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Advances in the use of surgery and multimodality treatment for N2 non-small cell lung cancer

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Abstract

Introduction: stage IIIA-N2 non-small cell lung cancer (NSCLC) represents a heterogeneous group of bronchogenic carcinomas with locoregional involvement. Different categories of N2 disease exist, ranging from unexpectedly encountered N2 involvement after detailed preoperative staging or "surprise" N2, to potentially resectable disease treated within a combined modality setting, and finally, bulky N2 involvement treated by chemoradiation.

Areas covered: Large randomised controlled trials and meta-analyses on stage IIIA-N2 NSCLC have been published but their implications for treatment remain a matter of debate. No definite recommendations can be provided as diagnostic and therapeutic algorithms vary according to local, national or international guidelines.

Expert commentary: From the literature, it is clear that patients with stage IIIA-N2 NSCLC should be treated by combined modality therapy including chemotherapy, radiotherapy and surgery. The relative contribution of each modality has not been firmly established. For patients undergoing induction therapy, adequate restaging is important as only down-staged patients will clearly benefit from surgical resection. Each patient should be discussed within a multidisciplinary team to determine the best diagnostic and therapeutic approach according to the specific local expertise. In the near future, it might be expected that targeted therapies and immunotherapy will be incorporated as possible therapeutic options.

Keywords: Lung cancer, stage IIIA-N2, treatment, prognosis, chemotherapy, radiotherapy, surgery, multimodality therapy, induction therapy

1. Introduction

Management of stage IIIA-N2 remains one of the most controversial topics in the treatment of non-small cell lung cancer (NSCLC). The main reason is that this specific category represents a grey zone between early-stage lung cancer which is technically resectable with good long-term results, and advanced stages which rarely qualify for surgical interventions (1). Highly controversial management issues in stage IIIA-N2 are summarised in table 1.

In this review of the literature, the different subsets of stage IIIA-N2 are discussed as well as the various staging and restaging methods currently available, the role of induction therapy, the relative contribution of surgery and radiotherapy in combined modality therapy, and finally, the relatively new concept of salvage surgery for locally recurrent or progressive disease. This review does not intent to review the full literature available on this topic and will focus on evidence published recently in the literature.

2. Different subsets of stage IIIA-N2

In the new, 8th edition of the TNM classification applicable from January 2017 onwards , some changes were incorporated in stage IIIA disease which currently comprises T3N1M0, T1-2N2M0 and T4N0-1M0 lung cancers (2). A comparison between the 7^{th} and 8^{th} edition is provided in table 2. The N2 category is not a homogeneous group and includes three major categories with an increasing disease burden (3, 4) as described below.

The first category includes N2 disease, which is incidentally discovered during lung resection or postoperatively when the final pathological report becomes available, so-called “surprise” N2 involvement (5). Adjuvant chemotherapy is administered in patients with a good performance status (1, 6). The role of adjuvant radiotherapy in this setting remains controversial and is mainly applied in cases

of incomplete resections. In the currently ongoing LungART trial patients (NCT00410683) who underwent complete resection of N2 disease are randomised between adjuvant radiotherapy or not (7).

The second category includes limited N2 involvement that may be detected during work-up of a presumed NSCLC by a minimally invasive or invasive technique. After discussion with a thoracic surgeon in a multidisciplinary team (MDT) this subset may be considered as being "potentially resectable". However, no uniform definition is available for "resectable N2" and this depends on the local treatment algorithms and specific expertise. Generally, factors to be considered are the presence of intranodal or extranodal disease, single-station versus multi-station involvement, and whether N2 disease is limited to one nodal zone or not. This category of N2 patients should be treated by combined modality treatment and most controversies arise from this category (table 1).

The third category comprises patients with large (> 2cm), fixed, bulky lymph nodes on chest computed tomography (CT), which may also be visible on a standard chest radiograph. Due to extensive involvement of the mediastinum often associated with extracapsular extension, complete surgical resection is not feasible in most cases. Standard therapy in this category consists of concurrent chemoradiation as indicated in the European Society of Medical Oncology (ESMO) consensus statement recommending a non-surgical multimodality treatment for extensive mediastinal N2 infiltration (1).

3. Mediastinal staging in lung cancer

In patients with proven or suspected lung cancer mediastinal staging is of utmost importance. In patients who have no distant metastases, prognosis will be determined by lymph node involvement. Specific recommendations on mediastinal staging were updated by a working group of the European Society of Thoracic Surgeons (ESTS) and published in 2014 (8).

When a suspicious lung lesion is detected on chest radiograph or CT scanning, initial staging is mostly performed by integrated positron emission tomography (PET) – CT scanning. This provides information

on the primary tumour and its extension, possible lymph node involvement and presence of distant metastases. After ruling out distant metastases, specific attention should be paid to the staging of nodes within the hilum and mediastinum. Only in case of a peripherally located tumour < 3 cm with lymph nodes <1 cm on chest CT scan and without isotope uptake on PET scanning, further mediastinal staging may be omitted. When suspicious lymph nodes are present or in case of central extension of the primary tumour, minimally invasive staging techniques represent the next step to obtain a pathological proof of lymph node involvement (8). Most complete, minimally invasive hilar and mediastinal evaluation is obtained by combined endobronchial ultrasound (EBUS) and endoscopic ultrasound (EUS) providing access to most lymph nodes in the hilum and mediastinum with exception of the pre-aortic stations 5 and 6 which are located in front of the large vessels.

In case of negative or equivocal results with minimally invasive staging techniques, further invasive staging is recommended, mostly by cervical or anterior mediastinoscopy, or in selected cases by video-assisted thoracic surgery (VATS), the latter providing the opportunity to explore the ipsilateral pleural space at the same time (8-10). It should also be recognized that invasive techniques provide the largest tissue samples to the pathologists allowing detailed molecular analysis. The flow chart of initial mediastinal staging used at the Antwerp University Hospital is depicted in fig. 1 (11). When the results of the pathological examination become available each patient should be discussed within a multidisciplinary thoracic oncology team consisting of pulmonary physicians, medical oncologists, radiologists, nuclear medicine physicians, pathologists, radiation oncologists and thoracic surgeons. The management of each patient will be established individually based on best available evidence, guidelines and local expertise (1).

4. Induction therapy for stage IIIA-N2 NSCLC

In case of proven mediastinal involvement single-modality therapy is generally associated with limited chance of long-term survival and most patients will die of distant metastatic disease. For this reason induction or neoadjuvant therapy consisting of cisplatin-based chemotherapy alone or combined chemoradiation, has been extensively evaluated. The main aim of such induction treatment is to obtain a pathological downstaging and convert locally advanced disease into a lower stage amenable to a local modality therapy such as surgery or radiotherapy (6). Initial studies showed that in case of persisting N2 disease after induction therapy, prognosis remains poor, and these patients generally do not qualify for further surgical resection. In a series of 157 patients with locally advanced NSCLC treated with neoadjuvant chemoradiation and resection, pathological complete response was identified as the most important prognostic factor (12).

Whether combined chemoradiation provides a better clearance of mediastinal nodes compared to chemotherapy alone, remains controversial. This question was addressed in a recently published phase III randomized trial (NCT000771) performed by the Swiss Cancer League (SAKK) (13). In total, 232 patients with pathologically proven stage IIIA-N2 were enrolled from 23 centres. Patients were randomized between 3 cycles of induction chemotherapy with cisplatin and docetaxel, and chemo-radiotherapy consisting of the same induction chemotherapy followed by 44 Gy of radiotherapy delivered in a sequential fashion. Primary endpoint was event-free survival which was not different between both groups. Median overall survival was 37.1 months in the radiotherapy group versus 26.2 months in the control group which proved not to be significant. The authors concluded that radiotherapy did not provide any benefit to induction chemotherapy followed by surgery. However, this study was not adequately powered to detect non-inferiority between the two induction regimens. Furthermore, sequential chemo-radiotherapy was applied which increases the overall induction treatment time prior to surgery and could be detrimental. Most clinical trials that have investigated induction chemo-radiotherapy have delivered the treatment concurrently, which is the current standard in unresectable

locally advanced NSCLC (14-16). Therefore, at the present time no definite answer is available regarding the most effective induction therapy. It should be outlined that induction treatment and the intent to deliver surgery should be decided upfront, in collaboration between an experienced thoracic surgeon and the oncological team.

5. Restaging after induction therapy

As downstaging after induction therapy is known to be a major prognostic factor, restaging is important to determine subsequent treatment. For this reason, only patients down-staged to N0 or N1 disease are considered for definitive surgical treatment in most centres. In a series of 111 patients who had lobectomy for stage IIIA-N2 disease after chemotherapy with or without radiotherapy, pathological mediastinal restaging was associated with improved survival (17). Different restaging techniques are available but none of them has the same accuracy as for primary staging. PET- CT after induction treatment is of rather low accuracy due to a high rate of false-positive and false-negative results (18, 19) Minimally invasive techniques may provide cytological or even histological proof of persisting nodal involvement but the false-negative rate is as high as 20 to 30 % (20, 21).

Repeat mediastinoscopy is generally used in patients with known involved lymph node stations before induction treatment as it will provide the large samples for pathological analysis. However, previous staging procedures followed by induction treatment will cause variable degrees of mediastinal fibrosis rendering remediastinoscopy technically more challenging and with a lower accuracy compared to the first mediastinoscopy. In a combined series of 104 repeat mediastinoscopies sensitivity was 71%, specificity 100% and accuracy 84% (22). In selected cases VATS can also be used for restaging but is limited to one hemithorax and its accuracy is not higher than remediastinoscopy (23).

The highest accuracy in restaging is obtained when initially, a cytological proof of N2 disease is obtained by a minimally invasive technique. Mediastinoscopy is then performed after the induction therapy with a reported accuracy of 91% (24).

No general agreement exists regarding the restaging process. Our current restaging algorithm of the Antwerp University Hospital is shown in fig. 2 (11).

6. Role of surgery versus radiotherapy in combined modality therapy

Although several major randomized trials enrolling patients with stage IIIA-N2 NSCLC were performed evaluating different combinations of chemotherapy, radiotherapy and/or surgery, the results of these studies continue to be hotly debated at lung cancer conferences (25, 26). The main reasons for this controversy are that 1) patients' inclusion criteria were not always uniform resulting in heterogeneous patient populations, 2) lack of standardized criteria or quality control for surgery and radiotherapy, and 3) morbidity and mortality in certain subgroups were very high, as e.g. after right pneumonectomy following induction chemoradiation (14). Moreover, surgery and radiotherapy cannot be directly compared as no pathological specimens are obtained in the groups of patients treated with radiotherapy rendering comparison between different ypN (i.e. pathological nodal staging after induction therapy) groups impossible.

The ultimate aim for every surgical intervention in NSCLC, whether early-stage or locally advanced, is to obtain a complete R0 resection according to the criteria established by a working group of the International Association for the Study of Lung Cancer (IASLC) (27). These include a macroscopic complete resection, confirmation of free resection margins on the pathology report, a systematic or at least a lobe-specific systematic nodal dissection including 6 nodal stations (of which 3 are from the mediastinum always including the subcarinal station 7), showing no extracapsular extension in nodes removed separately or at the margin of the lung specimen with the highest mediastinal lymph node

being negative. Without any doubt, these criteria are difficult to fulfil after induction therapy, especially chemo-radiotherapy, as mediastinal fibrosis may render mediastinal node dissection technically challenging.

The largest phase III trials addressing the question of induction treatment flowed by surgery compared to chemo-radiotherapy alone are the US Intergroup (INT) 0139 trial and the European Organisation for Research and Treatment of Cancer (EORTC) 08941 study (14, 28, 29). Both studies included patients with cytologically or pathologically proven N2 disease, however in the EORTC trial patients were considered to be upfront "unresectable" according to the local thoracic surgeon. In the EORTC trial induction therapy consisted of various regimens of cisplatin-based chemotherapy, and in the Intergroup trial it consisted of induction chemo-radiotherapy to a total dose of 45 Gy in 5 weeks. Subsequently, patients were randomized between surgery and further radiotherapy. During surgical resection every attempt was made to completely remove the primary tumour and locoregional lymph nodes. Complete resection was obtained in 50% of the patients in the EORTC trial and in 71% of the patients in the Intergroup study. However, it should be noticed that different criteria were used to determine complete resection underscoring the need for uniform guidelines (27). Regarding overall survival there was no significant difference between treatment arms in both trials but in the Intergroup study progression-free survival was significantly improved in the trimodality arm. As a high mortality was observed after pneumonectomy in the Intergroup trial, a secondary analysis was performed in patients undergoing lobectomy which were matched with similar patients treated with chemo-radiotherapy in the control arm. In this unplanned sub-analysis the surgical group had a significantly better survival underscoring that the final surgical results are clearly influenced by the operative mortality rate (30).

More recently, the ESPATUE phase III trial reported on the comparison of surgical resection to a definitive concurrent chemo-radiotherapy boost in patients with resectable stage IIIA-N2 and selected stage IIIB after induction chemotherapy followed by concurrent chemoradiation (15). Because of slow

accrual the trial was closed after 246 patients were enrolled. Five-year overall and progression-free survival did not differ between both arms. The authors concluded that both treatment strategies are acceptable for this selected population with a good prognosis (15). However as discussed above, the role of bimodality versus trimodality regimens is still not well established. In order to make more definitive recommendations a recent meta-analysis evaluated survival outcomes of patients with N2 disease in multimodality trials of chemotherapy, radiotherapy and surgery (31). Six trials with a total of 868 patients were included, 4 applying induction chemotherapy and 2 induction chemo-radiotherapy. There was no statistical evidence of heterogeneity. The pooled hazard ratio for overall survival was 1.01 with bimodality therapy (p=0.95) , and 0.87 with trimodality therapy (p=0.068). The authors concluded that these results support surgery as part of multimodality management with a 13% relative improvement in overall survival (31).

The results of the three key studies (EORTC 08941, INT 0139 and ESPATUE trial) are summarized in table 3.

Regarding the surgical approach, recently it has been shown that lung resection by VATS may be selectively employed without compromising long-term results (17). However, as already mentioned, hilar and mediastinal fibrosis may render dissection of the pulmonary vessels quite tedious necessitating an open approach in difficult cases. In the latter intrapericardial dissection of the large vessels may be required.

The role of postoperative radiotherapy (PORT) in incompletely resected R1 (microscopic) and R2 (macroscopic) or ypN2 (pathological residual N2 disease) after induction chemotherapy and surgical resection was studied in a retrospective series of 70 patients (32). PORT for a total dose of 50-66 Gy was found to be effective and safe in these particular settings.

7. Salvage surgery

In recent years “salvage surgery” has become a therapeutic option in combined modality therapy. It refers to surgical treatment when no other valid treatment options are available. It can be applied after high-dose stereotactic radiotherapy when after an initial response or stable disease there is evidence of progressive disease. With reference to the current topic, it may be considered in patients with locally advanced NSCLC considered initially unresectable who present with locoregional recurrent or progressive disease after full-dose chemo-radiotherapy. Without any doubt these interventions may be technically challenging as a full-dose of radiotherapy was delivered to the hilum and mediastinum several months or years earlier, rendering dissection of the pulmonary artery and mediastinal lymph nodes technically challenging. As a result, an intrapericardial dissection is frequently required. Each individual patient should be discussed thoroughly within a multidisciplinary board and the operation should be performed by an experienced team including a thoracic surgeon, anaesthesiologist and an intensive care physician. Mortality and mobility may be quite high, especially after an extended pneumonectomy. Currently, published experience on salvage surgery for locoregionally progressive or recurrent lung cancer after full-dose chemo-radiotherapy is limited. In a series of 18 patients, the median time between the last day of radiotherapy and surgical intervention was 38 weeks (33). Lobectomy was performed in 13 patients and pneumonectomy in 5. Complete resection rate was 89%. There was no operative mortality. Three-year overall and recurrence-free survival rates were 78 and 72%. This study demonstrates that salvage surgery in this difficult setting is feasible and may yield a substantial medium-term survival. A recent review concluded that salvage surgery may represent an alternative treatment option but that only small, retrospective and single-centre series are available at the present time (34).

8. Expert Commentary

The management of stage IIIA-N2 requires an integrated approach by a multidisciplinary team. As several subgroups exist and no definite guidelines are available, diagnostic and treatment plans should be

tailored to each individual patient. Not only the precise subcategory should be taken into account but also the comorbidity of the patient especially in relation to cardiopulmonary function testing to determine the operative risk. Patient's preference after adequate and informed discussion of the different treatment options is also a major factor in the final decision. For N2 disease diagnosed by a minimally invasive or invasive technique, combined modality treatment is indicated. The relative contribution of chemotherapy, radiotherapy and surgery has not been clearly established. However, pathological downstaging has been reported to be a major prognostic factor as persisting N2 disease heralds a poor prognosis and most of these patients will die of distant metastatic disease. Discussion remains concerning patients with minimal residual N2 disease as this is an intermediate state between complete mediastinal clearance and remaining multilevel or bulky N2 involvement (35). In recent literature there is no clear definition of "minimal residual N2" involvement. In our series of repeat mediastinoscopies those patients with false-negative repeat mediastinoscopies who underwent lung resection, had an intermediate survival rate between true-negative and true-positive repeat mediastinoscopies (36). Anyway, complete R0 resection remains a major prognostic factor for overall survival. There are also no literature data showing superiority of overall survival for radiotherapy versus surgery in patients who have residual N2 disease following induction therapy.

In general a pneumonectomy should be avoided, especially on the right side, due to a higher incidence of major complications such as empyema and bronchopleural fistula (37). However, it should be noted that in more recent, retrospective series 90-day mortality after pneumonectomy following induction therapy has been reduced to 3% (38, 39)

9. Five-year view

Due to the heterogeneity of stage IIIA-N2 disease more specific guidelines should be developed for the different subgroups. The role of surgery versus radiotherapy and the optimal combination of both

treatments is still to be defined but they will continue to play a major role as they provide the best local control and eradication of the primary tumour. Immunotherapy is currently emerging as a valid therapeutic option for patients with widespread disease. It is likely that , immunotherapy will also be incorporated in neoadjuvant and adjuvant protocols, not only for early-stage disease but also for locally advanced bronchogenic carcinoma. Recent studies are mentioned in table 4. As specific biomarkers become increasingly important to define a treatment plan incorporating chemotherapy, targeted therapy and immunotherapy, large biopsy samples will be necessary, especially when considering that most tumours are heterogeneous. Minimally invasive techniques are improving by combining endobronchial and endo-oesophageal techniques. In case of unclear or equivocal results, invasive staging techniques will still be required to provide adequate samples for detailed molecular analysis. This is especially true after induction therapy to determine the pathological response and decide on further treatment.

Stage IIIA-N2 disease will continue to be hotly debated at major conferences. The interplay between the different disciplines provides a fascinating discussion forum which will lead to tailored diagnostic and therapeutic algorithms. With such multidisciplinary and personalised treatments, there is hope that the prognosis of our patients with locally advanced lung cancer will improve in the coming years.

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Declaration of Interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Key issues

- every lung cancer patient with locoregionally advanced disease should be discussed at a multidisciplinary tumour board
- combined modality treatment is indicated in patients with stage IIIA-N2 disease
- downstaging is a major prognostic factor; therefore, restaging is of utmost importance
- the ultimate aim of surgical treatment is to obtain a complete resection
- the role of surgery versus radiotherapy in combined modality treatment remains controversial
- only the patients who are downstaged after induction treatment should undergo surgical resection

Table 1. Stage IIIA-N2 non-small cell lung cancer: controversial issues.

Precise definitions: potentially resectable, unresectable, bulky N2
Restaging after induction therapy
Role of surgery versus radiotherapy in combined modality therapy
Extent of resection after induction therapy
Treatment in relation to persisting mediastinal nodal involvement
Role of postoperative radiotherapy in completely resected N2 disease

Table 2. Stages IIIA-B non-small cell lung cancer according to the 7th and 8th TNM classification (40, 41).

TNM classification	**7th edition** **size stage**	**8th edition** **size stage**
T1a N2 M0 T1b N2 M0	≤ 2.0 cm IIIA 2.1 - 3.0 cm IIIA	≤ 1.0 cm IIIA 1.1 – 2.0 cm IIIA
T1c N2 M0	-	2.1 – 3.0 cm IIIA
T2a N2 M0 T2b N2 M0	3.1 - 5.0 cm IIIA 5.1 - 7.0 cm IIIA	3.1 - 4.0 cm IIIA 4.1 - 5.0 cm IIIA
T3 N1 M0	> 7.0 cm IIIA	5.1 - 7.0 cm IIIA
T3 N2 M0	> 7.0 cm IIIA	5.1 - 7.0 cm IIIB
T4 N0-1 M0	no size IIIA criterion	> 7.0 cm IIIA
T4 N2 M0	no size IIIB criterion	> 7.0 cm IIIB
T1-2 N3 M0	IIIB	IIIB
T3-4 N3 M0	IIIB	IIIC

Table 3. Results of large phase III studies including stages IIIA-N2 and stage IIIB.

	EORTC 08941 (28, 29) stage IIIA-N2		INT 0139 (14) stage IIIA-N2		ESPATUE (15) stages IIIA-N2 and selected IIIB	
	surgery	radiotherapy	surgery	radiotherapy	surgery	radiotherapy
induction therapy	CT	CT	CRT	CRT	CRT	CRT
complete resection	50%	-	71%	-	81%	-
mortality (overall) (bi)lobectomy pneumonectomy	3.9% 0% 6.9%	1%	5% 1% 26%	2%	7.1% 10.9% 0%	2.5%
MST (months)	16.4	17.5	23.6	22.2	NS	NS
5-year overall survival	15.7%	14%	27%	20%	44%	40%
progression-free survival	2-year 27%	2 year 24%	5-year 22%	5-year 11% *p=0.017*	5-year 32%	5-year 35%

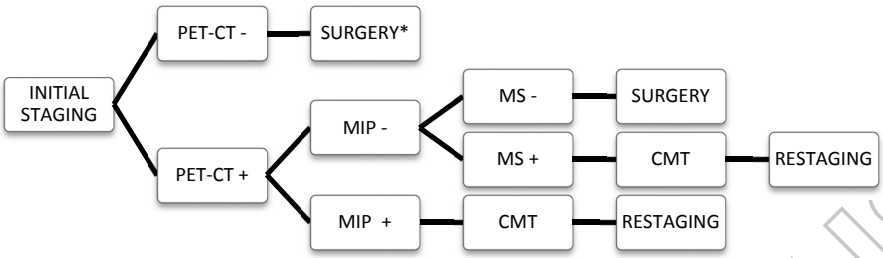
Regarding survival only progression-free survival in the INT 0139 trial was significant.

CT: chemotherapy; CRT: chemo-radiotherapy; MST: median survival time; NS not stated

Table 4. Current trials on epidermal growth factor receptor (EGFR) mutation-positive patients with advanced lung cancer in neoadjuvant or adjuvant setting.

trial	title	status
NCT01822496	Erlotinib Hydrochloride or Crizotinib and Chemoradiation Therapy in Treating Patients With Stage III Non-small Cell Lung Cancer	recruiting participants
NCT02434081	Nivolumab COnsolidation With Standard First-line Chemotherapy and Radiotherapy in Locally Advanced Stage IIIA/B Non-Small Cell Lung Carcinoma (NICOLAS)	recruiting participants
NCT02125461	A Global Study to Assess the Effects of MEDI4736 Following Concurrent Chemoradiation in Patients With Stage III Unresectable Non-Small Cell Lung Cancer (PACIFIC)	completed recruitment 2016

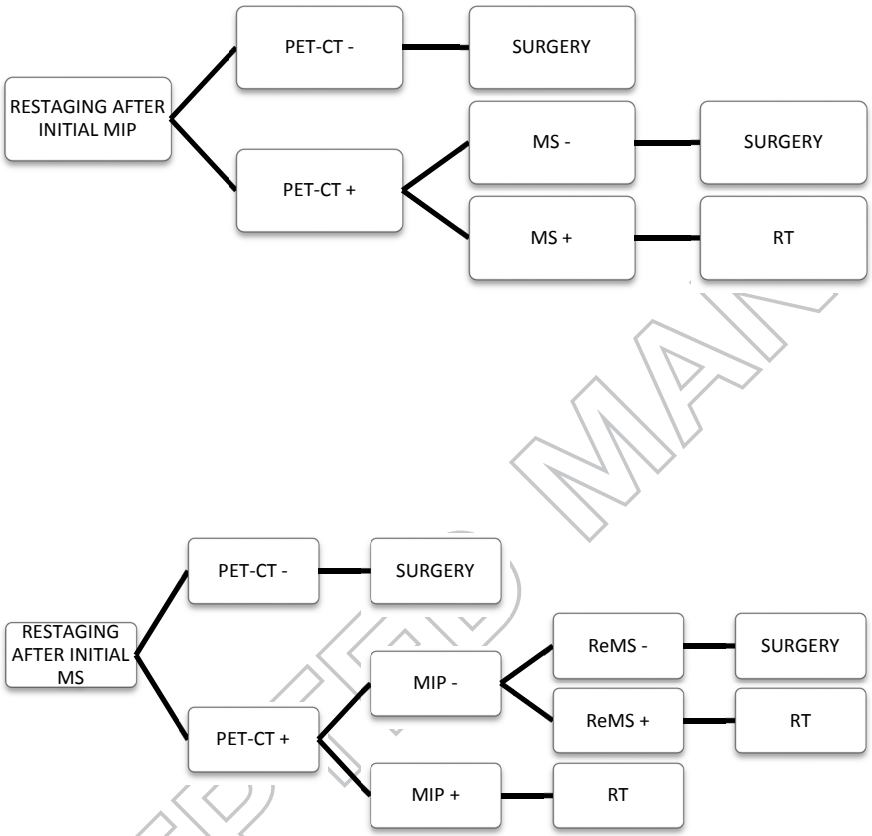
Figure 1. Flow chart for mediastinal staging of non-small cell lung cancer in Antwerp University Hospital. Adapted from (11).



PET-CT: integrated positron emission tomography and computed tomography; MIP: minimally invasive procedure (endobronchial [EBUS] or endoscopic ultrasound [EUS]); MS: mediastinoscopy; CMT: combined modality treatment

* Exceptions are centrally located tumours and + N1 nodes on PET-CT scanning where the PET-CT+ track is followed according to ESTS guidelines (8).

Figure 2. Flow chart for mediastinal restaging of non-small cell lung cancer in Antwerp University Hospital depending on whether initially a minimally invasive procedure or mediastinoscopy was performed. Adapted from (11).



PET-CT: integrated positron emission tomography and computed tomography; MIP: minimally invasive technique (endobronchial [EBUS] or endoscopic ultrasound [EUS]); MS: mediastinoscopy; RT: radiotherapy; ReMS: repeat mediastinoscopy

References

Papers of special note have been highlighted as:

* of interest

** of considerable interest

1. Eberhardt WE, De Ruysscher D, Weder W, et al. 2nd ESMO Consensus Conference in Lung Cancer: locally advanced stage III non-small-cell lung cancer. Ann Oncol. 2015;26:1573-1588.

** recent general guidelines on stage III lung cancer

2. Goldstraw P, Chansky K, Crowley J, et al. The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer. J Thorac Oncol. 2016;11:39-51.

3. Van Schil PE. Stage IIIA-N2 non-small-cell lung cancer: from 'surprise' involvement to surgical nightmare. Eur J Cardiothorac Surg. 2016;49:1613-1614.

4. McCloskey P, Balduyck B, Van Schil PE, et al. Radical treatment of non-small cell lung cancer during the last 5 years. Eur J Cancer. 2013;49:1555-1564.

5. Detterbeck F. What to do with "Surprise" N2?: intraoperative management of patients with non-small cell lung cancer. J Thorac Oncol. 2008;3:289-302.

* excellent review of unforeseen, unexpected or "surprise" N2

6. Van Schil PE, De Waele M, Hendriks JM, et al. Surgical treatment of stage III non-small cell lung cancer. Eur J Cancer. 2009;45 Suppl 1:106-112.

7. Le Pechoux C, Dunant A, Faivre-Finn C, et al. Postoperative Radiotherapy for Pathologic N2 Non-Small-Cell Lung Cancer Treated With Adjuvant Chemotherapy: Need for Randomized Evidence. J Clin Oncol. 2015;33:2930-1.

8. De Leyn P, Dooms C, Kuzdzal J, et al. Revised ESTS guidelines for preoperative mediastinal lymph node staging for non-small-cell lung cancer. Eur J Cardiothorac Surg. 2014;45:787-798.

** clinically useful update on staging and restaging of lung cancer

9. Call S, Obiols C, Rami-Porta R, et al. Video-Assisted Mediastinoscopic Lymphadenectomy for Staging Non-Small Cell Lung Cancer. Ann Thorac Surg. 2016;101:1326-33.

10. Van Schil P. Role of video-assisted thoracic surgery (VATS) in staging, diagnosis and treatment of lung cancer. Acta Chir Belg. 1999;99:103-108.

11. Van Schil PE HJ, Hertoghs M, Lauwers P, Choong CK. Advances in surgery of lung cancer. In: Stahel R, editor. Lung cancer therapy Annual 7. London: Informa Healthcare; 2012. p. 104-18.

12. Pottgen C, Stuschke M, Graupner B, et al. Prognostic model for long-term survival of locally advanced non-small-cell lung cancer patients after neoadjuvant radiochemotherapy and resection integrating clinical and histopathologic factors. BMC cancer. 2015;15:363.

13. Pless M, Stupp R, Ris HB, et al. Induction chemoradiation in stage IIIA/N2 non-small-cell lung cancer: a phase 3 randomised trial. Lancet. 2015;386(9998):1049-1056.

14. Albain KS, Swann RS, Rusch VW, et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. Lancet. 2009;374(9687):379-386.

15. Eberhardt WE, Pottgen C, Gauler TC, et al. Phase III Study of Surgery Versus Definitive Concurrent Chemoradiotherapy Boost in Patients With Resectable Stage IIIA(N2) and Selected IIIB Non-Small-Cell Lung Cancer After Induction Chemotherapy and Concurrent Chemoradiotherapy (ESPATUE). J Clin Oncol. 2015;33:4194-4201.

16. Eberhardt WE, Stuschke M. Multimodal treatment of non-small-cell lung cancer. Lancet. 2015;386(9998):1018-1020.

17. Yang CF, Adil SM, Anderson KL, et al. Impact of patient selection and treatment strategies on outcomes after lobectomy for biopsy-proven stage IIIA pN2 non-small cell lung cancer. Eur J Cardiothorac Surg. 2016;49:1607-1613.

18. de Cabanyes Candela S, Detterbeck FC. A systematic review of restaging after induction therapy for stage IIIa lung cancer: prediction of pathologic stage. J Thorac Oncol. 2010;5:389-98.

* nice overview of restaging techniques

19. Cerfolio RJ, Bryant AS, Ojha B. Restaging patients with N2 (stage IIIa) non-small cell lung cancer after neoadjuvant chemoradiotherapy: a prospective study. J Thorac Cardiovasc Surg. 2006;131:1229-1235.

20. De Waele M, Hendriks J, Lauwers P, , et al. Restaging the mediastinum in non-small cell lung cancer after induction therapy: non-invasive versus invasive procedures. Acta Chir Belg. 2011;111:161-164.

21. Annema JT, Veselic M, Versteegh MI, et al. Mediastinal restaging: EUS-FNA offers a new perspective. Lung Cancer. 2003;42:311-318.

22. De Waele M, Serra-Mitjans M, Hendriks J, et al. Accuracy and survival of repeat mediastinoscopy after induction therapy for non-small cell lung cancer in a combined series of 104 patients. Eur J Cardiothorac Surg. 2008;33:824-828.

23. Jaklitsch MT, Gu L, Demmy T, et al. Prospective phase II trial of preresection thoracoscopic mediastinal restaging after neoadjuvant therapy for IIIA (N2) non-small cell lung cancer: results of CALGB Protocol 39803. J Thorac Cardiovasc Surg. 2013;146:9-16.

24. Lardinois D, Schallberger A, Betticher D, et al. Postinduction video-mediastinoscopy is as accurate and safe as video-mediastinoscopy in patients without pretreatment for potentially operable non-small cell lung cancer. Ann Thorac Surg. 2003;75:1102-1106.

25. Bezjak A, de Perrot M. Trimodality Approach to Stage IIIA-N2 NSCLC: As Good as It Gets? J Thorac Oncol. 2016;11:1817-1818.

26. Tsao AS, Scagliotti GV, Bunn PA, Jr., et al. Scientific Advances in Lung Cancer 2015. J Thorac Oncol. 2016;11:613-638.

27. Rami-Porta R, Wittekind C, Goldstraw P, International Association for the Study of Lung Cancer Staging C. Complete resection in lung cancer surgery: proposed definition. Lung Cancer. 2005;49:25-33.

** this paper provides precise definitions of complete, incomplete abd uncertain resections

28. van Meerbeeck JP, Kramer GW, Van Schil PE, et al. Randomized controlled trial of resection versus radiotherapy after induction chemotherapy in stage IIIA-N2 non-small-cell lung cancer. J Natl Cancer Inst. 2007;99:442-450.

29. Van Schil P, Van Meerbeeck J, Kramer G, et al. Morbidity and mortality in the surgery arm of EORTC 08941 trial. Eur Respir J. 2005;26:192-197.

30. Van Schil PE. Mortality associated with pneumonectomy after induction chemoradiation versus chemotherapy alone in stage IIIA-N2 non-small cell lung cancer. J Thorac Cardiovasc Surg. 2008;135:718; author reply -719.

31. McElnay PJ, Choong A, Jordan E, et al. Outcome of surgery versus radiotherapy after induction treatment in patients with N2 disease: systematic review and meta-analysis of randomised trials. Thorax. 2015;70:764-768.

** most recent meta-analysis of trials dealing with N2 disease favouring trimodality therapy

32. Billiet C, Peeters S, Decaluwe H, et al. Outcome after PORT in ypN2 or R1/R2 versus no PORT in ypN0 Stage III-N2 NSCLC after Induction Chemotherapy and Resection. J Thorac Oncol. 2016;11:1940-1953.

33. Shimada Y, Suzuki K, Okada M, et al. Feasibility and efficacy of salvage lung resection after definitive chemoradiation therapy for Stage III non-small-cell lung cancer. Interact Cardiovasc Thorac Surg. 2016;23:895-901.

34. Uramoto H. Current Topics on Salvage Thoracic Surgery in Patients with Primary Lung Cancer. Ann Thorac Cardiovasc Surg. 2016;22:65-68.

35. Meacci E, Cesario A, Cusumano G, et al. Surgery for patients with persistent pathological N2 IIIA stage in non-small-cell lung cancer after induction radio-chemotherapy: the microscopic seed of doubt. Eur J Cardiothorac Surg. 2011;40:656-63.

36. De Waele M, Hendriks J, Lauwers P, et al. Nodal status at repeat mediastinoscopy determines survival in non-small cell lung cancer with mediastinal nodal involvement, treated by induction therapy. Eur J Cardiothorac Surg. 2006;29:240-243.

37. Van Schil PE, Hendriks JM, Lauwers P. Focus on treatment complications and optimal management surgery. Transl Lung Cancer Res. 2014;3:181-186.

38. Barnett SA, Rusch VW, Zheng J, et al. Contemporary results of surgical resection of non-small cell lung cancer after induction therapy: a review of 549 consecutive cases. J Thorac Oncol. 2011;6:1530-1536.

39. Weder W, Collaud S, Eberhardt WE, et al. Pneumonectomy is a valuable treatment option after neoadjuvant therapy for stage III non-small-cell lung cancer. J Thorac Cardiovasc Surg. 2010;139:1424-1430.

40. Rami-Porta R, Ball D, Crowley J, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the T descriptors in the forthcoming (seventh) edition of the TNM classification for lung cancer. J Thorac Oncol. 2007;2:593-602.

41. Rami-Porta R, Bolejack V, Crowley J, et al. The IASLC Lung Cancer Staging Project: Proposals for the Revisions of the T Descriptors in the Forthcoming Eighth Edition of the TNM Classification for Lung Cancer. J Thorac Oncol. 2015;10:990-1003.

* in this paper the T descriptors in the new 8th edition of the TNM classification are highlighted