· N2 Lung Cancer Special Topic ·

Is there a role for surgery in stage ⅢA–N2 non–small cell lung cancer?

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【**Abstract**】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 and these are subdivided into non–invasive, invasive and alternative or minimally invasive techniques. In contrast to imaging or functional studies, remediastinoscopy provides pathological evidence of response after induction therapy. Although technically more challenging than a first procedure, remediastinoscopy can select patients for subsequent thoracotomy and provides prognostic information. An alternative approach consists of the use of minimally invasive staging procedures as endobronchial or endoscopic esophageal ultrasound to obtain an initial proof of mediastinal nodal involvement. Mediastinoscopy is subsequently performed after induction therapy to evaluate response. In this way, a technically more difficult remediastinoscopy can be avoided. Stage ⅢA–N2 NSCLC represents a heterogenous 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 N2 disease detected during preoperative work–up will be treated by induction therapy followed by surgery or radiotherapy. In two large, recently completed, phase Ⅲ trials there was no difference in overall survival between the surgical and radiotherapy arm, but in one trial there was a difference in progression–free survival in favor of the surgical arm. In the surgery arm the rate of local recurrences was also lower in both trials. Surgical resection may be recommended in those patients with proven mediastinal downstaging after induction therapy who can preferentially be treated by lobectomy. Pneumonectomy has a significantly higher mortality and morbidity rate, especially after induction chemoradiotherapy. Patients with bulky N2 disease are mostly treated with combined chemoradiotherapy although the precise treatment scheme has not been determined yet.

【**Key words**】Lung neoplasms Neoplasm staging Induction therapy Mediastinoscopy Postoperative Intraoperative compliations

Introduction

Precise evaluation and management of stage ⅢA–N2 non–small cell lung cancer (NSCLC) remains controversial. This not only relates to the role of surgery and radiotherapy as locoregional treatment but also to the precise response evaluation after induction therapy, so–called restaging. In this manuscript the different restaging techniques which are currently used, are described. Afterwards, the combined modality therapy of stage ⅢA–N2 NSCLC is reviewed focussing on two large phase Ⅲ randomized trials which were recently completed. The role of surgery in the different subsets of N2 involvement is discussed.

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1 Restaging after induction therapy

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 not benefit from surgical resection[1-3]. So, precise restaging after induction chemotherapy or chemoradiotherapy is of utmost importance to determine subsequent treatment and prognosis. Different restaging methods are available.

There are listed in Tab 1 and can be subdivided into noninvasive, invasive and minimally invasive or alternative techniques.

Noninvasive imaging techniques such as computed tomography (CT) and also magnetic resonance imaging are not accurate enough for mediastinal restaging. In a study of 24 patients who underwent restaging by repeat mediastinoscopy (reMS), sensitivity of chest CT was found to be only 41% with an accuracy of 58%[4].

Positron emission tomography (PET) provides additional metabolic information, but there are conflicting data regarding its use. PET has been shown to be more accurate in predicting the T factor than the N status[5]. In a prospective study including 25 patients with NSCLC treated by induction chemotherapy, positive predictive value of PET to detect persisting nodal disease was 73%, but below 20% for residual N2 disease[6]. Unfortunately, downstaging of the latter nodes is of major interest to determine subsequent treatment and prognosis.

Although experience is rather limited, integrated CT-PET combining precise anatomical and functional information seems to be more accurate for restaging. In a prospective study of 30 patients the accuracy of CT-PET was 83% that was significantly better than reMS[7]. However, sensitivity of reMS in this study was much lower than reported in other series[8]. In a large prospective study of 93 patients who were restaged by chest CT and integrated CT-PET after induction chemoradiotherapy, repeat CT-PET was found to be more accurate than CT alone for all pathological stages[9]. However, there were 20% false-negative and 25% false-positive cases with repeat CT-PET. In case of suspicion of residual mediastinal disease, nodal biopsies are still required[9]. This underscores the continuous role of minimally invasive and invasive restaging procedures.

Results of recent series of reMS after induction therapy are summarized in Tab 2[3,7,10-14]. In all series sensitivity of reMS was at least 60%, except for the prospective study of De Leyn *et al*. comparing reMS to integrated CT-PET scanning[7]. This low sensitivity is largely explained by the fact that in 20 patients (67%) no adequate biopsies of the subcarinal lymph node station No.7 could be taken.

Recently, we were able to show that survival depends on

Tab 1 Techniques for mediastinal restaging

Noninvasive	Invasive	Alternative, minimally invasive
computed tomography (CT)	redo, second or repeat mediastinoscopy (reMS)	transthoracic fine-needle aspiration biopsy (FNAB)
magnetic resonance imaging (MRI)	video-assisted thoracic surgery (VATS)	transbronchial needle aspiration (TBNA)
positron emission tomography (PET)		endobronchial ultrasound with FNAB (EBUS)
integrated CT-PET		endoscopic esophageal ultrasound with FNAB (EEUS)

Tab 2 Results of remediastinoscopy after induction therapy

Author, year	Ref.	*n*	IT	Morbidity (%)	Mortality (%)	Sensitivity (%)	Specificity (%)	Accuracy (%)
Pitz, 2002	11	15	CT	0	0	71.4[d]	100	87
Rami-Porta, 2003	12	24[a]	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	7	30	CT	0	0	29	100	60
De Waele, 2007[b]	13	104	CT (*n*=79) CT-RT (*n*=25)	3.9	1	70	100	80
Marra, 2008[c]	14	104	CT-RT	1.9	0	61	100	88

[a] time period 1999-2003 (total series 48 patients); [b] combined, updated series; [c] subset of patients of ref [10]; [d] negative predictive value

Ref.: reference; *n*: number of patients; IT: induction therapy; CT: chemotherapy; CT-RT: chemoradiotherapy

the findings of reMS, for 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[13].

The largest series of reMS was reported by Stamatis *et al*. In 2005, which described a total of 279 reMS[10]. In a subset of 104 patients who underwent reMS after induction chemoradiotherapy for stage ⅢA–B NSCLC, results were similar to other series[14]. 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 Leukemia group B (CALGB), 70 patients with stage ⅢA–N2–NSCLC underwent restaging by VATS[15]. Sensitivity in this series was 75%, specificity 100% and negative predictive value 76%.

Minimally invasive techniques comprise promising staging modalities and are increasingly used for lung cancer staging and also restaging (Tab 1). However, false–negative rates between 20% and 30% have been reported. Mediastinal restaging was performed by endoscopic esophageal ultrasound (EEUS) after induction chemotherapy in 19 patients with proven N2 NSCLC[16]. There were no complications and patients with N0 disease underwent resection. Accuracy of EEUS in this setting was 83%; so, EEUS with needle aspiration might play a role in mediastinal restaging[16]. 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%[17]. Recent experience with CT–PET, EEUS and EBUS is summarized in Tab 3.

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[18]. A correct diagnosis was obtained in 71% of patients and more invasive procedures could be avoided in 35%.

For thoracic surgeons having no experience with reMS, an alternative approach consists of the initial use of minimally invasive staging procedures as TBNA, EBUS or EEUS to obtain a cytological proof of mediastinal nodal involvement[19]. 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[20]. 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 utilized, the precise choice depending on the availability of the technique and expertise of the centre[20].

2 Bulky N2: a case report

To introduce the controversial management of pathologically proven stage ⅢA–N2 disease a patient is presented in whom an impressive downstaging was observed.

A 54–year–old Caucasian female patient was investigated because of chronic cough, pain in the right hemithorax and weight loss of 3 kg. She had never smoked. History revealed a hysterectomy and bilateral ovariectomy for a stage IA ovarian cancer. CEA value was 0.8 mg/mL. Chest X–ray and CT scan showed a large tumor in the right upper lobe with bulky N1 and N2 disease (Fig 1, 2). On bronchoscopic biopsies no definite diagnosis was obtained. Screening for distant metastases

Tab 3 Recent experiences with CT–PET, EEUS and EBUS after induction therapy

Author, year	Ref.	Technique	*n*	Sensitivity (%)	Specificity (%)	Accuracy (%)
De Leyn, 2006	7	CT–PET	30	77	92	83
Cerfolio, 2006	9	CT–PET	93	62	88	79
Annema, 2003	16	EEUS	19	75	100	83
Krasnik, 2006	17	EBUS	83	70	100	75

CT–PET: computed tomography–positron emission tomography; EEUS: endoscopic esophageal ultrasound; EBUS: endobronchial ultrasound; Ref.: reference; *n*: number of patients

was negative. Mediastinoscopy showed ipsilateral nodal involvement of the pre-, paratracheal and tracheobronchial lymph nodes by a large cell carcinoma, clinical stage ⅢA-N2. Patient was treated with 3 cycles of induction chemotherapy consisting of cisplatin and vindesine.

On postinduction chest X-ray and CT scan a partial response was noted in the primary tumor and a complete response in the hilar and mediastinal lymph nodes (Fig 3, 4). Remediastinoscopy was negative. Subsequently, by right thoracotomy an extrapleural lobectomy of the right upper lobe was performed together with a systematic nodal dissection. A complete resection was obtained. Pathological examination showed a complete response as well in the primary tumor as in the hilar and mediastinal lymph nodes. After a follow-up of 9 years patient remains in complete remission without any sign of local recurrence or distant metastases. This exceptional case demonstrates that the biological behavior of a locoregionally advanced lung cancer remains difficult to predict but determines outcome.

3 Role of surgery in stage ⅢA-N2 NSCLC

Stage ⅢA-N2 NSCLC represents a heterogeneous spectrum of locally advanced disease. N2 disease implies ipsilateral mediastinal or subcarinal lymph node involvement. A lot of descriptors exist for N2 disease and these are listed in Tab 4. There is no real consensus about the precise definitions. Usually, N2 involvement is subdivided into unexpected N2 discovered at thoracotomy, N2 proven at preoperative staging which is potentially resectable, and unresectable, bulky N2[21].

3.1 Unexpected N2 When N2 disease is discovered during thoracotomy after negative careful preoperative staging a resection should be performed if this can be complete. This implies that all resection margins are free of tumor and the highest mediastinal node is negative.

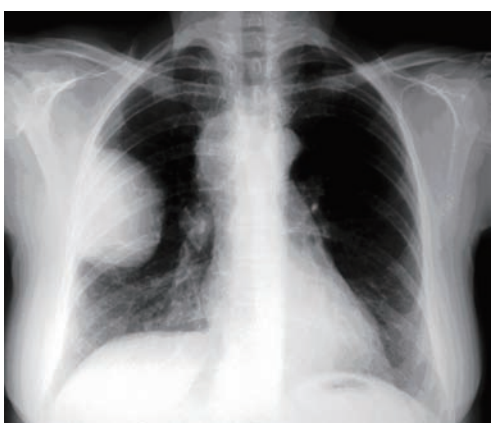

Fig 1 Chest radiograph showing large tumor in the right upper lobe with clearly enlarged mediastinal shadow

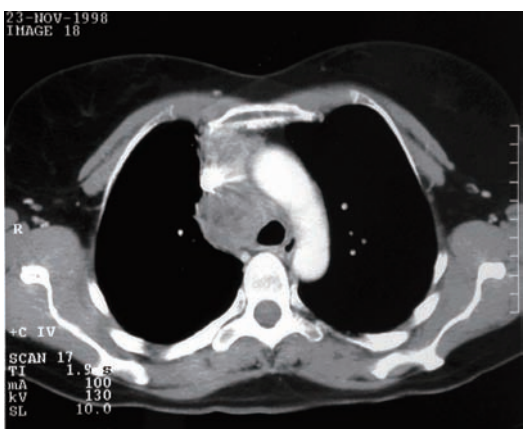

Fig 2 Chest CT scan demonstrating bulky N2 disease

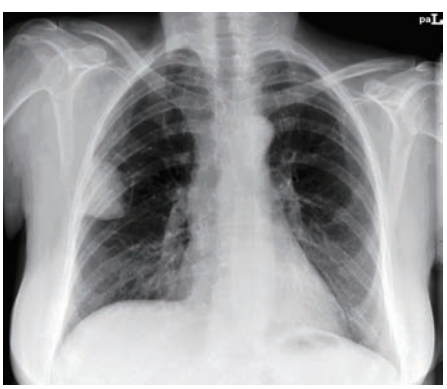

Fig 3 Chest radiograph after induction therapy showing partial response in the primary tumor with central necrosis

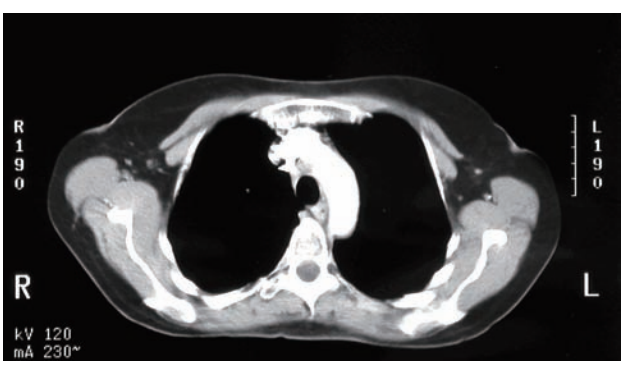

Fig 4 On postinduction chest CT there was a complete radiological response in the mediastinum

Tab 4 Different descriptors of N2 involvement

unexpected, minimal, bulky (> 2 cm)
technically resectable, marginally resectable, unresectable
biologically operable–inoperable
single–, multi–level disease
intra–, extracapsular involvement

In a recent paper unexpected N2 was also called "surprise" N2 and the necessity of careful preoperative staging was emphasized[22]. During thoracotomy a systematic nodal dissection should be performed to obtain a precise pathological staging. In case of unexpected N2 postoperative radiotherapy will decrease local recurrence rate but not overall survival. Adjuvant chemotherapy increases survival and is presently recommended in these cases[21].

3.2 N2 proven at preoperative staging 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 tumors is aimed at, 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 reports it is clear that surgery is feasible after induction therapy for locally advanced NSCLC, but is often more complex and carries a higher risk, especially when a right pneumonectomy has to be performed[23]. Prognostic factors include complete tumor resection and chemotherapy activity consisting of clinical, pathologic response and mediastinal downstaging[24].

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 randomized trials which were recently completed.

In the Intergroup 0139 trial which was only published in abstract form until now, patients with proven stage ⅢA–N2 NSCLC were randomized between a full course of chemoradiotherapy and induction chemoradiotherapy + surgery[25,26]. There was no significant difference in overall survival between both arms. However, there was a difference in progression–free survival favoring 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 EORTC 08941 phase Ⅲ trial, patients with proven stage ⅢA–N2 disease were randomized between surgery and radiotherapy after a response to induction chemotherapy[27,28]. There was no difference in overall and progression–free survival between 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 Tab 5. So, 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[29].

In the recent guidelines of the American College of Chest Physicians surgical resection for preoperatively proven stage ⅢA–N2 NSCLC is only considered as part of a clinical trial but these guidelines are only based on the abstracts of both studies[21].

3.3 Unresectable, bulky N2 The case of bulky N2 we presented has to be considered as very exceptional but it clearly shows that response to induction chemotherapy is essential for long–term survival. The majority 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[21]. However, the optimal

Tab 5 Comparison of EORTC 08941 with INT 0139 trial

	EORTC 08941			INT 0139		
induction therapy	chemotherapy			chemoradiotherapy		
complete resection*	50.0%			71%		
exploratory thoracotomy	13.6%			4.5%		
rate of pneumonectomy	46.8%			32.9%		
ypN0/1/2	N0/1	41.4%		N0	46%	
	N2	55.8%		N1–N3	54%	
ypT0N0	5.2%			14.4%		
30–day mortality						
overall	3.9%			5%		
lobectomy	0%			1%		
pneumonectomy	6.9%	R 5.3%		26%	R simple 29%	
		L 9.1%			R complex 50%	
					L simple 0%	
					L complex 16%	
exploratory thoracotomy	4.8%			0%		
90–day mortality	8.7%			NA		
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%		RT 22%	surgery 10%	
		P=0.001			*P*=0.002	
5–year survival						
lobectomy	27%			36%		
pneumonectomy	12%	*P*=0.009		22%		
ypN0/1/2	N0/1	29%		N0	41%	
	N2/3	7%	*P*=0.0009	N1–3	24%	*P*<0.0001

*definition was different in the two trials (INT 0139: macroscopic complete resection, EORTC 08941 also microscopic) RT = radiotherapy; NA = not available

treatment scheme has not been determined yet.

In conclusion, surgical resection for stage ⅢA–N2 disease is indicated in patients with unexpected N2 disease discovered at thoracotomy when a complete resection can be obtained, and in those patients with proven N2 disease discovered during preoperative work–up who have a proven mediastinal downstaging after induction therapy and who can preferentially be treated by lobectomy.

Conflict of interest statement

None of the authors has to disclose a conflict of interest.

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