Review Article

Initial extended resection or neoadjuvant therapy for T4 non-small cell lung cancer—what is the evidence?

Ilkka Ilonen, David R. Jones

Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY, USA

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Correspondence to: David R. Jones, MD. Professor & Chief, Thoracic Surgery Service, Memorial Sloan Kettering Cancer Center, 1275 York Ave, Box 7, New York, NY 10065, USA. Email: jonesd2@mskcc.org.

Abstract: Locally advanced non-small cell lung cancer (NSCLC) tumors that invade surrounding structures within the chest (T4) are a heterogeneous group, and, as such, there are no straightforward guidelines for their management. Advances in imaging, invasive mediastinal staging, and neoadjuvant therapies have expanded the role of surgery with curative intent for this patient group and have also diminished the rate of explorative thoracotomies. Unlike for T4 superior sulcus tumors, the use of neoadjuvant therapy for central T4 tumors is not clearly defined. The most important determinants of a successful outcome after surgery are achieving an R0 resection and avoiding incidental pathologic N2 disease. Use of neoadjuvant therapy in this setting may yield better outcomes after surgery, as both of these variables can be altered if the tumor responds to neoadjuvant therapy. Moreover, response to induction therapy has been shown to have prognostic value.

Keywords: Non-small cell lung cancer (NSCLC); T4; invasion; neoadjuvant therapy

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Introduction

Locally advanced non-small cell lung cancer (NSCLC) comprises a heterogeneous group typically involving larger tumors with or without invasion into surrounding structures. In the current 8th edition of the TNM classification, T4 tumors are defined as T size >7 cm, tumors invading the mediastinum, heart, diaphragm, carina, trachea, great vessels, recurrent nerve, esophagus, or spine, or separate tumor nodule(s) in a different ipsilateral lobe (1). T4 tumors are frequently associated with mediastinal involvement, pleural dissemination, and extrathoracic metastasis (2)—all of which make T4 tumors less suitable for surgical resection. However, as more therapeutic options have become available, including neoadjuvant therapy, the role of surgery for these tumors has expanded. Owing to the heterogeneity of patients with these tumors, published series are typically small and retrospective, from highly specialized centers with large case volumes, and they often employ a multimodality approach (3).

Previous studies have shown that local invasion by the primary tumor is not nearly as predictive of outcomes as mediastinal lymph node involvement (4,5). Superior sulcus (Pancoast) tumors (T3 and T4) have been shown to benefit from concurrent chemoradiation followed by surgery (6). In these cases, a complete response rate of 56% and 5-year overall survival (OS) of 56% have been achieved following complete resection. Importantly, no significant difference in OS was found between T3 and T4 tumors. On the basis of these findings, it is reasonable to posit that T4 tumors invading adjacent structures can be treated using a similar multimodality approach.

Following trimodality therapy, 5-year OS among patients with Pancoast tumors was 86%, compared with 60%

Table 1 Outcomes of surgical resection for non-small cell lung cancer tumors with left atrial involvement

Author	Year	N	pN	pN_{2-3}	R0	Mortality	5-year OS
Tsukioka (14)	2016	12	75%	42%	92%	0%	46%
Galvaing (15)	2014	19	95%	37%	89%	16% (90-day)	44%
Stella (16)	2012	31	84%	26%	94%	10%	30%
Kuehnl (17)	2010	35	89%	31%	69%	9%	16%
Riquet (18)	2010	25	88%	44%	40%	20%	9%
Wu (19)	2009	46	65%	22%	—	52%	22%
Spaggiari (20)	2005	15	100%	53%	100%	0%	39% (3-year)
Ratto (21)	2004	19	63%	57%	58%	0%	14%
Bobbio (22)	2004	23	96%	17%	83%	9%	10%
Fukuse (23)	1997	42	71%	22%	36%	0%	17% (3-year)
Total		267	80%	30%	60%	14%	26%

Neoadjuvant therapy was given to 26% of patients, and cardiopulmonary bypass was performed in 4%. OS, overall survival.

among patients with centrally located tumors, even without pathologic N2-positive disease (7). This result highlights the heterogeneity of T4 tumors, as treatment outcomes can vary on the basis of tumor location even in the absence of pathologic mediastinal lymph node involvement. In a case series of 57 patients with central T4 tumors who underwent neoadjuvant chemotherapy, 73% went on to have explorative thoracotomy and 63% had complete resection. Interestingly, if pathologic N2 disease were present at the time of surgery, the 5-year OS was dismal despite R0 resection (8).

Cardiopulmonary bypass (CPB) has been used selectively in the resection of T4 tumors (9-12). Use of CPB was mainly associated with aortic (43%) and left atrium/pulmonary vein resections (24%) (10). Institutional series reporting CPB were small and found favorable short- and long-term results associated with the use of CPB for NSCLC (9,11); however, a singular national registry study observed unacceptable mortality (>25%) and morbidity (>70%) associated with this procedure (12). All studies noted that unplanned use of CPB owing to vessel injury was associated with inferior overall results, compared with planned use (10,12). On the basis of the available literature, it can be concluded that planned use of CPB for highly selected patients in high-volume centers is safe and is associated with similar oncologic outcomes as in patients in whom CPB is not used (13).

The primary goal of this review is to examine (I) the evidence supporting the use of neoadjuvant therapy for T4 NSCLC tumors that involve the mediastinum, great vessels, left atrium, and vertebral bodies; and (II) the outcomes following surgical resection in these patients.

Left atrial involvement

Lung cancer that has invaded the heart is not usually amenable to surgical resection, with the exception of cases of left atrial involvement. The available studies concerning left atrial involvement are summarized in *Table 1* (14-17,19-23). Published series mostly did not administer induction chemotherapy or radiotherapy and did not include CPB. There are no historical data to support neoadjuvant therapy over straightforward surgery for these patients, as all available series were retrospective and neoadjuvant therapy was administered sporadically. All of these studies noted that pathologic nodal status was the most important factor for OS—especially incidental pathologic N2 disease, which was a factor of poor prognosis. Only two studies included patients who had received preoperative chemoradiation therapy (15,16), and both had very small sample sizes. Another small series, by Spaggiari *et al.*, excluded patients who had received preoperative radiation therapy, and only 9 patients (60%) in this study received neoadjuvant chemotherapy (20).

Although there is no substantial evidence supporting the use of neoadjuvant treatment for patients with these tumors, we do advocate for the use of neoadjuvant chemotherapy with non-cardiotoxic agents, as unsuspected mediastinal

Table 2 Outcomes of superior vena cava resection for non-small cell lung cancer

Author	Year	N	pN (%)	R0	pN_{2-3}	Mortality	5-year OS
Ciccone (25)	2011	8	—	100%	25%	6%	73%
Sekine (26)	2010	9	11%	100%	—	0%	19%
Lanuti (27)	2009	9	44%	100%	33%	5%	30%
Yildizeli (28)	2008	39	82%	85%	41%	8%	29%
Shargall (29)	2004	15	47%	93%	47%	14%	57% (3-year)
Spaggiari (30)	2004	109	51%	73%	50%	12%	21%
Suzuki (31)	2004	40	53%	83%	65%	10%	24%
Dartevelle (32)	1991	22	27%	–	10%	5%	48%
Total		234	45%	87%	43%	8%	40%

Neoadjuvant therapy was given to 36% of patients. OS, overall survival.

lymph node involvement is common in all the series presented in *Table 1*.

Superior vena cava (SVC) involvement

The SVC can be infiltrated by lung cancer in three patterns: (I) the tumor arises from the right upper lobe, invading the mediastinal pleura, phrenic nerve, and anterolateral part of the SVC; (II) a central right main bronchus tumor invades the SVC posteriorly; and (III) the SVC is infiltrated by level 4R lymph node metastasis. The most common form of SVC involvement is a right upper lobe tumor with SVC involvement, although this occurs in <1% of all patients with potentially resectable NSCLC (24). A summary of the published reports on T4 tumors involving the SVC is shown in *Table 2* (25-32). Unfortunately, the use of neoadjuvant therapy has not been examined as an independent predictive factor of outcomes or compared with surgery alone in these patients.

As T4 tumors involving the SVC are centrally located, there is a significant chance for mediastinal lymph node involvement; therefore, neoadjuvant therapy may be indicated. Alternatively, if aggressive preresection mediastinal staging reveals no evidence of N2 nodal disease, upfront resection should be considered.

Central pulmonary vessel involvement

Mediastinal involvement may include the central pulmonary vessels, which very often require a more extensive resection than a simple pneumonectomy to achieve negative margins (R0). Yang *et al.* observed that 56% of mediastinal T4 tumors involved the central pulmonary vessels (33). This series included 12 patients who had received neoadjuvant chemotherapy and was clearly underpowered to determine efficacy. In the case series by Yildizeli *et al.*, central pulmonary artery involvement occurred in 20 patients, and of these 17 also had SVC involvement (28). Stella *et al.* reported 31 patients with central T4 tumors invading main pulmonary vessels (16), 23% of whom received neoadjuvant therapy. The 5-year OS for these patients was 30%, with 26 (84%) having pathologic nodal disease and 8 (26%) having N2 disease. In-hospital mortality was high at 10%—pneumonectomy was performed in 77% of cases.

Aortic involvement

Advances in the use of preoperative endovascular stent placement have increased the ability to safely resect NSCLC tumors involving the aorta (34,35). In a small series (n=13) from the era before the adoption of endovascular stents, Misthos *et al.* observed tumor invading the aortic adventitia only in 69% of cases (36). Importantly, only 8% of patients had pathologic N0 disease, and unexpected N2 disease was found in 31% of patients. Other authors have suggested that aortic resection confers a survival benefit, compared with subadventitial dissection, although those studies were retrospective and included small sample sizes (37). None of the series analyzed the effect of preoperative chemotherapy or radiotherapy on outcomes. More series are expected to be reported in the future, as aortic endografts can be placed before neoadjuvant therapy to facilitate an aggressive

Table 3 Outcomes of vertebral resection for non-small cell lung cancer

Author	Year	N	pN (%)	R0	pN_{2-3}	Mortality	5-year OS
Mody (46)	2016	32	0	100%	0	3%	40.3%
Collaud (45)	2013	48	12.5%	88%	4.2%	6%	61%
Fadel (48)	2011	54	30%	91%	24%	0%	31%
Schirren (42)	2011	20	45%	80%	10%	0%	47%
Anraku (40)	2009	23	8.7%	83%	4.3%	8.7%	58% (3-year)
Grunenwald (44)	2002	19	31.6%	79%	21.1%	0%	14%
Total		196	21%	87%	11%	3%	39%

Neoadjuvant therapy was given to 71% of patients. OS, overall survival.

surgical approach including *en bloc* resection of the aorta if indicated.

Vertebral involvement

DeMeester *et al.* reported the first series of 12 patients treated with *en bloc* resection for NSCLC involving the vertebral body after neoadjuvant radiation therapy (38). Grunenwald *et al.* reported the first total vertebrectomy (39). Following these initial reports, several groups have published results (40-46), which were summarized in a recent review by Collaud *et al.* (47) (*Table 3*). In this review of 135 pooled cases, it was noted that 37% of patients received neoadjuvant chemoradiation and 22% received chemotherapy alone. No significant survival difference was noted when neoadjuvant treatment was compared with surgery or adjuvant therapy alone. However, there was a trend favoring neoadjuvant treatment, as 5-year OS was 80% among complete responders, compared with 35% among partial responders. Unsurprisingly, the most significant predictive factor was residual margin (R0 *vs.* R1). Complete pathologic response to neoadjuvant chemoradiation has been reported to be as high as 48% (40). On the basis of these findings, as well as data on T4 Pancoast tumors, the general consensus is to offer patients induction therapy if vertebral body involvement is suspected.

Conclusions

Evidence supporting the use of neoadjuvant therapy for T4 NSCLC has primarily been extrapolated from the use of induction therapy for Pancoast tumors (6). Given the rarity of T4 tumors, it is unlikely that there will be a randomized phase III clinical trial to assess induction versus no induction therapy for patients with these tumors. When considering resection of a T4 tumor, it is imperative to radiographically stage the patient and to perform invasive mediastinal staging. The presence of N2 disease, particularly if multistation, is a factor of poor prognosis and strongly argues against surgery as part of the treatment plan. Examination of the current literature reveals no clear consensus that neoadjuvant therapy is superior to upfront surgery. However, it has been shown that neoadjuvant therapy is safe, and there is evidence of improved outcomes and more favorable tumor biology among patients with tumors downstaged after neoadjuvant therapy.

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Footnote

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