



# Neoadjuvant Treatment for Resectable, Stage IIIA Non-Small Cell Lung Cancer



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## Abstract

The optimal treatment of patients with stage IIIA non-small cell lung cancer (NSCLC) remains highly controversial. In resectable stage IIIA NSCLC, there is still a considerable debate regarding the best strategy. Treatment choice is often a function of institutional and/or physician preference. Treatment consists of neo-adjuvant chemotherapy or chemoradiotherapy (CHRT) followed by surgery with or without post-operative radiotherapy (RT), definitive CHRT, or neoadjuvant immunotherapy followed by surgery and several other options. Neo-adjuvant therapy for operable NSCLC has been the subject of a large number of studies in the literature. We summarized existing data and also highlight ongoing trials, focusing on neoadjuvant immunotherapy. Neoadjuvant CHRT seems to be safe and efficient and is associated with an improved pathological outcome, but it has failed to demonstrate any advantage in terms of progression-free survival or overall survival compared to neoadjuvant chemotherapy. Contrary to previous fears, radiotherapy does not add a higher toxicity, nor does it increase post-operative mortality compared to chemotherapy alone. Studies with chemoimmunotherapy provide a higher rate of pathologic responses and downstaging compared to chemotherapy. On the other hand, it remains to be confirmed whether pCR is a sufficient surrogate for OS.

Results of ongoing neoadjuvant immunotherapy trials are awaiting and we believe, the next decades will bring much needed improvements for patients. Still the controversy is not being solved and further trials considering a better patients' selection, innovative radiotherapy and more efficient systemic treatments need to be undertaken.

**Keywords:** NSCLC; Stage IIIA; Neoadjuvant treatment; Chemotherapy; Chemoradiotherapy; Surgery; Immunotherapy

**Abbreviations:** NSCLC: Non-small Cell Lung Cancer; CHRT- Chemoradiation; CHT: Chemotherapy; RT: Radiotherapy; pCR: Pathological Complete Response; pRR: Pathological Response Rates; RND: Residual Nodal Disease; N-PCR: Nodal Pathologic Complete Response; TMT: Trimodality Treatment; DMFS: Distant Metastasis-Free Survival; MST: The Median Survival Time; CR: Complete Resection; MPR: Major pathologic response

## Introduction

The treatment of stage IIIA non-small cell lung cancer (NSCLC) remains one of the major areas of controversy in thoracic oncology. Patients with stage IIIA disease represent a heterogeneous group due to various extents of their tumor (T), and lymph node (N) status as well as frequent co-morbidities, hence, different classification approaches in this setting have been adopted. One pragmatic approach is to classify stage IIIA disease by resectability and operability. The current standard of care for unresectable/inoperable stage IIIA patients is definitive

chemoradiation (CHRT) with a platinum doublet which is nowadays frequently followed by consolidation durvalumab [1].

In resectable stage IIIA NSCLC, however, there is still a considerable debate regarding the best strategy, including surgery with either adjuvant or neoadjuvant chemo- and/or radiotherapy (RT) or definitive concurrent CHRT and several other strategies. Neo-adjuvant therapy for operable NSCLC has been the subject of a large number of studies in the literature, and in spite of progress in this field, many issues remain unsolved.

Neoadjuvant therapy has several theoretical advantages as in vivo assessment of response to chemotherapy (CHT) or CHRT helping to identify patients who will potentially benefit due to, early treatment of micrometastatic disease, potential downstaging with increasing resectability and the possibility of identification of surrogate clinical and biological markers that may correlate with response to therapy and potential long-term outcome. Also, neoadjuvant treatments are aimed at improving the overall outcome decreasing the rate of local failures and distant metastases observed after surgery alone [2]. The present manuscript reviews past studies and it also highlights ongoing trials including neoadjuvant immunotherapy.

### Discussion

#### Neoadjuvant Chemotherapy Followed by Surgery

The role for neoadjuvant CHT before surgery remains controversial. Several trials [3-5] have shown improved survival but all of them were with small patient numbers. However, the study of Gilligan and colleagues showed only a trend favoring neoadjuvant CHT in the subset of patients with resectable stage III NSCLC, but without statistical significance on survival [6]. Meta-analysis Collaborative Group on neo-adjuvant CHT for NSCLC has collected individual participant data from 2,385 patients included in 15 controlled randomized trials. Most patients included were stage IB-III A. The results showed a 13% reduction in the relative risk of death, with an absolute survival improvement of 5% at 5 years, from 40% to 45%. Looking at the first events, local recurrence occurred in 24%, distant recurrence in 31% and both local and distant recurrence in 9%. In this meta-analysis, stage did not seem to alter the effect of CHT [7]. In addition, positive effect of CHT was also observed in another meta-analysis, looking specifically at 8 studies on stage III, where the improvement in OS with CHT was also statistically significant [8].

While systematic reviews and meta-analysis from randomized controlled trials have suggested that it improves survival [9-12], disadvantages of these investigations are different combinations of trials (patients, treatments), making the specific effects of preoperative CHT difficult to discern. However, in many trials, the pathological complete response (pCR) rate was low, and the local-regional recurrence rate was high. In three more recent randomized trials comparing neoadjuvant CHT followed by surgery to surgery alone in stage III NSCLC, the complete pCR in the induction arm was only between 6% and 10.5% [13,14]. As pCR is an indicator of response and a possible surrogate for survival, it seems logical to improve pCR by an additional locoregional treatment to surgery such as RT. For these different reasons, it appears that the addition of RT to CHT in neo-adjuvant strategies deserves additional consideration.

#### Neoadjuvant CHRT Followed by Surgery

A large number of retrospective studies on neo-adjuvant CHRT in patients with operable stage IIIA NSCLC have been published,

using mostly cisplatin doublets while RT schedules mainly included conventional fractionation schemes with a few hyperfractionated schemes, with doses between 43-60 Gy [15-22]. The pCR, when reported, varied 16%-27 % [15,17-20,22], except in one study where it was as high as 40% [21]. The median survival time (MST) ranged between 21 and 36 months, and the 5-year overall survival (OS) ranged 31%-40% [15-22]. Some studies showed association of higher pCR with an increased survival [15,16,21,22], however results from these retrospective studies are to be interpreted with caution due to patients' selection and other existing biases.

The study by the German Lung Cancer Cooperative Group assessed the additional effect of preoperative CHRT on tumour resection, pathological response rates (pRR), and survival in patients with stage IIIA-III B NSCLC [23]. In both groups' patients received three cycles of cisplatin and etoposide, followed by CHRT and then surgical resection (intervention group) or surgery, and then further RT (control group). Study showed no significant difference in either PFS or OS between treatment groups. However, preoperative CHRT in patients undergoing surgery significantly increased the proportion of those with complete resection (CR); and in those with CR, preoperative CHT increased the proportion of patients with mediastinal downstaging and histopathological response. Significant increase in oesophagitis and haematological toxicity was observed in the interventional group, whereas pneumonitis increased significantly in the control group and contributed substantially to RT-related mortality in that group. A caveat against pneumonectomy was stated since treatment-related mortality reached 14% in patients treated by pneumonectomy [23].

In another landmark trial, Albain *et al.* compared concurrent induction CHRT (cisplatin-etoposide, 45 Gy) followed by surgery versus definitive concurrent CHRT(61 Gy) in potentially resectable patients [24]. This trial (INT0139), showed that surgical resection following induction CHRT results in improved local control and PFS in appropriately selected patients with stage IIIA NSCLC. However, this did not translate into an OS benefit, possibly because of treatment-related morbidity in the surgical arm. On subset, post-hoc analysis, when comparing those who underwent a lobectomy only to definitive CHRT patients, there was an improvement in MST of 33.6 months vs. 21.7 months and 5-year OS of 36% vs. 18% ( $p = 0.002$ ) in the lobectomy and CHRT arms, respectively. The percentage of death after pneumonectomy was 7,9%, which, however, rose to 26% when neoadjuvant CHRT was followed by right pneumonectomy. Thus, appropriate (i.e. limited) surgical resection after induction treatment seems to be an option in a selection of stage IIIA NSCLC patients, lobectomy with systemic mediastinal lymph nodes dissection being preferred over pneumonectomy because the latter carries higher surgical risk after CHRT [24].

Some Japanese studies [25,26] have reported a high rate of downstaging in stage IIIA patients treated with induction CHRT including S-1 and cisplatin-followed by surgery. These series

also included pneumonectomies without increased mortality. Although the reported rates of 5-year OS are good (around 60%), it is likely that these results were positively biased by very strict case selection criteria. The favorable outcomes for patients undergoing neoadjuvant CHRT followed by non-pneumonectomy surgery is corroborated in Asian patients in Samsung Medical Center where patients who achieved pathologic downstaging of N2 disease following neoadjuvant CRT achieved improved outcomes irrespective of initial cN2 bulk/extent [27,28].

The Swiss phase III randomized (SAKK) trial enrolled 232 patients with stage IIIA/N2 NSCLC into two treatment groups: in CHRT group three cycles of neoadjuvant cisplatin and docetaxel, was followed by RT with 44 Gy in 22 fractions over 3 weeks. The control group received the same CHT alone, and all patients were scheduled to undergo surgery. Overall tumor RR was 61% vs. 44% ( $P=0.012$ ) in CHRT and CHT alone groups respectively with acceptable toxicity [29]. Nodal downstaging (to N1 or N0) was observed in 64% and 53%, respectively, and the pCR in 16% and 12%, respectively in the CHRT group and CHT only group ( $P=NS$ ). The median event-free survival was 12.8 months vs 11.6 months and MST were 37.1 months and 26.2 months in the CHRT and control group, respectively, but survivals at 2-4 years were identical in the 2 treatment arms. Thus, this study showed that patients who received CHRT before surgery had an objective response, a pCR, a R0 resection rate and a mediastinal downstaging more frequently and less local progression than patients in the CHT alone group. In spite of all of these, the addition of RT neither improved event-free survival nor OS. Authors concluded that one definitive local treatment modality combined with neoadjuvant CHT might have been sufficient [29].

To improve results some trials focused on head-to-head comparison of various treatment sequences. A Japanese phase III randomized trial for stage IIIA/N2 NSCLC compared induction concurrent CHRT with carboplatin and docetaxel followed by surgery to induction CHT followed by surgery [30]. The study had to be stopped because of slow accrual, after 60 patients were randomized. Combined CHRT conferred a better local control, however there was no differences in PFS or OS when RT was added to CHT. Treatments were well tolerated without any toxic deaths [30].

Two recent meta-analyses attempted to answer the question of superior neoadjuvant treatment, i.e. neoadjuvant CHT followed by surgery versus neoadjuvant CHRT followed by surgery [31,32]. Shah et al. [31] identified seven studies, of which there was only one fully published RCT, and one Phase II randomized trial. Neither of the studies showed a survival benefit for induction CHRT and results remained the same when analysis was confined to two RCTs (one Phase III and one Phase II). It must, however, clearly be said that the inclusion of retrospective papers, and data presented in abstract form only, clearly limited the quality of this meta-analysis. In their meta-analysis, Xu Y-P et al. [32] found that

induction CHRT before surgical resection significantly increased the rate of pCR in resected mediastinal lymph nodes compared with those who received induction CHT, but there was no significant difference in tumour downstaging, OS or PFS. A recent prospective RCT [29] from SAKK which was not included in either meta-analysis confirmed these findings.

Unfortunately, still we do not have any predictive or prognostic factors for selecting surgery in the treatment of patients with stage IIIA/pN2 NSCLC. Jeremic et al did not identify any study investigating treatment-related predictive factors for the potential superiority of surgical outcomes in patients with Stage IIIA (mostly pN2) NSCLC. These authors concluded that currently it was impossible to identify any treatment-related predictive or prognostic factors for selecting surgery in patients with stage IIIA/pN2 NSCLC [33].

Patients with residual nodal disease (RND)—particularly positive mediastinal adenopathy—typically fare much worse. Important question whether pathologic response should guide the decision to proceed with surgical resection. Ziel et al. investigated nodal pathologic complete response (N-PCR) as a strong predictor of OS. They compared the outcomes of patients treated with trimodality treatment (TMT) versus CHRT, focusing on the importance of N-PCR. Actuarial OS, PFS, and distant metastasis-free survival (DMFS) were compared between patients treated with CHRT and TMT and between CHRT and N-PCR/RND. On multivariable analyses, N-PCR had superior OS (hazard ratio [HR], 0.38;  $p = 0.0012$ ), PFS (HR, 0.42;  $p = 0.0005$ ), and DMFS (HR, 0.42;  $p = 0.0007$ ) compared with CHRT. Conversely, there were trends for worse OS and PFS for RND versus CHRT, although only inferior DMFS was significant (HR, 1.83;  $p = 0.04$ ). Study showed that surgical patients with N-PCR experienced superior survival, but those with RND fared no better than CHRT alone. Authors concluded that mediastinal response might play an important role in the decision to proceed with surgical resection after CHRT for stage III NSCLC [34].

In conclusion, neoadjuvant CHRT is safe and efficient, with higher overall clinical response, pCR rates and a higher mediastinal clearing compared to neoadjuvant CHT alone. On the other hand, the yet available randomized studies have failed to demonstrate any advantage of adding RT in the neoadjuvant setting regarding PFS or OS. Admittedly the number of patients enrolled was modest.

### Neoadjuvant CHT followed by CRT vs Surgery

Van Meerbeeck et al performed a large multicenter prospective randomized trial in patients with stage IIIA-N2 NSCLC who showed a response to three cycles of platinum-based induction CHT. Responding patients were subsequently randomly assigned to surgical resection or RT. This large randomized multicenter study demonstrated that surgery did not improve survival after a radiologic response to induction CHT in patients with unresectable

stage IIIA-N2 NSCLC as compared with RT [35]. These results were important because several centers continued to routinely use induction CHT followed by surgery to treat patients with this stage of disease based on small, randomized studies that showed that surgery alone is inferior to perioperative chemotherapy and surgery in stage IIIA patients [36-38].

ESPAVUE study randomized patients after 3 cycles of induction cisplatin- paclitaxel and concurrent CHRT with a cisplatin and vinorelbine with 45 Gy in 1.5Gy fractions BID followed by definitive RT boost dose of 20 – 26Gy in 2Gy fractions or surgical resection [14]. There was no difference in 5-year OS (40% vs. 44%,  $p = 0.34$ ) or PFS (35% or 32,  $p = 0.75$ ) between the CHRT and surgical arms, respectively [39]. Results of these studies were the subject of four meta-analyses/systematic reviews [31,40-42] which were summarized by Jeremic et al. [43] who clearly showed that there is no place for surgery in a multimodality treatment in these patients. The most recent meta-analysis of Pottgen et al. also analyzed randomized trials comparing surgery with definitive RT as local curative treatment options within the framework of different multimodality treatments for patients with locally advanced (LA-NSCLC). Endpoints for comparison of treatment results were OS, PFS, and toxicity. This meta-analysis also did not find significantly different OS in patients with LA-NSCLC after induction treatment and surgery compared with those receiving definitive CHRT. Trials using concurrent CHRT in the neoadjuvant phase of the resection arm and simultaneous CHRT in the other arm showed a better OS than the other trials using induction CHT alone before surgery in the surgical arm and sequential CHT and RT or RT alone in the other [44].

Additional evidence came from the recent study which analyzed NCDB data from 1,076 patients with stage IIIA (N2) NSCLC, treated between 2003 to 2005, either with neo-adjuvant CHRT followed by surgery or neoadjuvant CHT followed by surgery. The 5-year OS for the entire cohort was 39%, namely 39.2% for the neo-adjuvant CHRT category vs. 38.6% for the neo-adjuvant CHT ( $P = NS$ ). On multivariate analysis, neo-adjuvant CHRT was associated with an improved pathological outcome [45].

### Neoadjuvant immunotherapy Followed by Surgery

Currently, a number of trials are studying neoadjuvant immunotherapy, mainly in stages IB-III A. One of the first studies (NADIM trial) testing combination CHT and immunotherapy as induction therapy in stage IIIA patients with histologic N2 confirmation enrolled 46 patients who received 3 cycles of paclitaxel/carboplatin plus nivolumab before surgical resection, followed by adjuvant nivolumab monotherapy for 1 year. Major pathologic response (MPR) was achieved in 82.9% of patients, 63.4% of whom had pCR. Down-staging was achieved in 90.2% and OS at 20 months was 90% [46]. In a randomized phase II study (NEOSTAR trial) of induction checkpoint blockade

for patients with untreated stage I-III A (single N2) NSCLC, patients received three doses of nivolumab (3 mg/kg) or nivolumab (3 mg/kg) plus ipilimumab (1 mg/kg) every 2 weeks followed by surgery. 39 of 44 patients underwent surgery (89% resectability). Major pathologic response (MPR) rate was 24% overall; 17% with nivolumab and 33% with the combination therapy [47].

The results of several studies of CHT and immunotherapy with surgery are awaited. NCT 02716038 study of neoadjuvant four cycles of atezolizumab plus carboplatin and nab-paclitaxel reported an MPR of 64% in 11 patients who underwent resection [48]. KEYNOTE-671 trial (NCT 03425643) investigates efficacy and safety of Pembrolizumab with platinum doublet as neoadjuvant/adjuvant therapy for patients with resectable stage IIB/III A NSCLC [49]. CheckMate-816 (NCT 02998528), a phase III open-label study, compares EFS and pCR rates among participants treated with neoadjuvant nivolumab plus platinum doublet CHT versus platinum doublet CHT alone in stage IB-III A NSCLC [50]. IMPower-030 (NCT03456063) trial with the surrogate objective MPR as its primary endpoint, randomized patients between four cycles of platinum doublet CHT with atezolizumab or placebo, followed by surgery and postoperative standard of care in stage II-III A/IIIB (T3N2) disease [51]. 77T trial (NCT04025879) is comparing neoadjuvant chemoimmunotherapy with nivolumab to neoadjuvant CHT plus placebo, followed by surgical removal and adjuvant treatment with nivolumab or placebo including patients with suspected or histologically confirmed, resectable stage IIA-III B NSCLC. The primary endpoint is EFS as assessed by blinded independent central review [52]. A randomized, two-arm, phase II, multi-center study (NADIM-II trial) compares neoadjuvant chemoimmunotherapy to neoadjuvant CHT alone. Patients in the experimental arm, receive nivolumab plus paclitaxel plus carboplatin for 3 cycles as neoadjuvant treatment followed by surgery and 6 months of adjuvant treatment with nivolumab. The primary objective is pCR [53]. Many of these studies include very different populations, which makes it difficult to draw firm conclusions for diverse stages or presentations. Homogeneous populations should be studied in very limited scenarios designed to answer a specific question. In addition, no molecular markers predicting increased survival and/or response in the immunotherapy setting have been reported to date. Longer follow up evaluating PFS and OS are urgently needed.

### Conclusion

Still the controversy is not being solved and further trials considering a better patients' selection, innovative RT and more efficient systemic treatments need to be undertaken. Selection of patients for a surgical resection is challenging, due to both patient (comorbidity, refusal) and tumor (no downsizing or downstaging) related factors. It seems that studies with chemoimmunotherapy provide a higher rate of pathologic responses and downstaging



than previous studies conducted solely with CHT. On the other hand, it remains to be confirmed whether pCR is a sufficient surrogate for OS. Hopefully, the next two decades will bring much needed improvements for our patients.

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## Conflict of Interest

The Authors Declare no Competing Interests Regarding this Study.

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