



Stage III N2 non-small cell lung cancer treatment: decision-making among surgeons and radiation oncologists

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Background: Stage III N2 non-small cell lung cancer (NSCLC) is a very heterogeneous disease associated with a poor prognosis. A number of therapeutic options are available for patients with Stage III N2 NSCLC, including surgery [with neoadjuvant or adjuvant chemotherapy (CTx)/neoadjuvant chemoradiotherapy (CRT)] or CRT potentially followed by adjuvant immunotherapy. We have no clear evidence demonstrating a significant survival benefit for either of these approaches, the selection between treatments is not always straightforward and can come down to physician and patient preference. The very heterogeneous definition of resectability of N2 disease makes the decision-making process even more complex.

Methods: We evaluated the treatment strategies for preoperatively diagnosed stage III cN2 NSCLC among Swiss thoracic surgeons and radiation oncologists. Treatment strategies were converted into decision trees and analysed for consensus and discrepancies. We analysed factors relevant to decision-making within these recommendations.

Results: For resectable “non-bulky” mediastinal lymph node involvement, there was a trend towards surgery. Numerous participants recommend a surgical approach outside existing guidelines as long as

the disease was resectable, even in multilevel N2. With increasing extent of mediastinal nodal disease, multimodal treatment based on radiotherapy was more common.

Conclusions: Both, surgery- or radiotherapy-based treatment regimens are feasible options in the management of Stage III N2 NSCLC. The different opinions reflected in the results of this manuscript reinforce the importance of a multidisciplinary setting and the importance of shared decision-making with the patient.

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

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Introduction

Stage III non-small cell lung cancer (NSCLC) with subcarinal and/or ipsilateral mediastinal lymphatic spread (N2, TNM UICC 8th edition) may be treated with curative intent. However, treatment outcome remains poor with 15–50% 5-year overall survival (OS) rates (1-4). The optimal treatment for potentially resectable N2 NSCLC patients is unclear due to the heterogeneity of the disease, a lack of a universal definition of resectability, and comparable outcomes with different treatment approaches. There is a variety of factors influencing the availability and suitability of various treatments (5) and a large number of clinical decision criteria used in daily decision-making (6). The two main multimodal treatment options for NSCLC N2 disease are surgery (with neoadjuvant chemotherapy (CTx)/chemoradiotherapy (CRT) or combined with adjuvant CTx) or CRT [with or without adjuvant immunotherapy (7)].

Both treatment options may be available for several decision criteria combinations, especially since there is no randomised evidence suggesting a clear survival benefit with one approach over another (4,8,9). This is reflected in international guidelines where radiotherapy and surgery are both options for selected stage III N2 NSCLC, especially in cases with limited lymph node involvement (10,11). In such a setting, patient preference becomes even more relevant and the focus may shift away from OS towards side effects, quality of life and logistical issues (e.g., hospital stay for surgery or receiving daily outpatient treatments for several weeks with radiotherapy).

In daily clinical routine, there are scenarios where multiple treatment options are available. It is important to recognize these situations for an optimal shared decision-making approach. The aim of this work was to identify

which disease characteristics are applied in current clinical practice among Swiss thoracic oncology centres for stage III N2 NSCLC and how they impact decision-making in clinical routine.

Methods

All Swiss centres providing both departments for thoracic surgery and radiation oncology with an established training program were asked to participate in this study. The initial search for qualifying centres was performed in October 2018 according to the list of the Swiss Institute for Medical Education (SIWF). Twelve centres were identified. The head of each radiation oncology and thoracic surgery department was asked to describe her or his practice in preoperatively diagnosed stage III N2 NSCLC. In some instances, a senior physician specialized in lung cancer represented the department. The collected answers from 11 surgeons and 12 radiation oncologists were anonymously analysed, one expert declined to participate. All university hospitals as well as most Swiss cantonal hospitals were represented.

All participating centres were asked to provide their recommendations and decision criteria for the management of preoperatively diagnosed stage III N2 NSCLC. The recommendations were reduced to the options of: a definitive surgical approach (with neoadjuvant or adjuvant CTx/CRT), definitive CRT approach or “patient preference” (no specific recommendation for either RT or surgery; both being options). Decision criteria collected were converted into decision trees, analysed and standardized if their meaning was not changed as described previously (12-14). For better comparison, universal criteria

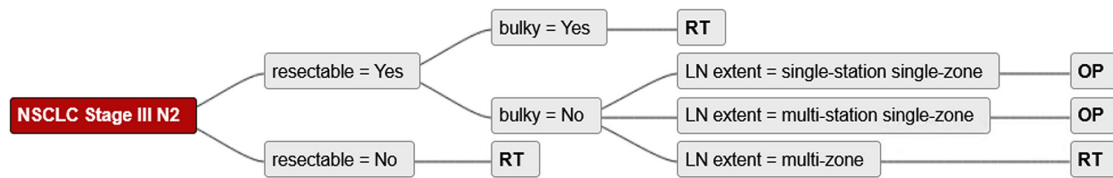


Figure 1 Example of the simplified decision tree. LN, lymph nodes; OP, surgery; RT, radiotherapy.

such as “ability to give informed consent” were not included in this analysis. In several instances, trial participation was a recommended option. This was excluded from the decision tree analysis, as trials are considered experimental and potentially not applicable to the routine clinical setting.

The resulting decision criteria included: resectability (potentially resectable or not), lymph node (LN) volume (bulky, non-bulky), and LN extent (single station, multi station and single zone, multi-zone). For the purpose of this analysis, “resectability” included the possibility of surgical tumour removal with an R0 margin based on preoperative imaging, as well as the required physical fitness for radical operative treatment.

The extent of mediastinal lymph node involvement was categorized as: (I) single station and therefore single zone; (II) multi-station but limited to single zone; and (III) multi-zone. This was in-line with the descriptions received from individual participants and was based on a previous analysis of international guidelines (11). In the British Thoracic Society (BTS) (15) and Irish guidelines (16) lymph nodes are grouped by zones according to the IASLC lymph node map (AJCC 7th edition), whereas most others, e.g., ESMO (10,17) or German (18) guidelines used nodal stations.

The descriptions used to characterise mediastinal lymph nodes varies among guidelines (11). Non-bulky lymph nodes are mostly described as lymph nodes with a diameter of less than 3 cm short-axis diameter, easily measurable and free of major mediastinal structures including the trachea and great vessels, or low volume lymph nodes (15,19-22). Many experts described bulkiness or size of lymph nodes, while no specific cut-off in cm was defined, these criteria were simplified and represented as “bulky *vs.* non-bulky”.

As the treatment of stage III N2 NSCLC is multimodal (11,23-26), the reduction to radiotherapy or surgery-based treatments represents a significant simplification. For multimodal treatment based on a surgical approach, no distinction was made between neoadjuvant and adjuvant

chemotherapy (19,20).

Statistical analysis

The resulting decision trees were analysed for consensus and discrepancies with the objective consensus methodology (12,27,28). Majorities were calculated by dividing the most common recommendation for any specific situation by the number of participants.

Results

Twenty-three management strategies with recommendations for all unified decision criteria were identified and converted into decision trees. An example of a single decision tree is shown in *Figure 1*.

The three major decision criteria that affected treatment decisions were resectability, bulkiness of lymph nodes and lymph node extent. The three simplified treatment options included surgery, radiotherapy, and patient preference.

For non-resectable cases, radiotherapy-based treatments were recommended by all experts.

For patients with non-bulky lymph nodes a majority recommended surgery. In case of single-station non-bulky disease, 91% of experts recommended surgery as the single most common recommendation. In case of multi-station, but single-zone disease, still 83% recommended surgery as the single most common recommendation. For multi-zone non-bulky disease, a slight majority (65%) for surgery was identified with 7 experts (30%) stating radiotherapy and one (4%) stating patient preference as their recommendation (*Figure 2*).

In bulky disease, the majority (74–83%, dependant on LN extent) recommended radiotherapy; however, for example in single-station disease, five experts (22%) recommended surgery and one (4%) recommended patient preference. In cases where surgery was recommended for bulky disease comment was added by the experts that a neoadjuvant approach (with chemotherapy or radio-chemotherapy) was

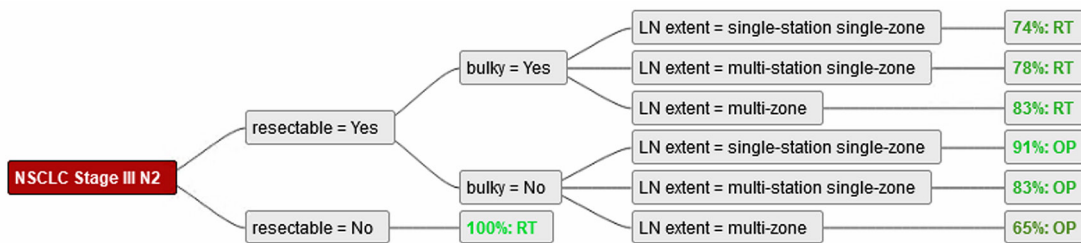


Figure 2 demonstrates the overall majority recommendations for each parameter combination. LN, lymph nodes; OP, surgery; RT, radiotherapy.

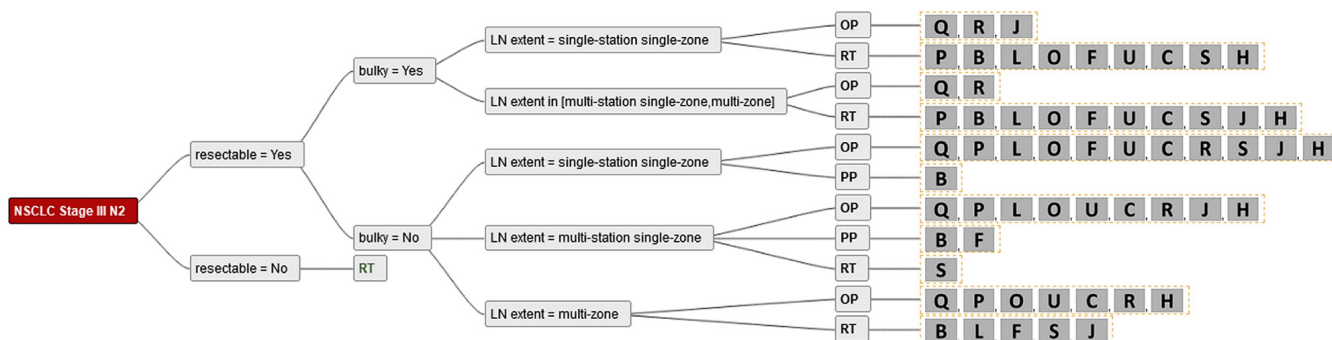


Figure 3 Demonstrates the answers from the radiation oncologists for all combinations of simplified criteria. Single alphabetic letters: participating sites. LN, lymph nodes; OP, surgery; PP, patient’s preference; RT, radiotherapy.

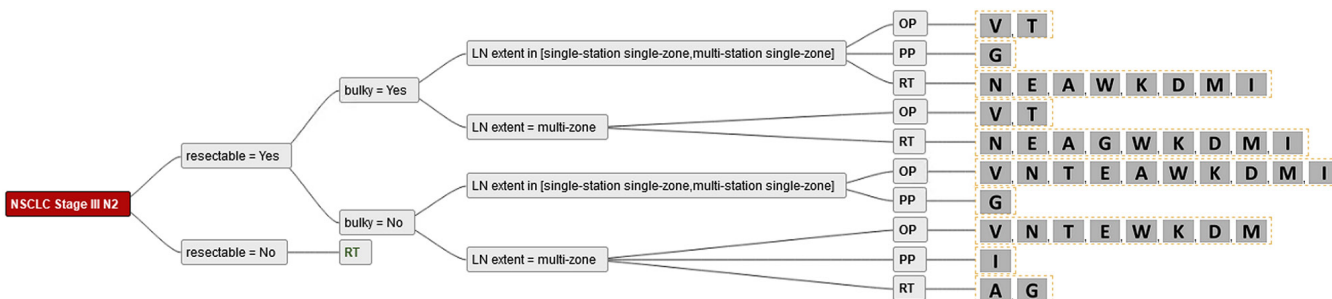


Figure 4 Demonstrates the answers from surgeons for all combinations of simplified criteria. Single alphabetic letters: participating sites. LN, lymph nodes; OP, surgery; PP, patient’s preference; RT, radiotherapy.

recommended and that the surgery would be performed only if a good response was observed (Figures 2-4).

Patient preference as a recommendation only occurred in 4 settings, this included 2 radiation oncologists and two surgeons in various situations (Figures 3,4). A trend towards radiotherapy among radiation oncologists and surgery among thoracic surgeons was observed (Figures 2,3). Seventy-three percent of participating surgeons would recommend a surgical approach and 18% would recommend

CRT in resectable, non-bulky, multizone stage III N2 NSCLC, whereas 42% of radiation oncologists would recommend CRT for the same condition and surgery in 58%.

Discussion

Our decision-making analysis revealed surgery-based approaches as the most commonly recommended treatments for resectable stage III N2 NSCLC, with a

significant proportion of recommendations considering radiotherapy as an alternative. Overall, there was a stronger preference for surgical approaches the smaller the lymph-node extent was (Figure 4). For non-resectable disease, there was a consensus for radiotherapy as well as a clear majority for radiotherapy in bulky disease.

Resectability is a prerequisite for surgery in stage III N2 NSCLC. Preoperative surgical evaluation can be challenging and dependent on the individual surgeon's expertise. Universally agreed-upon criteria to guarantee the resectability of disease are lacking. Additionally preoperative and postoperative findings may diverge (29). The difficulty in standardization lies in the surgeon's individual judgement on being able to achieve a clear resection margin, the assessment of which may be particularly challenging in more centrally located tumours. The definition of an unresectable tumour in this analysis was left to the decision of multidisciplinary tumour boards and was highly variable among institutions.

Overall, with increasing volume or extent of N2 disease, there was an increasing trend towards therapy based on RT. There was no consensus on a unified cut off for nodal volume related to surgery. In patients with low volume (especially single station) mediastinal N2 disease surgery was the preferred recommendation. Some guidelines recommend surgery for N2 disease without additional risk factors (such as bulky disease or multi-station disease, e.g., ESMO) or mention both radiotherapy- or surgery-based options (e.g., NCCN) (10,30). In our analysis, 91% of participating sites recommended a multimodal treatment based on surgery for single station (single-zone) non-bulky stage III N2 NSCLC, in two cases (9%) patients' preference was stated (offering CRT as an equivalent option in this setting). The recommendation rate for surgery-based approaches decreased with increasing mediastinal lymph node involvement, nevertheless 83% of participating surgeons as well as 75% radiation oncologists still recommended surgery as an option for multi-station, but single zone stage III N2 NSCLC. With multi-zone involvement, a slight preference for surgery could be shown (65%) even though this is not in-line with most guidelines (11). In this setting, a discrepancy between specialties was visible with 42% of radiation oncologists recommending radiotherapy, while only 18% of surgeons would not recommend surgery in NSCLC with multi-zone non-bulky LN involvement. A minor limitation of our simplification is that the primary multi-station nodal involvement described in a guideline using nodal stations as a descriptor could fall within a single zone or multiple zones (e.g., stations 2 & 4 would be a single zone, stations 4 & 7

would be multi-zone)

A lack of a clear definition of bulky lymph nodes leads to potential bias. Some consider 3 cm as the critical diameter for bulky definition (11), some authors consider bulky N2 disease as lymph nodes already greater than 2.5 cm in short axis (31). The preference of radiotherapy-based approaches increases when mediastinal lymph nodes present as bulky. For all settings with bulky lymph nodes, radiotherapy-based approaches were the most recommended treatment. The rate for recommending radiotherapy-based approaches in bulky disease increased from 74% for single-station to 78% for multi-station single zone and to 83% for multi-zone bulky lymph node involvement. This trend is clearly in line with guidelines advising against surgery in the presence of bulky lymph nodes. The individual experts recommending surgical approaches in this setting also recommended neoadjuvant chemotherapy or radiotherapy with the aim of downstaging and considered a good response as well as an expectation of an R0 resection to be prerequisites for surgery. However, with a neoadjuvant treatment approach the risk of mediastinal soft tissue fibrosis may increase and may complicate subsequent hilar and mediastinal dissections (31,32).

A meta-analysis including randomized studies comparing definitive radiochemotherapy versus surgery in stage III NSCLC (4) found no significant difference between bimodal treatments (surgery *vs.* radiotherapy based) related to overall survival. There was heterogeneity across studies at two years, resulting from the rate of pneumonectomies performed. The increased mortality following pneumonectomies however was not confirmed in other trials (3,33,34). Another previous meta-analysis by McElnay *et al.* (9) compared CRT and surgery versus definitive CRT. It combined data from the Intergroup 0139 trial (2) and a study from Sorensen *et al.* (35) comparing induction CTx followed by RT versus induction CTx followed by surgery followed by RT. Both studies were weighted equally in the analysis. The pooled HR for death in the surgery group was 0.87 (95% CI: 0.75 to 1.01; P=0.068) with no statistical evidence of heterogeneity (P=0.976). Trimodal therapy was associated with a trend towards improved survival compared to bimodal treatments. However, comparisons between surgery and RT are complicated by early perioperative mortality of surgical patients with potential advantages in survival later on (36).

The 2019 NICE guidelines cover the management of NSCLC. For potentially resectable stage III N2 NSCLC the guideline specifically recommended trimodality treatment for patients fit enough for multi-modality treatment (induction CRT followed by surgery) (37). This is a highly

significant change from previous NICE recommendations and a significant change in UK practice where only 1.1% of N2 patients currently receive trimodality treatment (38). The meta-analysis of the NICE guideline group compared CRT followed by surgery (CRS), CRT, and chemotherapy and surgery (CS). A statistically clear survival benefit could not demonstrate between treatment regimens, but there was a trend towards improved survival with CRS (in line with the trends from other meta-analyses). The PFS at 4 & 5 years (high quality evidence) was improved in the CRS group with an average of 4.5 month compared to CRT/CS. There was less grade 3+ adverse events with CRS than with CR/CS. The guideline also undertook cost-effectiveness modelling concluding that CRT is more cost effective than CS [Incremental cost-effectiveness ratio (ICER) £53,000/quality-adjusted life year (QALY)] and CRS is more cost effective than CRT (ICER £17,800/QALY). Even though the guideline recommended trimodality treatment, such practice would require careful and considered implementation within agreed protocols through high volume centres where outcomes are monitored closely. In our analysis only 2 of 23 experts recommended trimodality treatment in their clinical routine.

Overall, the evidence in this setting has several severe limitations. A number of key trials (Intergroup/EORTC) date from a time before routine ^{18}F FDG-PET/CT, endoscopic nodal staging and advances in surgical and RT techniques are not accounted for. Some trials, such as the ESPATUE trial (3) had a heterogeneous study population (e.g., 1/3 of patients with T4 N0/1) further hampering definitive conclusions on the management of N2 disease.

Over the past years, immunotherapy has changed the landscape for patients with stage III NSCLC. Also, in the management of stage III N2 NSCLC this approach is part of ongoing trials (NCT04202809, NCT04287894 and NCT04245514). The implementation of immunotherapy in international treatment guidelines is progressing, however has not directly affected the decision between surgical and RT-based approaches yet. In unresectable stage III N2 NSCLC treated with CRT, a significantly longer progression free survival (PFS) and OS was reached with the addition of maintenance durvalumab and this has become a recommended strategy in guidelines (7,39).

There are also considerations of using immunotherapy in the neoadjuvant setting. A study by Bott *et al.* (40) demonstrated a major pathological response in 45% of patients treated with nivolumab upfront of surgery, this trial enrolled NSCLC stage I–IIIA. However, more than

a half of the minimally invasive-intended operations were converted to thoracotomy due to hilar inflammation and fibrosis. While there was no operative mortality, perioperative morbidity was present and mostly due to atrial arrhythmia. Similar results were published by Forde *et al.*, with major pathological response rates on histologic examination of around 45%. Interestingly only two patients had a radiologic partial response (41). It was due to postulated immune-cell infiltration into the tumour, rather than true tumour mass. The phase II trial by Sacha Rothschild *et al.* (42) also demonstrated a high response rate and a very encouraging 1-year event-free survival by addition of perioperative durvalumab to standard of care cisplatin/docetaxel. To define the role of neoadjuvant immunotherapy long-term follow-up of currently recruiting phase 3 studies such as NCT02998528 need to be evaluated. The evolution of future treatment strategies involving immunotherapy need further prospective studies to answer the question whether CRT with Immunotherapy is superior to multimodal treatment based on surgery in potentially resectable stage III N2 NSCLC.

As shared decision-making is a complex process with various potential pitfalls (43), patient preference will become increasingly helpful if more than one treatment regimen can be offered with comparable outcome (5,44,45). Patient preference was a primary recommendation in selected settings, mentioned only by a limited number of experts (these represented both specialities). Patient preference may be challenging in clinical practice as a multitude of emotions and biases influence shared decision-making (43,46). This process is even further complicated by the limited availability of patient-relevant information—such as detailed information from side effects from clinical trials in this setting (47). Potentially a third party acting as an intermediary between the specialists may be of value in providing an un-biased view (e.g., pneumologist or general practitioner).

The results of this analysis are based on the input of specific individual experts in Switzerland, yet it is improbable that the trends observed would be significantly different if other experts from Switzerland would have been selected. A specialty bias was visible with trends towards surgery among surgeons and radiotherapy among radiation oncologists, this only reinforces the need for such analyses to be performed in a multidisciplinary setting.

Conclusions

Our analysis showed that in patients with low mediastinal lymph node involvement and resectable tumours a multimodal approach based on surgical resection is the preferred treatment practice in Switzerland, whereas with increasing mediastinal lymph node involvement, multimodal therapy based on radiation is being considered more frequently. Compared to recommended treatment pathways within international guidelines, surgery-based treatment for stage III N2 NSCLC in Switzerland is offered more extensively. Definitive evidence for the optimal treatment of resectable stage III N2 NSCLC remains elusive. The variability of recommendations among the participating sites may have multiple potential reasons. These may include local traditions (e.g., through the participation in the Swiss SAKK 16/00 trial investigation neoadjuvant radiochemotherapy in Stage IIIA N2 NSCLC), local technical equipment (ECMO), level of individual surgical or radiotherapy experience, incomplete definition of decision criteria (e.g., only broadly specified lymph node involvement, lacking definition of resectability) as well as different guideline used for development of local recommendation of the interdisciplinary tumour board.

The different opinions reflected in the results of this manuscript reinforce the importance of a multidisciplinary setting and the importance of shared decision-making with the patient.

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Footnote

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