

# What is the role of surgery in stage III NSCLC in the era of Immunotherapy?

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Lung cancer has become the leading cause of death among cancers worldwide. Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all cases and has a poor overall 5-year survival of about 15% [1]. At the time of presentation, at least 40% of patients are diagnosed in an advanced stage and about one third have locally advanced (stage III) disease, which represents a heterogeneous group of patients even in the most recent version of the IASLC/UICC TNM staging system (8th edition) [2]. Notably within this edition stage III has been further divided into stage IIIA, stage IIIB and Stage IIIC given their different prognosis. The main difference between the 7th and the 8th TNM edition are summarised in Table 1 and 2.

The treatment of such patients represents a major challenge because of their local presentation, especially in the case of an advanced primary tumour (T4 situation) with local infiltration of vital mediastinal organs or involvement of locoregional mediastinal lymph nodes (N2 or N3 nodes) and the risk of metastatic recurrence. The extent of mediastinal node involvement has an inverse correlation with survival (ref). The subgroup with unforeseen N2 involvement, incidentally found on final pathologic examination (IIIA-1) or recognized intraoperatively (IIIA-2), accounts for 14–24% of patients. However, the largest subgroup of stage IIIA (67%) consists of patients with clinical single or multiple level ipsilateral lymph node invasion (IIIA-3) to ‘bulky’ N2 disease at imaging (IIIA-4). Preoperatively proven stage IIIA-N2 disease is variably considered ‘resectable’ with or without induction or adjuvant therapy, whereas patients with bulky N2 and N3 are considered ‘primary unresectable’ [3,4]. These data highlight the heterogeneity of stage III disease and the poor long-term survival for patients with macroscopic or multistation N2 involvement. The best therapeutically strategy for NSCLC patients stage III remains debatable and the role of surgery has evolved and changed over the years.

## When then we should contemplate surgery?

The general argument in favour of surgery is based on the assumption that surgery results in better local control of primary disease than conventional RT. Although this may be true for early stage NSCLC, it is unproven for patients with N2 disease.

The collective 5-year survival rates for surgery alone in stage III (N2) disease are typically reported to be in the range of 14%–30% [5-7] but these are usually highly selected patients often with incidental, microscopic N2 disease discovered at the time of resection. Despite negative preoperative staging, including mediastinoscopy, approximately one-fourth of patients felt to be cT1-3N0-1 may have occult N2 disease [8]. The increased use of fluorine-18-2-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) scanning

**Table 1.** Innovations in the Descriptors Introduced in the Eighth Edition of the TNM Classification of Lung Cancer Compared With the Seventh Edition.

Descriptor	Seventh Edition	Eighth Edition
<b>T Component</b>		
0 cm (Pure lepidic adenocarcinoma ≤ 3 cm total size)	T1a if ≤ 2 cm; T1b if >2-3 cm	Tis (AIS)
≤ 0.5 cm invasive size (lepidic predominant adenocarcinoma ≤ 3 cm total size)	T1a if ≤ 2 cm; T1b if >2-3 cm	T1mi
≤ 1 cm	T1a	T1a
>1-2 cm	T1a	T1b
>2-3 cm	T1b	T1c
>3-4 cm	T2a	T2a
>4-5 cm	T2a	T2b
>5-7 cm	T2b	T3
>7 cm	T3	T4
Bronchus <2 cm from carina	T3	T2
Total atelectasis/pneumonitis	T3	T2
Invasion of diaphragm	T3	T4
Invasion of mediastinal pleura	T3	-
<b>N component</b>		
No assessment, no involvement, or involvement of regional lymph nodes	NX, N0, N1, N2, N3	No change
<b>M component</b>		
Metastases within the thoracic cavity	M1a	M1a
Single extrathoracic metastasis	M1b	M1b
Multiple extrathoracic metastases	M1b	M1c
<b>Abbreviations:</b> AIS: adenocarcinoma in situ; mi: minimally invasive adenocarcinoma; Tis: tumor in situ.		

has improved preoperative staging. FDG-PET compared to CT is more sensitive and specific at mediastinal nodal staging [9], and more sensitive in the detection of distant metastatic disease. Several factors predict a poor prognosis: preoperatively identified N2 disease, multiple involved lymph nodes or sites, bulky extracapsular disease, T3 tumors,

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**Table 2.** Changes to the seventh edition are highlighted in bold and underlined.

<b>Occult carcinoma</b>	<b>TX</b>	<b>N0</b>	<b>M0</b>
Stage 0	Tis	N0	M0
Stage IA1	T1a(mi)	N0	M0
	T1a	N0	M0
Stage IA2	T1b	N0	M0
Stage IA3	T1c	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T2b	N0	M0
Stage IIB	T1a-c	N1	M0
	T2a	N1	M0
	T2b	N1	M0
	T3	N0	M0
Stage IIIA	T1a-c	N2	M0
	T2a-b	N2	M0
	T3	N1	M0
	T4	N0	M0
	T4	N1	M0
Stage IIIB	T1a-c	N3	M0
	T2a-b	N3	M0
	T3	N2	M0
	T4	N2	M0
Stage IIIC	T3	N3	M0
	T4	N3	M0
Stage IVA	Any T	Any N	M1a
	Any T	Any N	M1b
Stage IVB	Any T	Any N	M1c

and nonsquamous histology [10-12]. The benefit of surgery in these patients is not defined.

Surgery as upfront treatment should no longer be considered a standard option for most patients with known pathologic N2 disease [13]. This extends even to patients with single-station aortopulmonary window nodal involvement (station 5), who have long been considered candidates for upfront surgery, as their prognosis is no better than other N2 patients [14].

Surgery after induction chemotherapy has been explored in numerous phase I/II and retrospective studies have addressed the use of induction chemotherapy before surgery in patients with stage IIIA/B disease [15-17]. The existing phase III randomized data for induction chemotherapy are contradictory; patients with stage I-III disease were enrolled, and a variety of chemotherapy combinations have been investigated. A French study randomized 355 resectable stage I (except T1N0), II, and IIIA patients to either preoperative chemotherapy (cisplatin, mitomycin, and ifosfamide for 2 cycles; 2 additional cycles were assigned postoperatively for responders) or surgery alone [18]. On the other hand, in a randomized study reported by Rosell, *et al.* [19] 60 patients were randomized to similar preoperative chemotherapy with cisplatin, ifosfamide, and mitomycin, given for 3 cycles every 3 weeks preoperatively, or to surgery alone. Median survival time was 26 months in the chemotherapy group compared to 8 months in the surgery-alone group ( $P < 0.0001$ ). The Roth and Rosell trials have been much discussed, and the results have been somewhat controversial because they were strongly positive, favouring neoadjuvant chemotherapy, and because of the small number of patients ( $n=60$ ) in both trials. Additionally, N2 involvement was not required, and mediastinoscopy was not mandated if the mediastinum was negative by CT. In the surgery only arm of the Roth trial, 40% of participants had stage IIIB disease, leading to speculation that an imbalance in the stage distribution between the 2 arms was skewed in favour of the chemotherapy arm. In contrast, the Rosell trial had

unexpectedly low survival rates (0% at 3 years) in the surgery-alone arm, even though 37% had only N0 or N1 disease. Other factors, such as potential imbalances in one or several prognostic factors between study arms for the 2 trials, may also explain the observed differences. In the S9900 trial, patients with stage IB-IIIa lung cancer were randomized to induction therapy with carboplatin/paclitaxel followed by surgery or to surgery alone. A statistically significant difference in progression-free survival rates (PFS) or OS was not observed [20]. The European Organisation for Research and Treatment of Cancer (EORTC) 08012 trial is the largest neoadjuvant trial of 519 patients with clinical stage IA-IIIa disease who were randomized to either neoadjuvant platinum-based chemotherapy or surgery alone [21]. Results did not reveal a benefit in PFS or OS, and neoadjuvant chemotherapy did not change the type of surgery performed.

In the Ch.E.S.T. study [22] cisplatin with gemcitabine was chosen as induction chemotherapy. The 3- year PFS rates were 48% in the surgery-alone arm and 53% in the induction chemotherapy arms ( $P=0.11$ ). The common result in these studies has been the inability to demonstrate a robust and significant improvement in survival with the addition of neoadjuvant chemotherapy to surgery alone. Several studies have had to close prematurely with incomplete accrual. Concurrent with the conduct of these studies, the positive results of adjuvant chemotherapy trials were announced. Hence it was no longer accepted to randomize patients to a surgery-alone arm, leading to early closure of neoadjuvant studies. The Berghmans, *et al.* [23] meta-analyses on 25 trials published between 1986 and 2004 showed that the 6 neoadjuvant trials demonstrated a HR of 0.66 (95% CI, 0.48– 0.93) in favor of addition of induction chemotherapy. The Burdett, *et al.* [24] meta-analysis included 7 randomized neoadjuvant clinical trials, which resulted in a HR of 0.82 (95% CI, 0.69-0.97) again in favor of neoadjuvant chemotherapy. Patients enrolled in neoadjuvant studies are frequently clinically staged, whereas patients enrolled in adjuvant trials are pathologically staged, which makes comparisons between the 2 trials difficult. The current clinical question is whether neoadjuvant therapy offers any advantages over adjuvant therapy.

The EORTC 08941 study [25] compared radical surgery versus 3 cycles of platinum-based induction chemotherapy followed by RT in selected patients with stage IIIA(N2) NSCLC. Only responding patients were randomized between radical resection with lymph node dissection and optional PORT versus thoracic RT (at least 40 Gy in 2 Gy daily fractions to the mediastinum with a boost to at least 60 Gy). Three hundred thirty-three patients were randomized. One hundred fifty-four patients actually had surgery, and 155 had radiation. Operative mortality was 4%, and 39% received PORT. With a median follow-up of 72 months, median survival times and 5- year OS rates for patients randomized to surgery compared to RT were 16.4 months versus 17.5 months and 16% versus 13%, respectively (HR: 0.95, 95% CI, 0.75–1.19). Median survival times and 2-year PFS rates for patients randomized to surgery and radiation were 9.0 months versus 11.4 months and 27% versus 24%, respectively ( $P=0.6$ ). In conclusion even in patients with a response to induction chemotherapy surgery does not improve either OS nor PFS compared to thoracic RT in stage IIIA (N2) patients. There exist limited prospective data on comparing induction chemotherapy alone (with/without PORT) versus induction concurrent chemotherapy and radiation [26].

A German Phase III study of stage III NSCLC randomized 558 patients to preoperative cisplatin/etoposide for 3 cycles followed by concurrent twice-a-day RT (45 Gy at 1.5 Gy per fraction) with carboplatin and vindesine or to preoperative cisplatin/etoposide followed by

PORT to 54 Gy [64]. Only 54% and 59% of patients underwent surgery following induction chemotherapy and chemoradiation therapy, respectively. The addition of chemoradiation increased mediastinal downstaging and pathological response rates compared to induction chemotherapy alone but did not significantly improve PFS (5-year rates of 30% versus 25%) or OS (39% versus 31%) in those patients who underwent resection. The surgical mortality rate doubled with the addition of chemoradiation, especially in pneumonectomy patients. The rates of complete pathological response in the mediastinum were not reported. However, the rate of clinical complete response was only 5% in the radiation arm. This study does not adequately address the question of induction chemotherapy versus induction chemoradiation or whether radiation should be used preoperatively or postoperatively in stage IIIA(N2) patients. First, the use of induction chemotherapy prior to chemoradiation may not improve outcomes [27,28]. Second, the study enrolled a large fraction of advanced IIIB (T4 or N3) patients, which comprised approximately two-thirds of all patients. These patients are rarely considered for trimodality therapy in the United States. In a subset analysis of 125 N2 patients from this trial, 3-year OS for patients on the induction chemoradiation arm compared to the induction chemotherapy alone arm was 31% versus 18%, respectively ( $P=0.21$ ) [28]. The therapeutic benefits of PORT in cN2 patients undergoing induction chemotherapy and surgery have not been well studied in prospective trials. In a retrospective 2-center experience of 153 patients with N2 disease who did not receive PORT, there was a high incidence of locoregional failure, particularly in patients with pN1 disease (5-year local failure rate of 62%) [29]. There is also a paucity of adequate level 1 evidence data comparing preoperative radiation to PORT for stage IIIA(N2) patients who are similarly staged. Retrospective data showing superior survival for preoperative radiation are subject to selection bias [30].

Radiotherapy (RT) has also been explored over the years in several trials as a possible tool to add to the treatment pack of these patients. The survival benefit of reducing distant failure by adding chemotherapy to RT as demonstrated in randomized phase III trials for inoperable NSCLC [31-33] stimulated interest in preoperative treatment with RT and chemotherapy instead of either RT or chemotherapy alone. The objectives of these trials were to use RT to shrink the primary tumor and nodal disease, use the chemotherapy to provide radiosensitization and sterilize distant micrometastases, and perform surgery to optimize the outcome by removal of residual tumor and enhance local control.

The phase III Intergroup 0139 (RTOG® 93-09) study was designed to address the role of surgery in combined-modality therapy [34]. Patients with T1-3pN2M0 tumours were eligible if the resection was technically feasible at registration. On pretreatment mediastinoscopy, the majority of patients had only one nodal station involved (76%), whereas 22% of patients had 2-3 positive stations. A total of 429 randomized patients received induction with cisplatin and etoposide for 2 cycles and daily RT to 45 Gy starting on day 1. Patients on arm 1 then had a resection if there was no progression, followed by 2 more chemotherapy cycles. Subjects on arm 2 had uninterrupted RT to 61.2 Gy with 2 more cycles of chemotherapy. With a median followup time of 69.3 months and 396 analyzable patients, the trial did not meet its primary endpoint of 10% absolute survival improvement in the surgical arm. For arms 1 and 2, the median survival times and 5-year OS rates were 23.6 versus 22.2 months and 27% versus 20%, respectively ( $P=0.24$ ). PFS rates were superior in the trimodality ACR Appropriateness Criteria® 6 Induction and Adjuvant Therapy - NSCLC arm, 22% versus 11% at 5 years ( $P=0.017$ ), respectively. When analyzing the site of first

relapse, there were fewer local failures in arm 1 compared to arm 2, 10% versus 22%, respectively. In the trimodality arm, patients with mediastinal sterilization (pN0) experienced improved 5-year OS of 41%, whereas survival in patients with residual nodal disease (pN1/2) was 24%. Importantly, in the Intergroup 0139 trial [39], the OS curves crossed at about 1 year of follow-up, owing to a high surgical mortality of 26% (14/54) in patients undergoing pneumonectomy (comprising approximately one-third of all resections) primarily due to respiratory causes, which the authors suggested offset any survival gain achieved with surgery. In an unplanned subset analysis of lobectomy-only patients, the surgical group was compared to a matched control group, revealing a statistically significantly improved 5-year OS rate of 36% versus 18% ( $P=0.002$ ). The authors noted that a prospective trial is unlikely to be completed to validate the hypothesis that a trimodality approach with lobectomy is better than nonsurgical therapy (based on 2-D planned radiation to 61.2 Gy). Various interpretations of this trial are possible, ranging from considering nonsurgical therapy as the standard in stage IIIA(N2) patients to selecting patients for lobectomy following induction therapy, particularly at experienced centers [35,36]. Furthermore, the use of pneumonectomy in the trimodality setting remains controversial. Institutional reports from large academic centres suggest that induction with chemotherapy and radiation does not necessarily increase mortality rates associated with pneumonectomy in carefully selected patients [37,38].

Impressive results of induction chemo-radiotherapy before surgical intervention for selected patients with stage IIIA-N2 NSCLC were published by Uy, *et al.* [39] who adopted the protocol from the surgical arm of the North American Intergroup trial.

Nevertheless the role of surgery after induction chemotherapy in patients with stage IIIB-N3 NSCLC remains unclear. No phase 3 data have presently shown that a neoadjuvant treatment followed by surgery results in prolonged survival compared with adequate chemoradiotherapy only. Furthermore there is no real consensus about the length of induction chemotherapy or about the need of any adjuvant treatment after induction chemotherapy. Even the role of postoperative radiotherapy in incompletely resected patients is uncertain, as the major relapse is still locoregional. There are only limited data available, but in selected patients with clinical T4N0-1 NSCLC with either multifocal ipsilateral disease or with central extension to the main carina, great vessels, or vertebral column, upfront surgery should be considered. Postoperative treatment should be dictated by the pathological findings and include postoperative radiotherapy in case of incomplete resection or chemotherapy in case of unforeseen hilar or mediastinal lymph node invasion.

Are we ever going to see a randomized trial comparing the role of surgery with a nonsurgical approach only in these subsets of stage III NSCLC without mediastinal lymph node invasion? Due to their low prevalence, it is highly unlikely.

As there are no randomized controlled data available, the reported role of surgery is often based on the centre expertise. It is hence crucial that these patients are evaluated and treated by expert multidisciplinary teams. In stage III-N2/3 NSCLC, the role of surgery compared with radical and adequate modern thoracic radiotherapy for local control after induction treatment is still a challenge.

In patients receiving induction chemo-RT, early toxicities (e.g., esophagitis and hematotoxicity) are increased and in those undergoing surgery, postoperative mortality rate is higher especially when a pneumonectomy is performed.

Whether chemo-RT is superior to chemotherapy alone as induction therapy has been investigated in a Swiss trial [40] (SAKK 16/00) that included patients with cytologically or histologically proven IIIA(N2) disease and randomised to induction chemotherapy followed by surgery versus induction chemotherapy followed by radiotherapy and then definitive surgery. Both the primary end point of the trial (OS) as well as the secondary end point (PFS) showed no significant differences between the arms. It is noteworthy that the employed induction chemotherapy protocol was cisplatin and docetaxel. Since a high percentage of patients could be taken to surgery following induction chemotherapy alone, the patient selection of this study included more potentially resectable IIIA(N2) disease patients and the induction chemotherapy turned out to be quite effective in inducing downsizing and downstaging. In conclusion the trial showed that RT did not add any benefit to induction chemotherapy followed by surgery. The authors suggested that one definitive local treatment modality combined with neoadjuvant chemotherapy is adequate to treat resectable stage IIIA/N2 non-small-cell lung cancer.

Based on these different trials results, it is the general perception that, in these complex treatment situations, the overall expertise of the multi-modality team at the treatment centre is probably of more importance for the overall outcome of the patient than the exact schedule and permutation of the multi-modality treatment protocol.

## Discussion

In some clinical trials, patients from different subgroups are included, the definitions of “unresectable” or “marginally resectable” are vague or absent, and methods of documentation of N2 status (radiographic versus pathologic) have varied. In trials that include surgical resection, patients undergoing surgery (those with stable disease or those with responding tumours), and in the definition of a complete resection (removal of gross disease versus complete resection with negative microscopic margins) has varied. Even the definition of “bulky” N2 disease has also varied. In the more recent trials, it has often been used to describe multiple nodes and/or nodes that measure >2–3 cm but for instance in the SAKK 16/00 the cut off was 5 cm and 8% of the patients were recruited in both arm had N2 bigger than 5 cm. Finally, in some of the surgical trials, resection and survival rates were stated only for those patients undergoing thoracotomy and did not include patients who received preoperative treatment and were unable to undergo surgery. The clinical criteria for enrollment (eg, pulmonary function, performance status, and the presence and degree of weight loss) have varied within trials as well.

The heterogeneity of the patient population and different treatment approaches has also been compounded by the small size of many of the trials, furthermore it is even more difficult comparing different trials with different modality done at different time whereas for instance the PET was not used routinely, or the node sampling was not a well established procedure.

## Conclusion

It is our opinion that surgery could and should still play a role in the treatment of stage III NSCLC. Interpretation of literature data is complicated by inconsistent diagnostic procedures for N2 disease (pretreatment pathological confirmation versus imaging studies only), heterogeneity of N2 disease (ranging from single-station microscopic tumor to bulky, multistation disease), and pooled analysis of N2 patients with other stage III patients. The patients with the best results after surgery are those with no evidence of mediastinal disease on

preoperative studies, including mediastinoscopy, who are found to have incidental N2 involvement at time of resection or in the final pathological report (IIIA-1,-2; see Introduction). In surgically resected patients such as these, adjuvant cisplatin-based chemotherapy is the standard of care and improves OS. Options for patients presenting with clinical, nonbulky N2 disease (IIIA-3) diagnosed preoperatively include 1) definitive chemoradiation +/- adjuvant chemotherapy; 2) induction chemoradiation followed by surgery +/- adjuvant chemotherapy; and 3) induction chemotherapy followed by surgery +/- PORT. Based on the overall negative results of the Intergroup 0139 trial, level 1 evidence exists for the approach of ChemoRT alone. Furthermore, from our summary, the strongest evidence in favour of surgery comes from the SAKK 16/00 trial [41] where neoadjuvant chemotherapy followed by surgery seems to be a valid option for potentially operable Stage IIIA. However, for selected patients and in expert hands, trimodality therapy, especially if restricted to lobectomy, remains a reasonable option.

Immunotherapy has been explored initially in inoperable stage IIIA-B (ref pacif) which showed an increased PFS in the durvalumab (anti PDL1) trial (questo lo devo espandere forse un po'), but there is an increasing interest in earlier stage. The Swiss group has been running and actively recruiting patients within the trial SAKK 16/14 (ref). This is a randomized Phase II trial designed to evaluate the addition of perioperative immunotherapy with the anti-PD-L1 antibody durvalumab to the previously established standard of care for stage IIIA(N2) patients, which is based on the trials SAKK 16/96. Patients whose tumour is deemed resectable at diagnosis receive three cycles of chemotherapy with cisplatin 100 mg/m<sup>2</sup> and docetaxel 85 mg/m<sup>2</sup> every three weeks followed by two cycles of durvalumab 750 mg every two weeks. Following surgery, patients will be treated with durvalumab 750 mg every two weeks for 12 months. Patients with R1/R2 resection and patients with extracapsular spread of mediastinal lymph node metastases may undergo standard radiotherapy prior to adjuvant treatment with durvalumab. The primary endpoint of the trial is event-free survival at 12 months. Secondary endpoints include OS, objective response, nodal down-staging, complete resection, pattern of recurrence and toxicity.

In conclusion, we believe that surgery has a well-defined position with the stage II NSCLC patient treatment and, with the exception of exceptional circumstances, it has to be combined with a multi modality approach.

However, Despite several trials and huge effort from the scientific community, further research is needed to define the best treatment approach based on the number and bulk of involved nodal stations and the presence of microscopic versus gross disease on preoperative studies.

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