FNA has been shown to provide greater diagnostic efficacy and accuracy than either technique alone, with a significant improvement in sensitivity and NPV for the detection of metastases.[36]

Mediastinal re-staging after induction therapy is always preferred butis technically difficult due to the presence of fibrosis, adhesions, and tissue necrosis. The latest meta-analyses show that the diagnostic precision of endosonographic imaging for restaging is lower than for the initial staging, with a sensitivity ranging from 63–77%, although specificity remains high (99%).[37]

Mediastinoscopy/ VATS:

Video assisted mediastinoscopy (VAM) shows good sensitivity and NPV (89% and 96%, respectively).[38] It can access stations 2R, 2L, 4R, 4L and 7. But stations 5, 6, 8 and 9 are not accessible through VAM. Parasternal mediastinotomy and extended cervical mediastinoscopy have shown same sensitivity and NPV, 71% and 91%, respectively, for the exploration of nodal stations 5 and 6.[38] A more invasive alternative to these two techniques is video-assisted thoracoscopic surgery (VATS), which is capable of reaching nearly all mediastinal lymph node stations, including stations 8 and 9, except in cases with pleural adhesions. However, VATS is used only to assess ipsilateral disease. The median sensitivity is 99%, with an NPV of 96% and a 4% false negative rate.[39] Invasive mediastinal re-staging after neoadjuvant treatment can be difficult due to the presence of treatment-related adhesions and fibrosis; however, when feasible, this procedure offers important advantages in that it allows for the collection of sufficient histological material to accurately restage the patient. Remediastinoscopy for restaging after induction therapy is feasible, with a sensitivity ranging from 61% to 74%, an NPV of 79% to 85%, and a diagnostic accuracy of 88%.[40] Restaging with VATS yields a sensitivity and NPV of 83% and 64%, respectively.[41]

Due to advances in imaging and endosonographic imaging, surgical techniques are, in most cases, no longer considered the first step in the diagnostic algorithm. Hence, EBUS/ EUS is the investigation of choice for mediastinal staging and VAM/ VATS is used if EBUS/ EUS fails to detect metastasis in suspected cases.

Role of Surgery in Stage IIIA–N2 NSCLC

Rationale:

Clinical trials evaluating concurrent CTRT show that about one-third of the patients (35–43%) will develop locoregional failure. Therefore, incorporating surgical resection to the treatment regimen of patients with stage III NSCLC may reduce the locoregional failure and improve the cure rate. Furthermore, surgical resection allows to examine treatment pathological response and tumor downstaging more accurately compared with radiological assessment. Induction therapy allows to start systemic treatment earlier and may increase compliance and tolerability of systemic therapy compared with adjuvant treatment.

Occult N2:

In cases with unsuspected N2 disease, which is revealed after surgery, prognosis is better, but the best adjuvant therapy is still unclear.[42] . A phase II RCT from Korea randomized 101 patients to adjuvant concurrent CTRT to CT after upfront curative lung resection in pN2 – IIIA disease. Patients were preoperatively evaluated with CT-PET, MRI of brain and mediastinal staging with mediastinoscopy/ EBUS to exclude N2 disease. Pulmonary resection with mediastinal nodal dissection was carried out to achieve no residual disease and a negative resection margin. CCRT arm received 50 Gy radiation therapy (RT) with 5 concurrent weekly paclitaxel + cisplatin followed by 2 additional cycles of same chemotherapy at 3 weekly interval. Adjuvant CT arm consisted of 4 cycles of 3 weekly carboplatin – paclitaxel. There was no difference in OS (74.3 months in CTRT and 83.5 months in CT arm, p=.38).[43] Hence, After R0 resection, adjuvant chemotherapy is recommended.

Proven N2:

There have been eight RCTs assessing various combination of multimodality treatment. Four RCTs (NTOG, EORTC, INT, ESPATUE) compared definitive CTRT versus neoadjuvant CT/ CTRT prior to surgery.44-47 Four RCTs (SAKKOO; GLCCG, WJTOG and IFCT) 48-51 compared neoadjuvant CT vs CTRT prior to surgery (Table 1.)

Trial	Control arm	Experimental arm	Resectable	Stage
NTOG	sCTRT	CT-S-RT	Resectable	IIIA/ N2
EORTC08941	sCTRT	CT-S-RT	Unresectable	IIIA/N2
INT 0139	cCTRT	cCTRT-S	Resectable	IIIA/N2
ESPATUE	CT-cCTRT	CT-cCTRT-S	Potentially resectable	IIIA/N2; IIIB
SAKK00/16	CT-S-RT	sCTRT-S	Resectable	IIIA/N2
GLCCG	CT-S-RT	sCTRT-S	Resectable	IIIA/ N2
WJTOG9903	CT-S-RT	cCTRT-S	Resectable	IIIA/ N2
IFCT-0101	CT-S-RT	cCTRT-S	Resectable	IIIA/ N2

CTRT: Chemoradiotherapy; CT: chemotherapy; cCTRT: concurrent chemoradiotherapy; RT: radiotherapy; S: surgery; sCTRT: sequential chemoradiation.

NTOG trial[44]

This phase III clinical trial randomized patients with IIIA– N2 NSCLC to induction with paclitaxel 225 mg/m2 plus carboplatin AUC6 every 3 weeks for 3 courses, followed by surgery and then postoperative radiotherapy (arm A) versus definitive sequential CTRT (arm B). Pathologic complete response (pCR) was achieved in 4% of patients. Median PFS, OS and 5-year survival rates were numerically longer in arm A (10 months, 17 months, and 20%, respectively) compared with arm B (8 months, 15 months, and 16%, respectively); however, these differences were not statistically significant. Despite carrying out this trial over 11 years in more than 300 patients, it was not sufficiently powered to detect a clinically relevant advantage of surgery after sequential CTRT.

EORTC-08941 trial[45]

IIIA–N2 patients deemed unresectable at baseline were enrolled in this trial. Cisplatin-based induction chemotherapy was administered to 579 patients recruited over 8 years. Only 332 responding patients (57%) were randomized to either surgery (with a 47% rate of pneumonectomy) or sequential radiotherapy (60 Gy in 30 fractions). In the surgery arm, only half of the 332 patients achieved complete resection, with persisting ypN2 disease in 57% of the patients. The rate of pCR was low (5%) and there was no significant difference in OS (5-year OS was approximately 15% in both groups). A high mortality rate (7%) was observed after pneumonectomy, leading to an extremely low long- term OS compared with other lung resections (5% vs. 27% of patients attaining 5-year OS, respectively). Overall, there was no survival difference in two arms. .

INT 0139 trial46

Patients received two cycles of cisplatin-etoposide concurrently with radiotherapy at a dose of 45 Gy in 25 fractions and were randomized to either surgery or completion of full dose radiotherapy (61 Gy). No significant differences in survival were observed between both arms (the 5-year OS in the surgery arm was 27% vs. 20% in the non-surgery group; P=0.10). A strikingly high mortality after pneumonectomy (25%) was observed, with 14 of 16 treatment-related deaths occurring in the surgical group compared with only 3 (2%) in the non-surgical group. In an adhoc exploratory analysis, there was an improvement in OS for patients who underwent lobectomy compared with a matched cohort of patients treated with chemoradiation, but not for those who underwent pneumonectomy.

ESPATUE trial[47]

This trial addressed the use of an intensive regimen in a population with a more advanced disease. Patients with stage IIIA–pN2 or highly selected, potentially resectable stage IIIB disease received induction chemotherapy (3 cycles of cisplatin plus paclitaxel) followed by hyperfractionated radiotherapy (45 Gy) given concurrently with cisplatin plus vinorelbine. Only responding patients deemed resectable by a tumor board were randomized to either surgery or definitive radiotherapy boost with 20–25 Gy (up to a total dose of 65–71 Gy). The trial started in 2004 and used contemporary staging methods such as brain imaging and 18F-FDG PET-CT. Among 81 patients allocated to surgery, 70 underwent surgery (25% had a pneumonectomy) and 66

achieved a complete resection, with a pCR rate of 33% (27/81). Mediastinal downstaging was not reported. Intriguingly, none of the treatment-related deaths in the surgery arm (5/70) were after pneumonectomy, in contrast with what was observed in other trials in this setting. The trial was negative at the futility analysis because the control arm performed as well as the experimental arm, with an impressive 5-year OS of 40% and 44%, respectively; the highest reported in this setting. Stage migration and selection bias after an intensive induction regimen might partially explain these outcomes.

SAKK00/16 trial[48]

Patients with stage IIIA–pN2 disease were randomized to induction treatment either with chemotherapy alone (cisplatin plus docetaxel) or with sequential CTRT (44 Gy in 22 fractions in 3 weeks), followed by surgery. Although the rates of response (61% vs. 44%), complete resection (91% vs. 81%), mediastinal downstaging (64% vs. 53%) and pCR (16% vs. 12%) were higher in patients treated with induction CTRT, there were no statistically significant differences either in event free survival (12.8 vs. 10.5 months) or in OS (37.1 vs. 26.2 months).

GLCCG trial[49]

Eligible patients had stage IIIA–N2 (30%) or stage IIIB (70%) that was deemed potentially resectable; Patients were randomized to receive an induction regimen of 3 cycles of cisplatin plus etoposide alone or followed by twice daily radiation with concurrent carboplatin and vindesine. The rate of pneumonectomy was similar in both arms (35%). Addition of CTRT to induction showed higher rates of complete resection (55% vs. 69%), mediastinal downstaging (29% vs. 46%), and major pathologic response (MPR, 20% vs. 60%), which did not translate into a significant improvement in PFS or OS (median OS 17.6 vs. 15.7 months). Treatment-related deaths were higher in the interventional group compared with the control group, particularly after pneumonectomy (14% vs. 6%) but also after lobectomy (7.5% vs. 2%).

WJTOG9903 trial[50]

This study compared chemotherapy (carboplatin plus docetaxel) alone with chemotherapy plus 40 Gy of concurrent radiotherapy in patients with stage IIIA–N2. The addition of radiotherapy to induction chemotherapy conferred better local control but differences observed in OS were not significant due to lack of statistical power. Mediastinal downstaging was associated with better outcome after surgery.

IFCT-0101 trial[51]

Patients with stage IIIA/pN2 tumors were randomized into 3 arms: chemotherapy alone with cisplatin plus gemcitabine or radiotherapy concurrent with either cisplatin plus vinorelbine or carboplatin plus paclitaxel. About 50 patients in each arm were needed to demonstrate the primary endpoint of feasibility, but the trial closed early due to very slow accrual after enrolling only 46 patients over 4 years. Amongst the 42 patients with resected tumors, 35 patients had a complete resection, 16 patients showed mediastinal downstaging, and 2 (5%) patients achieved pCR. Feasibility was superior in the chemotherapy alone arm (93%) but the study was not powered to detect meaningful differences.

A systematic review and meta-analysis of 12 studies with 2,724 patients demonstrated higher tumor downstaging (P=0.01), pCR (P=0.028), and local control (P=0.002) with preoperative CTRT compared with chemotherapy alone; however, it did not translate into a higher 5-year OS rate or a PFS benefit.52 Real world data has supported these findings. A study based on the SEER database showed that induction with CTRT led to a higher rate of mediastinal downstaging than chemotherapy alone in a cohort of T1–2N2 patients. However, induction with CTRT did not improve OS compared with chemotherapy alone (5-year OS of 41.4% vs. 40.8%, respectively).53

Role of Post-Operative Radiotherapy (Port)

The role of PORT in Stage IIIA-N2 NSCLC is controversial. In cases with incompletely resected disease, data support the use of PORT is strong, showing that this approach improves OS.[54] However, in completely resected Stage IIIA-N2 NSCLC, PORT has been a subject of intense debate for more than two decades, ever since a meta-analysis[55] cast doubts on the benefits associated with this approach. The Lung ART RCT found no benefit for PORT.[56] In that trial, 501 patients with completely resected NSCLC with pathologically

confirmed N2 disease were randomized to receive PORT (54 Gy/27–30 fractions) or no PORT. The 3-year DFS and OS with PORT versus no PORT was 47.1% versus 43.8% and 66.5% versus 68.5%, respectively, but these differences were not statistically significant. Given these contradictory reports, more research is needed to better determine the patient profile most likely to benefit from PORT.

Surgery and Targeted Therapy

Activating EGFR mutation is a frequent oncogenic driver event,especially among Asian patients with NSCLC. A systemic review and global map of EGFRmutaion incidence by ethnicity in lung adenocarcinoma showed that 47% of tumors from the Asia-Pacific subgroup harbored EGFRmutaion compared to 15% in the European subgroup.[57]

Role of Targeted therapy with tyrosine kinase inhibitor (TKI) is well established in stage IV NSCLC and its excellent results in stage IV led the researchers to look for its use in stage IIIA-N2 disease as well.

Adjuvant TKI:

Two recent randomized trials, ADJUVANT/CTONG1104 and EVAN, showed superior outcomes with adjuvant EGFR tyrosine kinase inhibitors (TKIs) (gefitinib and erlotinib, respectively) when compared with adjuvant chemotherapy.[58,59] The results of the Phase III ADAURA trial[60] comparing 3 years of adjuvant osimertinib to placebo in patients with completely-resected, EGFR-mutated Stage IB-IIIA NSCLC were recently published. The 2-year DFS was statistically significant, with a clinically meaningful improvement in DFS in the osimertinib group (90% vs. 40%, respectively). Despite these promising findings, OS data are needed before osimertinib can be considered standard of care in these patients. Therefore, EGFR mutation testing for surgically treated stage III NSCLC is encouraged, whereas the role of routine adjuvant EGFR TKI continues to be debated.

Neoadjuvant TKI:

A small Phase II trial evaluated the efficacy of neoadjuvant erlotinib in patients with EGFR-mutated Stage IIIA NSCLC. After surgery, the patients who received erlotinib had a marginally better clinical ORR (67% vs. 19%), pathological response rate (67% vs. 38%), and OS (51.0 vs. 20.9 months) compared with those who received chemotherapy.[61] Another multicenter study, EMERGING- CTONG 1103, reported a significant improvement in DFS with erlotinib versus gemcitabine-cisplatin chemotherapy (21.5 vs. 11.4 months; HR 0.39) in the same group of patients.[62] The ASCENT trial[63] compared afatinib, a second-generation EGFR TKI, to standard CTRT in the neoadjuvant setting in patients with Stage III NSCLC. Patients who received neoadjuvant afatinib had high overall response (69%) and major pathologic response (MPR) rates to surgery. That trial is still underway, as is the neo ADAURA trial (NCT04351555).

Surgery and Immunotherapy

The role of programmed death ligand 1 (PD-L1) immunohistochemistry as a predictive biomarker for stage III NSCLC has not been defined. In the PACIFIC study, consolidation durvalumab after CCRT in unresectable stage III dis ease has shown progression-free survival (PFS) and OS benefit. [64] Hence, it is the established modality of treatment in unresctable stage III disease if patients have not progressed after 2 or more cycles of concurrent platinum based chemoradiation. But, as of now it is not recommended after surgical resection.

Neoadjuvant immunotherapy:

The first clinical study to explore the safety and antitumor activity of neoadjuvant chemo-immunotherapy (paclitaxel – carboplatin plus nivolumab) in resectable stage IIIA NSCLC was the NADIM trial.[65] At 24 months, the DFS (primary endpoint) was 77.1%, with an OS rate of 90%. All patients who underwent surgery showed an MPR, with 63% having a pCR. A new Phase II RCT (NADIM-2) is currently in progress to compare the same neoadjuvant chemo-immunotherapy regimen followed by a shorter (6 months) adjuvant nivolumab monotherapy versus standard chemotherapy.

Adjuvant immunotherapy:

Several clinical trials are currently evaluating the role of adjuvant immunotherapy, but no results have been published to date.

Summary of Various Proposed Guidelines

Evidences from various RCTs clearly suggest that surgery alone is not justified for stage IIIA-N2 NSCLC. There has been several published guidelines and a summary has been presented in table 2.

Table 2. Summary of guidelines.

Guideline	Definition of "resectable"	Recommendation
BTS and SCTS (2010)66	Non-fixed lymph nodes; non-bulky nodes; single zone N2 disease; reasonable chance of complete resection; clear pathological margins	Consider surgery as part of multimodality treatment in non-fixed, non-bulky, single zone N2 NSCLC. Further research into the role of surgery in non-fixed, non-bulky multi-zone N2 NSCLC.
ACCP (2013)67	Discrete nodes, easily measurable and defined nodes, free major structures such as trachea and great vessels	Definitive CTRT or induction therapy (CT or CTRT) followed by surgery. Surgery followed by CT – not recommended.
ESMO (2015)68	Minimal, non-bulky N2 disease; single station N2	Definitive CTRT or induction CT/ CTRT followed by surgery
NCCN (2019)69	Low-volume nodes; non-invasive nodes; pathologically proven; < 3 cm in diameter	Definitive CTRT or induction CT/ CTRT followed by surgery.
Definitive CTRT followed by Durvalumab		
NICE (2019)70	None provided	Induction CTRT followed by surgery
ATORG (2020)71	Discrete nodes; single station nodes; less than 3 cm in size	Incidental pN2 after surgery – adjuvant chemotherapy with or without RT Induction CT/ CTRT followed by surgery In EGFR nutation positive cases, induction Erlotinib followed by surgery may be an alternative op

BTS: British Thoracic Society

SCTS: The Society of Cardiothoracic Surgery in Great Britain and Ireland
ACCP: American College of Chest Physicians
ESMO: European Society of Medical Oncology
NCCN: National Comprehensive Cancer Network
NICE: National Institute for Health and Care Excellence
ATORG: Asian Thoracic Oncology Research Group

Conclusion

Locally advanced NSCLC is a highly heterogeneous disease requiring a multidisciplinary team-based treatment approachwith at least a thoracic surgeon, a medical oncologist, and a radiation oncologist. As more than a third of the patients (35–43%) will develop loco-regional failure and only a quarter of the patients (20–25%) will achieve long-term survival with concurrent CTRT, surgery has been intensively studied in patients with discrete N2 involvement and resectable disease. However, most trials evaluating surgery in stage III NSCLC following induction treatment were not powered to detect small differences in survival outcomes. Induction chemotherapy with radiotherapy was associated with higher rates of tumor downstaging and pCR than chemotherapy alone (4–5% vs. 16–60%, respectively); however, these did not translate into better long-term outcomes, nor higher cure rates (5-year OS 41.4% vs. 40.8%, respectively). Therefore, both induction chemotherapy or induction chemoradiation followed by surgery remains a valid option for non-bulky/ single station stage IIIA NSCLC.

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