Surgical treatment of stage III non-small cell lung cancer

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Introduction

The role of the thoracic surgeon in the evaluation and treatment of stage III non-small cell lung cancer (NSCLC) remains controversial. New technologies for locoregional staging are emerging and the definite role of surgical treatment to obtain adequate local control has not been established yet. Most patients with stage III NSCLC will be treated by combined modality therapy. Recently finished and currently ongoing trials are evaluating the relative contribution of chemotherapy, radiotherapy and surgery. In this review the role of minimally invasive and invasive techniques for restaging after induction therapy are discussed, followed by the surgical indications and treatment strategies for stages IIIA and IIIB NSCLC.

Restaging after induction therapy: Minimally invasive and invasive techniques

Mediastinal downstaging after induction therapy for locally advanced NSCLC is an important prognostic factor for long-term survival. Patients with persisting mediastinal involvement have a poor prognosis and will usually not benefit from surgical resection [1–3]. Therefore, precise restaging after induction chemotherapy or chemo-radiation is of utmost importance to determine subsequent treatment and prognosis. The different minimally invasive and invasive restaging methods which are currently available are listed in Table 1.

Table 1
Minimally invasive and invasive techniques for mediastinal restaging

Minimally invasive
transthoracic fine-needle aspiration biopsy (FNAB)
transbronchial needle aspiration (TBNA)
endobronchial ultrasound with FNAB (EBUS)
endoscopic (oesophageal) ultrasound with FNAB (EUS)
Invasive
redo, second or repeat mediastinoscopy (reMS)
video-assisted thoracic surgery (VATS)

Minimally invasive techniques comprise promising staging modalities and are increasingly used for lung cancer staging and also restaging. However, false-negative rates are at least 20 to 30% (Table 2) [4–6].

Mediastinal restaging was performed by endoscopic oesophageal ultrasound (EUS) after induction chemotherapy in 19 patients with proven N2 NSCLC [4]. There were no complications and patients with N0 disease underwent resection. Accuracy of EUS in this setting was 83%; therefore, EUS with needle aspiration might play a role in mediastinal restaging. In a series of 83 patients with proven stage IIIA-N2 NSCLC treated by induction chemotherapy, mediastinal restaging with endobronchial ultrasound (EBUS) and transbronchial needle aspiration (TBNA) yielded a sensitivity of 70% and an accuracy of 75% [5]. In a large series of 124 patients with stage IIIA-N2 disease who underwent induction chemotherapy, sensitivity and accuracy of EBUS-TBNA in restaging were 76 and 77%, respectively [6]. However, negative predictive value was only 20%; therefore, negative findings should still be confirmed by surgical restaging. Recent experience with EUS and EBUS for restaging is summarised in Table 2 [4–6].

Also, TBNA without systematic use of ultrasound or EBUS might provide accurate results. In a smaller series, 17 lymph nodes were sampled in 14 patients who had undergone induction therapy for stage IIIA-N2 NSCLC [7]. A correct diagnosis was obtained in 71% of patients and more invasive procedures could be avoided in 35%.

Repeat mediastinoscopy (reMS) is technically more difficult than a first procedure resulting in a lower accuracy but provides pathological proof of response after induction therapy. Results of recent series of reMS after induction therapy are summarised in Table 3 [3,8–13]. In all series, sensitivity of reMS was at least 60%, except for one prospective study comparing reMS to integrated CT-PET scanning [11]. The low sensitivity in the latter study is largely explained by the fact that in 20 patients (67%) no

Table 2
Recent experience with EUS and EBUS after induction therapy

Author, year	Ref.	Technique	*n*	Sensitivity (%)	Specificity (%)	Accuracy (%)
Annema, 2003	[4]	EUS	19	75	100	83
Krasnik, 2006	[5]	EBUS	83	70	100	75
Herth, 2008	[6]	EBUS	124	76[a]	100	77

EUS: endoscopic (oesophageal) ultrasound; EBUS: endobronchial ultrasound; Ref.: reference; *n*: number of patients.
[a] Negative predictive value was only 20%.

Table 3
Results of remediastinoscopy after induction therapy

Author, year	Ref.	*n*	IT	Morbidity (%)	Mortality (%)	Sensitivity (%)	Specificity (%)	Accuracy (%)
Pitz, 2002	[8]	15	CT	0	0	71.4[a]	100	87
Rami-Porta, 2003	[9]	24[b]	CT	0	0	83	100	91
Stamatis, 2005	[10]	165	CT-RT	2.5	0	74	100	93
De Waele, 2006	[3]	32	CT ($n=26$), CT-RT ($n=6$)	3.1	0	71	100	84
De Leyn, 2006	[11]	30	CT	0	0	29	100	60
De Waele, 2007[c]	[12]	104	CT ($n=79$), CT-RT ($n=25$)	3.9	1	70	100	80
Marra, 2008[d]	[13]	104	CT-RT	1.9	0	61	100	88

[a] Negative predictive value.
[b] Time period 1999–2003 (total series 48 patients).
[c] Combined, updated series.
[d] Subset of patients of Stamatis 2005 [10].
Ref.: reference; *n*: number of patients; IT: induction therapy; CT: chemotherapy; CT-RT: chemoradiotherapy.

adequate biopsies of the subcarinal lymph node station number 7 could be taken.

Recently, we were able to show that survival depends on the findings of reMS, patients with a positive reMS having a poor prognosis compared to those with a negative reMS [3]. In a combined, updated series of 104 patients, identical survival results were found with nodal status being the only significant factor in multivariate analysis [12].

The largest series of reMS was reported in 2005, describing a total of 279 reMS [10]. In a subset of 104 patients who underwent reMS after induction chemoradiation for stage IIIA-B NSCLC, results were similar to other series [13]. So, even combined chemo- and radiotherapy does not give rise to increased difficulties or a lower accuracy of reMS compared to chemotherapy alone.

Video-assisted thoracic surgery (VATS) has been used for restaging but experience is limited. In a phase II study of the Cancer and Leukaemia group B (CALGB), 70 patients with stage IIIA-N2 NSCLC underwent restaging by VATS [14]. Sensitivity in this series was 75%, specificity 100% and negative predictive value 76%.

For thoracic surgeons having no experience with reMS, an alternative approach consists of the initial use of minimally invasive staging procedures such as TBNA, EBUS or EUS to obtain cytological proof of mediastinal nodal involvement [15]. After induction therapy, patients are subsequently restaged by mediastinoscopy. In this way, a technically more demanding reMS can be avoided. Recently, the European Society of Thoracic Surgeons (ESTS) published guidelines for preoperative lymph node staging in NSCLC [16]. Regarding restaging after induction therapy, an invasive technique providing cytohistological information is still recommended at the present time. Endoscopic or surgical invasive procedures may be utilised, the precise choice depending on the availability of the technique and expertise of the centre [16].

Stage IIIA

Stage IIIA non-small cell lung cancer (NSCLC) represents a heterogeneous spectrum of locally advanced disease. The different subgroups are listed in Table 4.

Table 4
Stage III non-small cell lung cancer: different subgroups

Stage IIIA	T3N1M0	
	T1–3N2M0	N2 discovered at thoracotomy (unexpected, "surprise" N2)
		N2 detected during preoperative work-up, potentially resectable
		unresectable, bulky N2
Stage IIIB	T4N0–1M0[a]	
	T4N2M0	
	T1–4N3M0	

[a] T4N0–1M0 will be reclassified as stage IIIA in the 7th edition of the TNM classification [17].

T3N1 disease is usually an incidental finding during thoracotomy when operating a clinical T3 tumour. The thoracic surgeon should proceed with the intervention when a complete resection can be obtained. Adjuvant chemotherapy is indicated [18].

N2 disease implies ipsilateral mediastinal or subcarinal lymph node involvement (stage IIIA-N2 disease). It is subdivided into unexpected N2 discovered at thoracotomy, N2 proven at preoperative staging which is potentially resectable, and unresectable, bulky N2 (Table 4) [19,20].

When N2 disease is discovered during thoracotomy after negative careful preoperative staging a resection should be performed if this can be complete (free margins and highest mediastinal node is negative). In a recent paper, unexpected N2 was also called "surprise" N2 and the necessity of careful preoperative staging was emphasised [20]. During thoracotomy a systematic nodal dissection should be performed to obtain a precise pathological staging. Postoperative radiotherapy will decrease local recurrence rate but will not improve overall survival. Adjuvant chemotherapy increases survival and is presently recommended in these cases, followed by radiotherapy, if feasible [18,19].

Most patients with pathologically proven N2 disease detected during preoperative work-up will be treated by induction therapy. With induction or neoadjuvant therapy a downstaging of locally advanced tumours is aimed for, together with an eradication of systemic micrometastases and a diminished stimulus to cancer cells by a subsequent surgical procedure. Possible theoretical advantages include a significant cytoreduction, increased resectability, conservation of functional lung parenchyma and a better long-term survival. Disadvantages of induction therapy are an increased morbidity and mortality due to the chemotherapy, chemoradiation, or a subsequent surgical procedure. The latter is often more difficult due to an intense fibrotic reaction. In case of complications hospital stay is significantly increased. From recent literature it is clear that surgery is feasible after induction therapy for locally advanced NSCLC, but is often more complex and may carry a higher risk. In initial series, mainly from North America, mortality from pneumonectomy was high, especially that from a right complex pneumonectomy after induction chemoradiation [21,22]. In other series a lower mortality is reported although the incidence of bronchopleural fistula remains elevated [23–27]. Prognostic factors after induction therapy include complete tumour resection and chemotherapy activity consisting of clinical, pathologic response and mediastinal downstaging [28].

For locally advanced stage IIIA-N2 lung cancer the major question remains whether a better local control and survival are obtained by induction therapy followed by surgery compared to standard chemoradiotherapy. This specific question was explored in two large randomised trials which were recently completed.

In the Intergroup 0139 trial patients with proven stage IIIA-N2 NSCLC were randomised between a full course of chemoradiotherapy and induction chemoradiotherapy followed by surgery [29,30]. There was no significant difference in overall survival between both arms. However, there was a difference in progression-free survival favouring the surgical arm, and patients downstaged to N0 disease had a far better prognosis. The rate of locoregional recurrence was significantly lower in the surgical arm. In an exploratory analysis patients undergoing lobectomy were matched to a similar group treated by chemoradiotherapy. There was a significant survival advantage for the surgical group. However, no difference was found for a matched group undergoing pneumonectomy.

In the European Organisation for Research and Treatment (EORTC) 08941 phase III trial patients with proven stage IIIA-N2 disease were randomised between surgery and radiotherapy after a response to induction chemotherapy [23,31]. There was no difference in overall and progression-free survival between

Table 5
Comparison of EORTC 08941 with INT 0139 trial [23,29–31]

	EORTC 08941		INT 0139	
Induction therapy	Chemotherapy		Chemoradiotherapy	
Complete resection[a]	50.0%		71%	
Exploratory thoracotomy	13.6%		4.5%	
Rate of pneumonectomy	46.8%		32.9%	
ypN0/1/2	N0/1 41.4% N2 55.8%		N0 46% N1–3 54%	
ypT0N0	5.2%		14.4%	
30-day mortality				
overall	3.9%		5%	
lobectomy	0%		1%	
pneumonectomy	6.9%	R 5.3% L 9.1%	26%	R simple 29% R complex 50% L simple 0% L complex 16%
exploratory thoracotomy	4.8%		0%	
90-day mortality	8.7%			
Median survival (months)				
overall	RT 17.5	Surgery 16.4	RT 22.2	Surgery 23.6
progression-free	RT 11.3	Surgery 9.0	RT 10.5	Surgery 12.8
Local recurrence	RT 55%	Surgery 32% $P = 0.001$	RT 22%	Surgery 10% $P = 0.002$
5-year survival				
lobectomy	27%		36%	
pneumonectomy	12%	$P = 0.009$	22%	
ypN0/1/2	N0/1 29% N2/3 7% $P = 0.0009$		N0 41% N1–3 24% $P < 0.0001$	

[a] Definition was different in the two trials. RT = radiotherapy.

both arms. In an exploratory analysis patients with a downstaging to N0 or N1 disease had a significantly better prognosis than those with persisting N2 disease. Also, the rate of locoregional recurrence was significantly less in the surgical arm. Patients treated by lobectomy had a significantly better survival than those who had a pneumonectomy. A comparison between both trials is provided in Table 5. Therefore, surgical resection could probably provide a survival benefit in downstaged patients when a pneumonectomy can be avoided, as the latter intervention carries a much higher mortality and morbidity rate than lobectomy, especially after induction chemoradiotherapy [22].

The recent guidelines on the management of preoperatively identified N2 disease published in Chest in 2007 recommend a multidisciplinary approach including advice from a thoracic surgeon [19]. Surgical resection should only be performed within a clinical trial in those patients in whom a complete resection can be obtained by lobectomy after induction therapy. Platinum-based combination chemoradiotherapy is recommended as primary treatment. However, it should be noted that these guidelines are only based on the abstracts of the two mentioned randomised studies.

The majority of patients with bulky N2 disease are treated with combination platinum-based chemotherapy and radiotherapy. In case of good performance status and minimal weight loss, concurrent chemoradiotherapy is preferred to sequential application [19]. However, the optimal treatment scheme has not been determined yet.

Stage IIIB

In general, patients with stage IIIB NSCLC (T4-N3 disease) are not good candidates for surgical resection because of an overall poor prognosis. However, in some specific cases, long-term survival may be obtained after surgical resection, sometimes in combination with chemo- or radiotherapy. Most important prognostic parameters include a complete surgical resection, excellent performance status and no involvement of mediastinal lymph nodes [32]. In certain subgroups of T4N0 disease a 5-year survival of 30% has been reported. This specifically relates to tumours invading the main carina or distal trachea, left atrium, superior vena cava and vertebral bodies [33]. An extended resection is often necessary, sometimes followed by a technically demanding and difficult reconstruction which should be performed by a specialised, multidisciplinary team. Induction therapy may improve resectability but more prospective studies are necessary. Because of this better prognosis, T4N0–1 lung cancers will be reclassified as stage IIIA disease in the 7th edition of the TNM classification [17]. This was confirmed by a recent Spanish phase II study including 136 patients with stage IIIA and IIIB disease who were treated by induction chemotherapy with a cisplatin-based triplet followed by surgical resection [34]. In patients with T4N0–1 disease in whom a complete resection was obtained, 5-year survival rate was 53%, which is remarkably high.

Satellite nodules in the primary lobe represent a special situation. In the 1997 TNM classification (6th edition), these were considered to be T4 disease. Many reports have shown that they represent a more favourable subgroup than the other T4 subcategories, even when malignant pleural effusion is excluded. These findings were confirmed by a survival analysis of the large International Association for the Study of Lung Cancer (IASLC) database [17]. Satellite nodules in the primary lobe are reclassified as T3 disease. Additionally, ipsilateral, malignant nodules in the non-primary lobe were considered metastatic disease in the 6th TNM classification. Again, in the IASLC database these patients had a significantly better prognosis than the other patients with distant metastases. For this reason they are reclassified as T4 disease in the new 7th edition [17].

In contrast, patients with malignant pleural effusion were included in the T4 subdivision in the 6th TNM classification. Although attempts have been made to perform a complete resection by pleuropneumonectomy, overall results are poor. In the 7th edition malignant pleural effusion is included in the new M1a subcategory together with contralateral malignant nodules [35].

Generally, patients with stage IIIB-N3 disease are treated by combined chemoradiotherapy and are not candidates for surgical resection [36]. In the SWOG 8805 trial selected patients with stage IIIA-N2 and stage IIIB-T4 N3 underwent induction chemoradiotherapy followed by surgical resection when there was no progressive disease on chest CT scan [37]. There was no survival difference between stages IIIA and IIIB. The strongest predictor of long-term survival was absence of tumour in the mediastinal nodes. Therefore, in case of N3 disease, an intervention can only be considered when mediastinal downstaging is proven by minimally invasive or invasive techniques, which represents a rather exceptional situation.

Pancoast or superior sulcus tumours with clinical T4 characteristics such as Horner's syndrome, invasion of brachial plexus or vertebral bodies, are very challenging. They represent a particular entity as significant downstaging can be obtained by induction chemoradiotherapy. Also, patients with stable disease should undergo thoracotomy as pathological downstaging can be observed without any clinical response on chest CT scan due to necrosis developing inside these tumours. In a series of 110 patients including T3–4N0–1 superior sulcus tumours (SWOG 9416 trial) induction chemoradiation consisted of two cycles of cisplatin and etoposide given concurrently with 45 Gy of radiotherapy, followed by surgical resection in case of clinical response or stable disease [38]. Postoperatively, two more cycles of chemotherapy were administered. Five-year survival rate for all patients was 44%, and even 54% for those patients who had a complete resection, without any significant difference between T3 and T4 tumours.

Conclusion

The role of surgery in stage IIIA-N2 non-small cell lung cancer (NSCLC) remains controversial. Most important prognostic factors are mediastinal downstaging and complete surgical resection. Different restaging techniques exist to evaluate response after induction therapy. In contrast to imaging or functional studies, remediastinoscopy provides pathological evidence of response after induction therapy. An alternative approach consists of the use of minimally invasive staging procedures as endobronchial or endoscopic oesophageal ultrasound to obtain initial proof of mediastinal nodal involvement. Mediastinoscopy is

subsequently performed after induction therapy to evaluate response.

Stage IIIA-N2 NSCLC represents a heterogeneous spectrum of locally advanced disease and different subsets exist. When N2 disease is discovered during thoracotomy after negative, careful preoperative staging, a resection should be performed if this can be complete. Postoperative radiotherapy will decrease local recurrence rate but not overall survival. Adjuvant chemotherapy increases survival and is presently recommended in these cases. Most patients with pathologically proven, potentially resectable N2 disease detected during preoperative work-up will be treated by induction therapy followed by surgery or radiotherapy. Surgical resection may be recommended in those patients with proven mediastinal downstaging after induction therapy who can preferentially be treated by lobectomy. Unresectable, bulky N2 disease is mostly treated with combined chemoradiation.

In stage IIIB primary surgical resection is only rarely indicated. However, in selected cases, long-term survival can be obtained after complete resection which remains a major prognostic factor.

Conflict of interest statement

None declared.

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