Review Article

Heterogeneity of stage IIIA non-small cell lung cancer—different tumours, different nodal status, different treatment, different prognosis: a narrative review

Dominik V. Flury[1]^, Fabrizio Minervini[2], Gregor J. Kocher[1]

[1]Department of Thoracic Surgery, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland; [2]Department of Thoracic Surgery, Kantonsspital Luzern, Lucerne, Switzerland

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Correspondence to: Gregor J. Kocher. Division of General Thoracic Surgery, Department of Thoracic Surgery, Inselspital, Bern University Hospital, University of Bern, 3010 Bern, Switzerland. Email: gregor.kocher@insel.ch.

Abstract: Stage IIIA non-small cell lung cancer (NSCLC) consists of a heterogeneous group of disease, ranging from small T1a tumours with ipsilateral mediastinal lymph node involvement over T3 tumours with chest wall invasion, up to T4 tumours with mediastinal invasion with or without positive hilar lymph nodes. Based on this heterogeneity, treatment approaches as well as prognosis are very dependent on specific subgroups. Therapy recommendations should be based on multidisciplinary case discussions in high volume centres including medical and radiation oncologists, pneumologists and experienced thoracic surgeons specialized in thoracic cancer surgery. Recommendations may differ from standards in highly selected cases. Therefore, independent of age, in medically fit (operable) patients with resectable stage IIIA tumours, an aggressive approach in a curative setting is key to obtain good overall survival rates. Moreover, maintaining quality of life is essential. In this narrative review, the different aspects of all the subgroups of stage IIIA NSCLC and their heterogeneity as well as the variety of treatment modalities, their combined treatment approaches and survival rates are discussed. Again, the reported 5-year survival rates, ranging from 5% in patients with bulky N2 disease, up to 50% for patients with superior sulcus tumours with hilar lymph node disease, reflect the heterogeneity of stage IIIA NSCLC.

Keywords: Non-small cell lung cancer (NSCLC); stage IIIA; multimodal therapy

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Introduction

Lung cancer is one of the most common cancers (1) and by far the leading cause of cancer deaths worldwide with a 5-year survival rate of approximately 19%, including both non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) (2). According to the WHO classification, lung cancer is divided into two major types based on its molecular characterization, therapy and prognosis, comprising about 95% of all lung cancers. These two groups are NSCLC and SCLC. The remaining 5% are other cell types (2,3).

Stage IIIA TNM classification, pre-treatment evaluation and prognosis

To stage lung cancer, the current eighth edition of the

^ ORCID: 0000-0002-5829-4692.

Table 1 Lung cancer stage grouping (eighth edition) (4): TNM-constellation for stage IIIA is highlighted

T and M	N0	N1	N2	N3
T1			IIIA	
T2			IIIA	
T3		IIIA		
T4	IIIA	IIIA		
M1				

TNM, tumor, node, metastasis.

Tumor, Node, Metastasis (TNM) classification is used (4). The TNM staging system combines patients with differences in extent and localization of the primary tumour with patients with ipsilateral peribronchial, hilar or mediastinal lymph node metastasis to create the highly heterogeneous group of stage IIIA NSCLC (*Table 1*). Reported 5-year overall survival rates are 36% for clinical stage IIIA and 41% for pathologic stage IIIA disease (4-6).

Adequate staging using contrast-enhanced CT scan of the chest and upper abdomen followed by a positron emission tomography (PET) scan is indicated in order to rule out extrathoracic, extracranial metastasis and assess a potential mediastinal lymph node involvement. Evaluation of possible existence of brain metastasis by contrast-enhanced brain magnetic resonance imaging (MRI) is also recommended for patients with stage IIIA NSCLC, especially in those who could potentially receive treatment in a curative intent (7-12). In patients with sulcus superior tumours a thoracic MRI for evaluation of the thoracic inlet with vascular, brachial plexus or vertebral invasion is recommended. In these T3-4 sulcus superior tumours, exclusion of mediastinal lymph node involvement or metastatic disease is particularly important, because these tumours would then be classified as stage IIIB or IV, where resection is contraindicated (13).

Assessment of the nodal status is an exceedingly important component in pre-treatment evaluation because it will highly affect the individual treatment plan. Based upon enlargement in the CT scan or FDG-avidity in the PET scan, hilar and especially mediastinal node involvement should be pathologically confirmed (7-12). This can be done using minimally invasive endoscopic techniques such as endoscopic ultrasound fine needle aspiration (EUS-FNA) and endobronchial ultrasound with transbronchial needle aspiration (EBUS-TBNA) (14-19). Consequently, performing a mediastinoscopy is appropriate and recommended by many authors for patients with T2 to T3 lesions even if the CT scan or/and the PET scan do not suggest a mediastinal lymphadenopathy and despite a previous negative EBUS-TBNA (7,9,12,20,21). However, in already assumed cN2 disease and if complete resection is anticipated, the necessity of an additional invasive pathological confirmation is questioned by some authors and remains controversial (22).

Pathologic confirmation of diagnosis and complete staging are essential in treatment evaluation of stage IIIA disease. After the clinical evaluation and when tumour stage is determined, a multidisciplinary evaluation should be done to assign the patient to one of the treatment pathways according to TNM stage, location of the tumour and cardiopulmonary fitness as well as patient performance status regardless of age (7-12).

Based on the heterogeneity of stage IIIA and especially regarding mediastinal nodal involvement, many aspects of therapy have not clearly been defined and recommendations overall remain controversial.

Significance of available data is often limited. For example, considering the redefinition of stage IIIA disease over time, the included heterogeneous patient populations or missing randomization in available trials and the limited follow-up duration together with major changes in staging and therapy modalities, it is difficult to generally apply these results in clear treatment recommendations.

The histopathologic cell type together with the TNM classification and the disease stage have the biggest impact on prognosis. As Asamura *et al.* reported, nodal status is considered one of the most reliable prognostic indicators in patients with lung cancer. The number of involved nodes as well as their distribution have a significant impact on prognosis. The difference between separate nodal categories also significantly differs between the clinical (cN) and the pathological (pN) N status. For the subgroups of pN status, single-station N2 metastasis without N1 involvement or skip N2 (N2a1) had numerically a better prognosis than multiple-station N1 involvement (N1b), but results were not statistically significant. N1b status and single station N2 with N1 involvement (N2a2) had overlapping survival curves. The 5-year survival rates according to the cN and pN status were 60% and 75% for N0, 37% and 49% for N1, 23% and 36% for N2, and 9% and 20% for N3 nodal disease, respectively (23-26). For complete resected N1-2 disease, reported 5-year survival rates were as follows: 59% in N1a, 50% in N1b, 54% in N2a1, 43% in N2a2 and 38% in N2b involvement (23).

Table 2 Stage IIIA NSCLC—treatment recommendations and prognosis for resectable tumours and operable patients

Tumour situation	T	N	M	Stage	Treatment recommendations		5-year survival rates
					No.	Content	
Resectable and operable	T1-2	N2	M0	*$IIIA_1$ & $IIIA_2$	1	Surgery and adjuvant CTx	14–44% (30-35)
					Add.	Adjuvant RTx	
	T1-2	N2	M0	*$IIIA_3$ & $IIIA_4$	1	Neoadjuvant CTx and surgery	See above, but lower for multi-level N2 (7-9,26,34,36,37), down to 2–5% for bulky N2 (10)
					2	Surgery and adjuvant CTx	
					Add.	Adjuvant RTx	
					3	Definitive concurrent CRTx	
	T3	N1	M0	IIIA	1	Concurrent neoadjuvant CRTx and surgery	20–40% after R0 resection (13,38-43)
					2	Surgery and adjuvant CTx	
					Add.	Adjuvant RTx	
	$T3_{Satell}$	N1	M0	IIIA	1	Surgery	Approx. 40% (44)
					Add.	Adjuvant CTx	
	T3-4 SST	N1	M0	IIIA	1	Concurrent neoadjuvant CRTx and surgery	Approx. 50% (13,44-58)
					2	Surgery and adjuvant CTx	
					Add.	Adjuvant RTx	
	T4	N0	M0	IIIA	1	Concurrent neoadjuvant CRTx and surgery	Approx. 25% (**)
					2	Surgery and adjuvant CTx	
					Add.	Adjuvant RTx	
	$T4_{Ipsi\ Nod}$	N0	M0	IIIA	1	Surgery	Up to 40% (44)
					Add.	Adjuvant CTx	
	T4	N1	M0	IIIA	1	Concurrent neoadjuvant CRTx and surgery	Approx. 25% (**)
					2	Surgery and adjuvant CTx	
					Add.	Adjuvant RTx	
	$T4_{Ipsi\ Nod}$	N1	M0	IIIA	1	Surgery	Approx. 30% (44)
					Add.	Adjuvant CTx	

*, Robinson classification; **, T4 tumours with invasion ($T4_{Inv}$) of: mediastinum (53,59-62), diaphragm (63-68), heart and great vessels (60), left atrium and pulmonary veins (13,69-84), SVC (13,53,69,78,83-96), inferior vena cava (83), pulmonary artery (53,70,84,97,98), aorta (13,69,81,84,88,99-104), recurrent laryngeal nerve (70), carina and trachea (13,38,53,70,84,105-110), esophagus (53,70), vertebral bodies and spine (13,38,57,58,111-119). NSCLC, non-small cell lung cancer; CTx, chemotherapy; RTx, radiotherapy; CRTx, chemoradiotherapy; add., additionally; SST, sulcus superior tumours; SVC, superior vena cava.

Another important clinical parameter is the performance status (26-29). There is no standard approach in patients with poor performance status who are high risk candidates for a multimodality treatment and individual therapy recommendations should be formed by a multidisciplinary board.

Whenever feasible, patients with stage IIIA NSCLC are treated with a curative intent using a combined approach of two or more of the following modalities: surgery, chemotherapy, radiotherapy and in case of unresectable stage IIIA disease, added immunotherapy may be beneficial in highly selected cases (7-12). We present the following article in accordance with the Narrative Review reporting checklist (available at https://ccts.amegroups.com/article/view/10.21037/ccts-20-97/rc).

Therapy recommendations and prognosis are

Table 3 Stage IIIA NSCLC—treatment recommendations for unresectable tumours and/or inoperable patients

Tumour situation	T	N	M	Stage	Treatment recommendations	
					No.	Content
Unresectable and/or inoperable	T1	N2	M0	IIIA	1	Concurrent CRTx
					2	Sequential CTx with definitive RTx
					3	RTx alone
					Add.	Consolidation therapy with durvalumab, if no tumour progression
	T2	N2	M0	IIIA	1	Concurrent CRTx
					2	Sequential CTx with definitive RTx
					3	RTx alone
					Add.	Consolidation therapy with durvalumab, if no tumour progression
	T3	N1	M0	IIIA	1	Concurrent CRTx
					2	Sequential CTx with definitive RTx
					3	RTx alone
					Add.	Consolidation therapy with durvalumab, if no tumour progression
	T4	N0	M0	IIIA	1	Concurrent CRTx
					2	Sequential CTx with definitive RTx
					3	RTx alone
					Add.	Consolidation therapy with durvalumab, if no tumour progression
	T4	N1	M0	IIIA	1	Concurrent CRTx
					2	Sequential CTx with definitive RTx
					3	RTx alone
					Add.	Consolidation therapy with durvalumab, if no tumour progression

NSCLC, non-small cell lung cancer; CTx, chemotherapy; RTx, radiotherapy; CRTx, chemoradiotherapy; add., additionally.

summarized in *Tables 2,3*.

Methods

To determine the current clinical evidence of evaluation and management of NSCLC, we searched two electronic databases (PubMed and the Cochrane Library) for articles from 1988 to March 2020 as well as the most recent guidelines in English and German language. Date of last search was March 14, 2020.

The rarity of advanced T-stages and the heterogeneity of these subgroups making randomised controlled trials nearly impossible. Therefore, regarding the limited data published, we also included multiple case series to identify survival rates and outcome of specific heterogenous subgroups of stage IIIA disease.

We checked cross-references and searched references from all the mentioned guidelines, review articles and published series. The articles included were assessed for eligibility by the three authors.

Therapeutic approaches

After complete staging and prior to definitive therapy it is strongly recommended to determine the resectability of the tumour, the extent of pulmonary resection and the operability of the patient according to pre- and postoperative pulmonary function and concurrent comorbidities in a multidisciplinary tumour board (7-11,13,120,121). If this board deems that even after

induction therapy a complete resection (R0) of the tumour is not possible, surgery should not be attempted and concurrent chemoradiotherapy offers the most beneficial treatment option for this subgroup of stage IIIA disease (7-9,122-128).

In patients with stage I and II disease, radical and anatomical surgical resection provides the best long-term survival. For stage IIIA disease and medically operable patients with resectable tumours, surgery may be appropriate for carefully selected cases in a combined-modality treatment approach, even in locally advanced tumours with chest wall involvement, in sulcus superior tumours or T4 with mediastinal organ invasion (7-11,13).

The extent of anatomical pulmonary resection depends on cardiopulmonary reserve and extent of disease. In T1a and T1b tumours before staged as $IIIA_1$ and $IIIA_2$, sublobar resection with either segmentectomy or even wedge resection (patients with poor pulmonary reserve or major comorbidities with contraindication for lobectomy) is appropriate (7,129-134). For tumours >2 cm (T1c-T4) lobectomy or pneumonectomy should be considered if allowed by cardiopulmonary function and medical comorbidities, and whenever possible, lung-sparing anatomical resection such as sleeve lobectomy should be performed, rather than pneumonectomy (7,9,129).

Besides pulmonary resection hilar and mediastinal lymphadenectomy plays a key component in lung cancer surgery (7-11,13). It is controversial whether complete mediastinal lymph node dissection (MLND) or mediastinal lymph node sampling (MLNS) is the preferred approach. Current evidence suggests that MLND adds a small to moderate improvement in survival compared to MLNS (10,135-137). In case of MLNS, a minimum of three hilar and three mediastinal stations should be sampled and if there is N2 nodal involvement in stage $IIIA_3$ or in selected cases of $IIIA_4$ (e.g., multi-level), radical MLND is clearly indicated to achieve a complete resection (4,7).

In all patients with stage IIIA disease pre- or postoperative chemotherapy and/or radiation therapy should be considered (7-11,13). Radiotherapy as another local therapeutic modality in stage IIIA disease is mostly performed in a combined setting together with resection in a curative intent (neoadjuvant chemoradiotherapy, adjuvant radiotherapy). It is also used as either definitive therapy combined with chemotherapy for locally advanced disease or in unresectable tumours, medically inoperable patients or even those patients who refuse surgery. The goals of local radiotherapy are to maximize tumour control and to minimize toxicity of treatment (7-12,138-141). In patients with stage IIIA disease, prophylactic cranial radiotherapy is not recommended (8,142,143).

Treatment approaches according to subgroups

Stage IIIA N2 NSCLC

The subgroup N2 of stage IIIA disease has a poor 5-year overall survival rate (30-32,144) and is divided into subsets according to the Robinson classification (145).

As Putora *et al.* showed, there is a lack of consensus in definition for resectable or limited N2 disease (144). The definition of nodal involvement varies across international guidelines and organizations, using categorizations of levels/stations (1 to 14) or nodal zones [supraclavicular, upper, aortopulmonary (AP), subcarinal, lower, hilar/interlobar and peripheral zone] (60). Especially for the term of bulky N2 no holistic definition exists and indication for surgery in stage IIIA bulky N2 remains highly controversial (38).

According to the NCCN Clinical Practice Guidelines in Oncology for NSCLC (7) single lymph nodes smaller than 3 cm can be considered for a multimodality approach that includes surgical resection, but the authors do not define bulky disease. While the National Cancer Institute (10) as well as the American College of Chest Physicians Evidence-Based Clinical Practice Guidelines for NSCLC (12) classify bulky disease involving multiple nodal stations as unresectable or a contraindication to surgery, the German guidelines S3-Leitlinie-Prävention, Diagnostik, Therapie und Nachsorge des Lungenkarzinoms (9) address, that patients might not benefit from surgery, but overall give no clear recommendation. The National Institute for Health and Care Excellence (NICE) Guidelines for lung cancer (11) and the European Society for Medical Oncology (ESMO) Clinical Practice Guidelines for early and locally advanced NSCLC (8) do not refer to bulky disease at all in their guidelines.

The INT 0139, ESPATUTE, EORTC 08941 trials and Decaluwé *et al.* compared neoadjuvant therapy plus surgery with other bimodality approaches including combinations of chemotherapy and radiotherapy and showed similar 5-year overall survival rates ranging from 14% to 44% (30-35). Decaluwé *et al.* also showed that there is no significant difference in 5-year survival in ypN1a compared to ypN2a1-2 (40.6% *vs.* 37%, P=0.89) as well as in ypN0-1a compared to ypN2a1-2 (49.1% *vs.* 37%, P=0.52). In a merged subgroup of ypN0, ypN1a and ypN2a1-2 compared to ypN2b alone the 5-year survival rates significantly differed

(43.4% *vs.* 0%, P<0.0005), the same for the comparison of the same merged subgroup with ypN2b-3 (43.4% *vs.* 7.1%, P<0.001), emphasizing the prognostic impact of mediastinal nodal involvement of multiple levels (34).

Resected tumours in patients with mediastinal downstaging following neoadjuvant therapy as well as a highly selected cases of persistent N2a1-2 disease show a satisfying survival with 5-year survival rates around 30% (34,36,146-148), surprisingly up to 42% (148) in case of complete or R0 resection in persistent N2a1-2 disease. Non-responders have a disappointing survival.

Radiotherapy compared to surgery after induction or neoadjuvant chemotherapy offers similar survival benefits in patients with resectable stage IIIA tumours (31).

T1-2 N2 recognized by staging prior to resection (Robinson IIIA$_3$)

This subgroup contains T1 and T2 tumours with single or multiple non-bulky N2 disease diagnosed by complete staging prior to any therapy.

If there is N2a1 or N2a2 status in stage IIIA$_3$ in medically operable patients with resectable tumours, combined modality treatment approaches are appropriate. Corresponding approaches are resection followed by adjuvant chemotherapy, neoadjuvant chemotherapy followed by surgery and optional radiation therapy or even potentially neoadjuvant chemoradiotherapy (38,149,150).

In resectable tumours, surgery improves long-term survival and is the preferred treatment (34,36). Especially in patients with response due to (neoadjuvant or induction) chemotherapy (26,36). As long as feasible, radical anatomical resection is recommended but indication for pneumonectomy after neoadjuvant chemoradiotherapy is controversial but might be appropriate in carefully selected patients (30,151-157). Adjuvant radiotherapy following complete resection with MLND should be discussed (9).

Neoadjuvant chemotherapy may accomplish a reduction in tumour size, making resection more feasible and eradicate micrometastatic disease. Neoadjuvant chemotherapy also significantly improves overall survival, time to distant recurrence and recurrence-free survival (26,158-165). A combined neoadjuvant chemoradiotherapy may achieve nodal clearance, therefore, being appropriate in highly selected cases (T3 or T4 tumours), but indication remains controversial in T1-2 N2 disease (13,26,149,151,165-168). There is minimal risk of additional surgical complications following neoadjuvant chemoradiotherapy (49,146,169-173).

Data and results comparing adjuvant versus neoadjuvant chemotherapy in early and locally advanced disease are controversial. Recommendations on timing of chemotherapy varies, but some studies suggest that neoadjuvant chemotherapy is better tolerated than adjuvant chemotherapy and compliance to treatment is higher (26,129,159,160,174-181). An explanation for this might be the comorbidities and/or an incomplete recovery after surgery, overall making it difficult for these patients to tolerate additional adjuvant chemotherapy (182). Because of the heterogeneity of N2 disease included in studies, it is even more difficult to account whether neoadjuvant or adjuvant chemotherapy is superior in these patients.

Reevaluation after neoadjuvant treatment including restaging is important for prognosis. Patients with good therapy response and disease regression with negative lymph nodes (hilar and especially mediastinal) documented in the PET scan have a better survival (34,183). Additionally, downstaging of N2 status could be pathologically evaluated to be confirmed after negative PET scan in restaging. But some authors postulate that as long as progressive disease was excluded and the tumour deemed resectable prior to neoadjuvant treatment there is no consequence of an additional or even initial invasive mediastinal restaging (mediastinoscopy or EBUS/EUS) if complete resection is anticipated, especially because false negative rates can be up to 25% (mediastinoscopy) or 15% (EBUS/EUS), respectively (22,184). Progressive disease after neoadjuvant therapy should not be considered for surgery. Therefore, local radiotherapy with or without systemic therapy might be discussed (7-11,13,26).

Multi-level IIIA$_3$ and IIIA$_4$

In stage IIIA$_4$ or if there is N2b (multi-level) lymph node involvement in stage IIIA$_3$ in medically operable patients with resectable tumour, definitive concurrent chemoradiotherapy is the preferred approach, but surgery might be still an option in carefully selected patients (7-9,34,36,37). In resectable stage IIIA$_3$ or potentially stage IIIA$_4$ disease radical *en-bloc* resection following neoadjuvant chemotherapy can be an appropriate strategy (7-9,34,36).

After neoadjuvant chemoradiotherapy, regression of the primary tumour and mediastinal downstaging are independent prognostic factors for long term survival (9,34,36,37,185,186). Nevertheless, although persistence

of N2 nodes is present, the initial trimodality approach including surgery should be continued, as long as disease progression is excluded after restaging (34,36,187-189). The surgical approach is also appropriate in multi-level N2 involvement in highly selected cases, even if these cases are associated with lower 5-year survival compared to N2a1 or N2a2 disease (7-9,26,34,36,37).

Sensitivity and specificity as well as positive and negative predictive values of PET scan after neoadjuvant treatment is limited. Therefore, FDG-avidity in ycN2 nodes does not precisely correspond with ypN2 status and incorrect diagnosis through over- or even underdiagnosis may be provided (37,190). Hence, when a neoadjuvant setting is chosen and disease progression is excluded after restaging, proceeding with a radical resection even in case of persistent N2 disease is appropriate without invasive mediastinal re-evaluation (see also above) (22,184,191).

Bulky N2 disease at staging (Robinson IIIA$_4$)

In the heterogeneous group of N2 nodal disease, the term bulky N2 also received a heterogeneity of definitions, even among guidelines (7,9,12,144,192,193). It is mostly defined as mediastinal lymph nodes exceeding diameters of 3 or 2–3 cm. Bulky N2 is rarely evaluated separately as a subgroup of patients with N2 disease. Some authors reported a negative impact on survival (36,194), while international guidelines classify bulky disease as unresectable or even a contraindication for surgery. In these guidelines, patients mentioned to most likely benefit from surgery in IIIA N2 disease are those with single station N2 involvement and non-bulky lymph nodes, for other subgroups indication for surgery in a multimodality setting remains controversial and might be applicable in highly selected cases. Reported 5-year survival rates for bulky N2 disease are 2–5% (10).

Incidental or unforeseen N2 (Robinson IIIA$_1$ and IIIA$_2$)

This subgroup contains T1 and T2 tumours with N2 disease found macroscopically during resection or microscopically in frozen section analysis intraoperatively or in the final pathology examination of the resected specimen. In these patients, resection is mostly indicated because of clinical stage I or II NSCLC.

For completely resected stage IIIA$_1$ and stage IIIA$_2$ tumours, adjuvant chemotherapy significantly improves overall survival and remains the standard of care (195-205). If not given preoperatively, additional postoperative radiation therapy (PORT) in N2 disease may improve survival, but remains controversial and mostly optional (163,206-211). Adjuvant radiotherapy might be considered in selected patients to reduce the risk of local recurrence in multiple nodal station involvement, with performed MLNS in IIIA$_1$, extracapsular tumour spread or as described below, in positive resection margins (7-11,210,212). If chemoradiotherapy is used in a trimodality approach following surgery, radiotherapy should be performed sequentially after chemotherapy. Adjuvant radiotherapy is not recommended for stage I and II, because it has been shown to have a detrimental effect on long-term survival in these patients (203).

Incomplete resection, unresectable or inoperable stage IIIA N2 disease

In R1 resection, either sequential or concurrent chemoradiotherapy is recommended, whereas in R2 resection concurrent chemoradiotherapy is the recommended adjuvant approach. In R1 situation re-resection might be discussed, if feasible (7,9,213,214).

According to the prognostic impact of the R-status, survival of uncertain resection or R-classification ranges between that of R0 and R1 resected tumours (215).

In case surgery is not feasible based on inoperability or unresectable stage IIIA N2 tumours, these patients can be treated by definitive chemoradiotherapy without surgery (7-11,13,26).

T3 N1

Locally advanced tumours classified as T3 are 5 to 7 cm in size or directly invading the parietal pleura, the chest wall (including sulcus superior tumours), the phrenic nerve and/or the parietal pericardium. T3 also includes tumours with separate nodule(s) in the same lobe, which is discussed separately below. T3 tumours are potentially resectable even with present chest wall, pericardium or phrenic nerve invasion. Trials evaluating survival rates and outcome of this heterogeneous group often include T3$_{Satell}$ tumours with a much better survival, resulting in general survival rates with less validity for the whole group of stage IIIA T3 N1 disease. Isolated subgroups are described below.

Pericardial or phrenic nerve involvement

Resection of tumours with pericardial involvement with

subsequent net reconstruction is feasible in most of the cases. Same applies for phrenic nerve involvement with potential later phrenoplasty or phrenoplication if indicated. Inoue *et al*. reported 5-year survival rates of 43% for patients with T3 tumours and pericardium invasion (67).

Chest wall involvement

Depending on extent and location of the locally advanced tumours such as T3 N1 or even T4 N0-1 with either chest wall involvement or in sulcus superior tumours, which are potentially resectable, provided that a complete resection (R0) can be performed, a combined modality approach with concurrent neoadjuvant chemotherapy or chemoradiotherapy followed by radical *en-bloc* resection after multidisciplinary evaluation is recommended in selected cases. Complete resection followed by adjuvant chemotherapy with or without radiation is also appropriate in selected cases of tumours invading the chest wall, if not classified as sulcus superior tumours (7-9,13,216,217). Surgical planning and reevaluation after chemoradiotherapy have to be emphasized, regarding older reported complete resection rates of 64% and 39% in T3 N0 and T4 N0 tumours, respectively (218).

Survival of patients with stage IIIA NSCLC with T3 N1 tumours and chest wall invasion highly depends on completeness of resection and extent of nodal involvement. The depth of chest wall invasion is less important. Associated 5-year survival rates after R0 resection range from 20–40% for T3 N1 (13,38-43), whereas 5-year survival rates for T3 N2 does not exceed 10% (42).

Sulcus superior tumours

Sulcus superior tumours according to their extent can be classified as T3 (involvement of inferior branches of the brachial plexus such as C8 and/or T1) or as T4 if vertebral or spinal canal invasion, involvement of the subclavian vessels and/or brachial plexus (C8 and above) is present (60). Anatomical resection with at least a lobectomy following neoadjuvant chemoradiotherapy in selected patients offers the best survival benefit for these patients (13,219,220). Using such an aggressive curative and surgical approach in sulcus superior tumours in a trimodality setting can reach 5-year survival rates around 50% (44) up to nearly 80% after complete resection (57,58), with small up to no differences between T3 or T4 tumours. N0 or N1 status did not significantly affect overall survival in these trials, but mediastinal lymph node involvement is associated with poor survival after resection (13,44-56).

T4 N0-1

Tumours bigger than 7 cm in greatest dimension, lung cancer of any size invading one or more of the following: mediastinum, diaphragm, heart, great vessels, recurrent laryngeal nerve, carina, trachea, esophagus, vertebral body or tumours with additional nodule(s) in a different ipsilateral lobe are classified as the heterogenous group of T4.

There is only limited data regarding extended surgical resections of these subgroups of T4 tumours and there is no consensus in international guidelines which subgroups should be classified as unresectable. Even invasion of the carina and trachea, the left atrium, the superior vena cava (SVC), one or multiple vertebral bodies, the aorta or combination of these may allow resection as discussed below. However, only inconsistent data and small retrospective case series are reported for the specific subgroups (69). Same as for T3 tumours, in trials including patients with locally advanced or only stage IIIA disease, T4 tumours are summarized including $T4_{Ipsi\ Nod}$ resulting in survival rates that are much better than these reported for the specific subgroups described below.

Most of these patients with $T4_{Inv}$ tumours involving the structures mentioned above have positive mediastinal lymph nodes, making this entity of $T4_{Inv}$ N0-1 tumours a rarity. In general, these patients with locally advanced $T4_{Inv}$ are not considered good candidates for surgery. Therefore, these patients should be discussed in multidisciplinary boards after completed staging with a careful indication for surgery with only a subset of patients being candidates with a beneficial outcome after resection. Only if complete R0 resection is ensured, these patients can benefit from a surgical approach in a bi- or trimodality setting with neoadjuvant treatment. There is no consensus regarding these locally advanced tumours, whether neoadjuvant chemotherapy or chemoradiotherapy is superior to immediate surgical *en-bloc* resection (13,59,69,82,221,222). These extensive *en-bloc* resections should be performed in specialized centers only (13).

Radical *en-bloc* resection in a combined modality approach appears to be beneficial compared to definitive chemoradiotherapy alone (7,9,13). In a planned bi- (without surgery) or trimodality approach, restaging and surgical reevaluation will show if resection is still or is now feasible. If the tumour is still or newly confirmed to be unresectable, adjuvant treatment with durvalumab or consolidation chemotherapy is an option (7).

When considering surgical resection in patients with T3-4 tumours, mediastinal staging is key because mediastinal nodal involvement is associated with poor prognosis (69). Patients with T3-4 N2 disease are not surgical candidates, same as patients, where incomplete resection is inevitable. In patients with T3 and T4 tumours with occult N2 status after surgery (stage IIIB), sequential or concurrent chemoradiotherapy should follow resection (7). Therefore, it is important to emphasize that local invasion of the tumour is not nearly as predictive of outcome and survival as N2 status (39,40,43,223).

In R1 resection of these locally advanced tumours (T3 N1, T4 N0-1) either sequential or concurrent chemoradiotherapy is recommended, whereas in R2 resection concurrent chemoradiotherapy is the preferred adjuvant treatment approach (7,214). Incomplete resection in general is associated with a very poor prognosis.

$T4_{Inv}$—mediastinum

Mediastinal involvement may include other central structures. Tumours with mediastinal fat or mediastinal pleural invasion are potentially resectable (59). In case this invasion of the mediastinal fat is only limited to the hilum, these tumours might be classified as T2a or T2b (60). Watanabe *et al.* reported similar survival rates without significant difference between $T4_{Inv}$ tumours invading only the mediastinal fat compared to those with other mediastinal organ invasion, 36.1% for mediastinal fat invasion *vs.* 36.2% for invasion of other structures (61). Other authors reported different survival, but this subgroup contains a heterogeneity of extent of mediastinal invasion, making comparisons more difficult (53,62). On the contrary, resectability is highly depending on mediastinal organs or structures involved (see below).

$T4_{Inv}$—diaphragm

In tumours invading the diaphragm, latter can generally be partially or even completely resected. Reconstruction can be achieved using direct sutures in smaller or prosthetic material in larger defects. There is only a small amount of reported series with $T4_{Inv}$ tumours invading the diaphragm and most of them are older case series. Yokoi *et al.* reported 5-year survival rates of 14–33% depending on depth of diaphragm invasion, while other authors showed similar outcome (63-68).

$T4_{Inv}$—heart and great vessels

The great vessels mentioned in the TNM classification include the superior and inferior vena cava, the pulmonary trunk, the intrapericardial parts of the left and right pulmonary artery and the intrapericardial parts of the superior and inferior left and right pulmonary veins (60).

$T4_{Inv}$—left atrium and pulmonary veins

Usually, NSCLC invading the heart is not amenable to resection, but there is the exception of left atrial and/or intrapericardial superior and inferior vein involvement. $T4_{Inv}$ tumours invading the left atrium and its inflow are potentially resectable with reported 5-year survival rates around 15–26% (13,69,70). Involved hilar or mediastinal lymph nodes are associated with poorer survival and resections may be performed with or even without cardiopulmonary bypass (71-84).

$T4_{Inv}$—SVC

Patients with $T4_{Inv}$ tumours invading the SVC may be candidates for radical resection. The SVC can be partially or completely resected and reconstructed and prosthetic replacement of the SVC can be safely performed. Five-year survival rates are reported around 25–40% (13,53,69,78,83-96).

$T4_{Inv}$—inferior vena cava

There are only very few cases reported with involvement of the inferior vena cava following radical resection and specific results are unavailable (83).

$T4_{Inv}$—pulmonary artery

Involvement of the main pulmonary artery (pulmonary trunk) or its intrapericardial portions often require pneumonectomy (97). Depending on extent, resection and reconstruction of the pulmonary artery is technically feasible (53,70,84,97,98). No specific survival rates are reported in $T4_{Inv}$ tumours of this subgroup.

$T4_{Inv}$—aorta

The aorta can be infiltrated by NSCLC. Preoperative endovascular stent placement allows a safe and complete

resection of these tumours with better outcome than subaortic dissection (69,99,100). Five-year survival rates are reported around 17–50% (13,69,81,84,88,101,102) up to 70% (103,104) in smaller case series. Absence of nodal involvement is associated with better outcome (13).

$T4_{Inv}$—recurrent laryngeal nerve

Resection of invaded recurrent laryngeal nerve by $T4_{Inv}$ tumours is technically feasible and patients should be carefully selected. Reported data is involving only few patients with less information given about their outcome, making interpretation of data of this subgroup extremely difficult (70).

$T4_{Inv}$—carina and trachea

Based on extent of tracheal involvement, carinal and tracheal resections are potentially feasible. Reported 5-year survival rates are around 33% up to 44% (13), with lymph node involvement having a strong influence on survival (38,53,70,84,105-110).

$T4_{Inv}$—esophagus

For tumours invading the esophagus and where resection was attempted, there are only few reported cases in larger series summarizing $T4_{Inv}$ tumours. Yildizeli *et al.* and Pitz *et al.* reported a very small number of patients with only resection of the muscular layer of the esophagus, where no invasion of the mucosa was present (53,70). Because of poor outcome of these subgroup, invasion of the esophagus is generally stated as a contraindication for surgery.

$T4_{Inv}$—vertebral bodies and spine

Although T4 tumours involving vertebral bodies are usually classified as unresectable, several case series reported good long-term survival. Therefore, in highly selected cases these patients may be candidates for radical resection followed by reconstruction including thoracic and spine surgeons to perform laminectomy, single or multi hemivertebrectomy or even total resection of one up to three vertebral bodies (38,111). Reported 5-year survival rates are around 21–47% (13,111-119) up to 79.6% in meticulously selected patients with R0 resection following neoadjuvant chemoradiotherapy and complete response (57,58).

$T3_{Satell}$ and $T4_{Ipsi\ Nod}$

For patients with T3 disease with separate tumour nodule(s) in the same lobe ($T3_{Satell}$) or in T4 disease with tumour nodule(s) in a different ipsilateral lobe ($T4_{Ipsi\ Nod}$) without any systemic metastasis, surgery with optional adjuvant chemotherapy is recommended as in smaller singular tumours (treatment strategy stage-specific for dominant tumour) (44,224,225). Lee *et al.* reported 5-year survival rates about 30% for $T3_{Satell}$ and $T4_{Ipsi\ Nod}$ tumours without significant difference between each other (226). However, Kozower *et al.* reported an average 5-year survival rate of 37% for $T3_{Satell}$ and 19% for $T4_{Ipsi\ Nod}$ tumours (13), whereas Blasberg *et al.* stated an average overall 40% 5-year survival rate for $T3_{Satell}$ (50% for N0) and 30% for $T4_{Ipsi\ Nod}$ (40% for N0) (44).

According to Nagai *et al.* survival significantly differs depending on nodal involvement in $T3_{Satell}$ tumours, resulting in 5-year survival rates of 45.8% for pN0, 25.3% for pN1 and 11.1% for pN2 status (227). Port *et al.* showed, that $T3_{Satell}$ N0 disease (in Port *et al.* classified as T4 according to 6th edition of TNM staging system) has 5-year survival rates similar to early stages of NSCLC (228). It is important to note, that stage IIIA NSCLC is only including $T3_{Satell}$ N1 but also $T4_{Ipsi\ Nod}$ N0-1 disease.

For $T4_{Ipsi\ Nod}$ N0, Blasberg *et al.* noted an average 5-year survival rate of 40% (44). Nagai *et al.* reported significant survival differences between pN0 and pN1 as well as pN0 compared to pN2. No significant difference was shown between pN1 and pN2 disease in $T4_{Ipsi\ Nod}$ tumours. Five-year survival rates were reported as follows: 42.1% for pN0, 7.9% for pN1 and 10.0% for pN2 status and 46.2% for completely (R0) resected $T4_{Ipsi\ Nod}$ N0 disease (227).

Unresectable T3/T4 and inoperable patients

For unresectable T3 or T4 tumours, definitive concurrent chemoradiotherapy is a non-surgical alternative (7). Based on performance status in functional and medical inoperable patients, definitive treatment is individually. Concurrent or sequential chemoradiotherapy in patients with low comorbidities or ECOG <2 or even definitive radiotherapy alone in case of severe comorbidities are alternative strategies (9). Definitive concurrent chemoradiotherapy is preferred compared to the sequential regimen. Concurrent chemoradiotherapy provides a greater survival benefit but on another side bears an increased toxic effect. If for any reason a concurrent regimen is not possible, chemotherapy

followed by definitive radiotherapy (sequential approach) is a valid alternative (8,122-128).

Radiotherapy alone in locally advanced disease is mostly used in a palliative setting in stage IIIA disease. In these patients, radiotherapy may be beneficial in palliating symptoms of local tumour involvement (pain, hemoptysis and hemoptoe, recurrent laryngeal nerve paralysis and tracheal, esophageal or SVC compression). Long-term outcomes are poor based on local and systemic recurrence (10).

The role of VATS anatomical resection in locally advanced NSCLC

In the last decades thoracoscopic pulmonary surgery and its technique has advanced offering surgical resection for patients who previously might not have been considered candidates for radical resection (7). Compared to the conventional open thoracotomy, the reasonable technical feasibility, safety and advantages of minimal invasive approaches such as video-assisted thoracic surgery (VATS), especially in major anatomical pulmonary resections performed by VATS, has been demonstrated. It has also been illustrated, that VATS lobectomy is potentially superior compared to open lobectomy (7,229-246). Additionally, published data shows a trend towards improved tolerance of adjuvant chemotherapy following VATS anatomical resections with higher compliance rate and fewer delayed or reduced doses (244,247). Data also shows that most resected lung cancers by robotic-assisted thoracic surgery (RATS) are in early stage disease. Furthermore, it has been shown, that RATS seems to be accompanied by higher hospital costs and longer operating times, but without any differences in adverse events (248,249). Therefore, RATS is of limited importance in resection of stage IIIA disease and might only be indicated in highly selected cases.

Anatomical resections performed by VATS are an appropriate therapeutic approach in operable patients with resectable tumours, even in locally advanced stage IIIA, as far as there are no compromises of oncological principles and complete R0 *en-bloc* resection is feasible (7,229,245,246,250). VATS has also been shown to be a safe and feasible approach following neoadjuvant chemotherapy in these locally advanced tumours, even in limited sulcus superior tumours (170,171,251,252).

As discussed earlier, it could not be shown so far, whether neoadjuvant or adjuvant chemotherapy is superior approaching clinical stage IIIA N2 disease and the commonly held view favouring neoadjuvant chemotherapy is still vague (177).

Preoperative chemotherapy as well as radiotherapy can induce local tissue inflammation and edema, resulting in tissue adhesions with partially fused interlobar fissure, hilar and mediastinal fibrosis with anthracofibrosis and perivascular/peribronchial lymph node calcification as well as increased tissue and especially vascular fragility. Thus, making surgery in general more difficult and adhesiolysis and anatomic dissection more tedious with potentially higher operation time (35,170,171,253). These apply for open and for minimally invasive thoracic surgery.

Villamizar *et al.* noticed an increased complication rate in patients undergoing VATS resection followed by neoadjuvant chemotherapy compared to non-preoperative treatment (254). Since safety has always been of highest importance for surgeons, this implies that thoracic surgeons may favor adjuvant therapy, avoiding possible tedious dissection. On the contrary, other authors confirmed the safety and feasibility of VATS following neoadjuvant treatment without an increase of postoperative complications (170-173). Therefore, it is important to highlight the uniportal VATS approach, resulting in a direct view, the same way as provided due to open thoracotomy (172,173), with an easier access for dense adhesions after neoadjuvant treatment in locally advanced NSCLC.

Regarding a possible publication bias with cases reported only after uneventful postoperative courses and based on the heterogeneity of stage IIIA disease, it remains unclear, whether neoadjuvant or adjuvant treatment should be favored, when minimally invasive thoracic surgery is planned.

Conclusions

Stage IIIA NSCLC comprises a very heterogeneous group of different subsets of disease with large differences in therapeutic approaches and outcome. Therefore, it is important to discuss each case in a multidisciplinary setting following complete staging to form an individual recommendation in a multimodality treatment regimen.

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