



Carinal sleeve pneumonectomy: oncological recommendations

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Introduction

Tracheal sleeve pneumonectomy is the surgical excision of a whole lung including carina and lower trachea resection. It is usually performed for tumors involving the tracheobronchial angle. Differently to traditional pneumonectomy, this surgical procedure is characterized by reconstruction of the residual contralateral airway entirety between lower trachea and the main bronchus.

Tracheal sleeve pneumonectomy is a challenging procedure affected by high risks of perioperative complications and poor overall and cancer free survival. Therefore, poor outcomes and rarity of eligible cases made this surgery infrequent; it probably represents 1% of all pulmonary resections for lung cancer. However, in the last 2 decades surgical and anaesthesiologic improvements allowed this procedure to become safer and more successful.

Surgical difficulties are represented by the followings topics: (I) gentle dissection of trachea and main bronchi; (II) R0 carina resection; (III) trachea and bronchus free-tension reconstruction. Whereas, patient selection, anesthetic management and postoperative recovery are the main perioperative complexities.

Despite sleeve pneumonectomies should be performed rather in specialized centers, they represent an essential knowledge in every thoracic surgeon expertise. But, since these procedures are rare even in high volume centers, few recommendations addressing the main topics are available.

Therefore, technical complexity, perioperative complications rate and poor survival often alarm thoracic surgeons in the decision making whether or not refer central T3/T4 patients to surgery.

In our opinion, oncological indications and correct clinical staging are very important topics when considering

surgery in central tumor with carinal involvement. Therefore, our aim is to give an overview on these items representing a further challenge for surgeons since before operatory room.

Oncological indications and surgical implications

Main indications for tracheal sleeve pneumonectomy are bronchogenic carcinoma interesting the origin of ipsilateral main bronchus (T3) or invading the main carina or the wall of lower trachea or the origin of contralateral main bronchus (T4). Sleeve pneumonectomy could be also needed for endobronchial tumor with different behavior from NSCLC such as carcinoids and adenoid cystic carcinomas. Cases requiring sleeve pneumonectomy usually are right sided probably because left main bronchus is longer.

Since diagnosis is often done when tumor is already advanced, many patients present nodal involvement making the choice of surgical approach very demanding and questionable. Indeed, it is common opinion that patients with metastatic disease or clinical N3 involvement should not be referred to surgery. Whereas, it is widely accepted that T4 selected patients without mediastinal nodes involvement (N0/N1) should be candidates for primary surgery. The real issue is represented by patients with N2 disease. The question is if they should have no indications to primary resection and be treated with definitive chemoradiotherapy or if selected cases should deserve to be treated as a special group, apparently outside of paradigmatic therapy. These cases are summarized as follows:

N2 multistation patients successfully treated by induction therapy and N2 single station patients

These two scenarios are the most challenging for thoracic surgeons since guidelines are not definitive and therefore the decision to treat is often based on personal experience that, unfortunately, is limited the most of time.

Parameter T

Parameter T investigation should be focused on the following topics: (I) adjacent organs invasion; (II) extent of airway resection. According to the latest NCCN guidelines for NSCLC treatment “T3 invasion and T4 local extension tumors require *en bloc* resection of the involved structure with negative margins” (1). Therefore, carinal resection is not an absolute contraindication to surgery in itself, if R0 resection can be obtained.

The latest ACCP Guidelines (2), state that patients with T4 involvement could be viewed as candidates for surgery as well and report that, despite the rarity of cases, the largest experience of resections is represented by carinal resection and tracheal sleeve pneumonectomy. Left atrium, superior vena cava, vertebral bodies and aorta resection are very rare.

Focusing on the extent of airway resection, one of the most meaningful criteria during airway reconstruction is the achievement of a tension-free anastomosis, otherwise, estimated risk of postoperative tracheobronchial fistula is very high. At the same time, oncological criteria for R0 resection recommend disease free edges at least 1 cm far from the tumor. The most of authors agree that the maximal safe length of the airway resected between the lower carina and the bronchus should be 4 cm. This mean that tumor should not extend beyond 2 cm of the lower trachea or beyond 1.5 cm of the opposite main bronchus (3).

Parameter N

Parameter N investigation is highly conditioning because significantly influences prognosis and therapeutic approach decision-making. We know that prognosis decreases progressively from pN0 to pN1 and pN2, but the questions is when nodal involvement should deny surgery in patients with carina involvement.

According to guidelines, the role of surgery in patients with pathologically documented N2 disease remains controversial. We know that surgery alone does not increase survival but it is commonly known as well that N2 patients

represent a heterogeneous population and that the likely oncologic benefit of surgery in specific clinical situations, and in a multimodal therapy context, should be always considered.

Multistation mediastinal nodal involvement

Surgery alone does not usually present any advantages in terms of survival in N2 stages. Therefore, patients should be referred to induction therapy with the aim to reach nodal disease complete regression; indeed, patients with negative mediastinum after neoadjuvant therapy have a better prognosis (1). Therefore, surgery should be considered only in case of nodal downstaging or, at least, absence of disease progression (1).

It is a common opinion that the optimal induction therapy regimen consists of chemotherapy eventually associated with radiotherapy since guarantees the higher rates of pathologic complete response and negative mediastinal lymph nodes (4). But, unfortunately, it is also correlated to higher rates of acute toxicity. Focusing on pneumonectomy, data from different large multi-institutional trials indicate that surgery after induction chemoradiotherapy has unacceptable morbidity and mortality (5). Whereas, complications seem to reduce with induction chemotherapy alone. In addition, there is no evidence that adding RT to induction regimens for patients with operable stage IIIA (N2) disease improves outcomes compared to induction chemotherapy alone (6). Moreover, overall survival appears similar, if radiotherapy is not administered preoperatively, provided that it is given postoperatively (7,8).

These data underscore that decision making criteria for N2 patients suitable for surgery are not univocal and that correct therapeutic strategy for N2 patients eligible for tracheal sleeve pneumonectomy is n unclear topic for both oncologist and thoracic surgeons.

In order to have an overview of the common behavior among thoracic surgeons, the NCCN (1) submitted a survey about their approach to patients with N2 involvement. Their responses represent the routine practice when facing this challenging clinical problem. We report three meaningful questions:

- (I) Would consider surgery in patients with one N2 lymph node station involved by a lymph node smaller than 3 cm: (90.5%);
- (II) Would consider surgery with more than one N2 lymph node station involved, as long as no lymph node was bigger than 3 cm: (47.6%);

(III) Would consider neoadjuvant therapy followed by surgery when a patient is likely, based on initial evaluation, to require a pneumonectomy: (54.8%).

The survey showed once more the heterogeneity of approaches adopted by different thoracic surgeons.

In 2007, Rea *et al.* (9) published their experience with 49 cases of carinal resection for non-small cell lung cancer (NSCLC). They reported perioperative complications in 14 patients (overall morbidity 28.6% and overall mortality 6.1%) not statistically associated with induction therapy. The overall 5- and 10-year survival rates were 27.5% and 12.8%, respectively. N0 patients had a significantly better prognosis than N1 and N2 patients (5-year survival: 56%, 17%, and 0%, respectively; $P=0.002$) and multivariate analysis showed that nodal status was the only independent prognostic factor ($P=0.00007$). So, they concluded that sleeve pneumonectomy is a recommended procedure in N0 and N1 cases, whereas in N2 patients they mildly support surgery only in case of response or stable disease after induction therapy.

In 2005, de Perrot *et al.* (10), in a series of 119 patients, presented a 5- and 10-year survival of 44% and 25% respectively, with severe worse prognosis at 5 years in N2 cases (15% *vs.* 53% in N0/1). Their conclusions supported once more the feasibility of this surgery in early stage patients.

In 2013, Eichhorn *et al.* (11) reported a 64-sleeve pneumonectomy study. Their results confirmed the interesting survival and nodal status influence (5-year survival rates of 70%, 35%, and 9% for N0, N1, and N2 subgroups, respectively). Focusing on N2 cases they concluded that single station patients should undergo straightly to surgery because the benefit of induction therapy is still uncertain whereas higher postoperative mortality rates have been frequently reported as well as a negative impact on anastomotic healing.

In 2014, Shin *et al.* (12) reported very successful outcomes, as well (5-year overall survival rate and disease-free survival rate 66.3% and 52.9%, respectively). Interesting, these successful data can be explained since they always considered any N2 involvement an absolute contraindication to surgery, in particular if bulky or multistation. Anyway, single pN2 station cases (occult) were accidentally found and presented better survival than in other papers.

According to the series above, it seems to be evident that N2 cases surgically treated after induction therapy present poor survival and severe perioperative morbidity.

To date, this is a common opinion despite some Authors, focusing their attention on postoperative complication after neoadjuvant therapy, reported encouraging data. In 2003, Ohta *et al.* (13) reporting their experience with bronchoplastic procedures (included pneumonectomy) after induction therapy, confirmed that preoperative irradiation could determine severe anastomotic complications and should be avoided. Whereas, they showed that chemotherapy alone, despite associated with some perioperative complications, is an effective and feasible treatment even before sleeve pneumonectomy. Surprising, they concluded that adopting high standard of care in selected patients, complication rate is acceptable and should not preclude surgery.

The latest ACCP guidelines treated T4N0/1M0 tumors (central tumor with direct invasion) in a distinct chapter entitled "Special treatment issues in NSCLC" (2). Unfortunately, their recommendations were based on few data obtained from only 12 published series, underlining that cases eligible for sleeve pneumonectomy are very rare and evidences are few.

To summarize, their data suggest that survival for T4N2N3 multistation disease is so poor (<10% at 5 years after surgery) that N2 involvement should be a strong contraindication to primary surgery. Induction chemotherapy should be potentially considered only in very selected patients and surgery should be proposed only if complete downstaging is obtained, because of high comorbidity rate following sleeve pneumonectomy, limited long-term survival and technical difficulty of the surgery. However, an optimal performance status allowing to tolerate such an invasive resection is highly suggested. Given the rarity of occasional series comprising patients treated with induction therapy, guidelines do not recommend induction therapy and surgery in patients with mediastinal nodes involvement beyond experienced centers.

To conclude, further studies are needed to understand the role of chemotherapy in NSCLC involving the carina and with N2 disease. Induction therapy may improve oncologic outcomes if mediastinal nodes are completely cleaned before surgery. However, operative and postoperative comorbidity and mortality are highly increased after sleeve resection when chemotherapy has been administered. In particular, mortality has been doubled in some series (10), reaching an outstanding 24% of cases.

Single station mediastinal nodal involvement

A further special issue is the management of N2 single

station. We already know that occult N2 single station have favorable survival (14). Moreover, in the last years some authors have shown that prognosis of patients with single-station N2 disease at PET/CT scan treated by primary surgical resection and mediastinal lymphadenectomy was similar to those with occult N2 disease (15). This support the hypothesis that primary surgery followed by adjuvant therapies is a reasonable approach in resectable single station N2 disease, simplifying patient care and reducing cost (16).

In particular, Maniwa *et al.* (17) proposed a selection of specific criteria to identify N2 patients who could have favorable outcomes when referred straight to surgery. Their criteria were the following: (I) single-station N2; (II) non-bulky N2; (III) N2 with regional mode of spread; (IV) N2 without N1.

The main reason to skip induction therapy in these patients should be the possibility to reduce perioperative morbidity. Since bronchial anastomotic complications rate strongly increases after induction therapy, accounting for poor survival after sleeve pneumonectomy, it is reasonable to consider N2 single station with carinal involvement as a special group of patients to treat outside of paradigmatic multimodal therapy scheme.

Eichhorn *et al.* (11) in their series never proposed induction therapy for cN2 single station patients and reported that mean survival was 13 months for pathologic multilevel N2 disease and 21 months for single level N2 disease ($P=0.03$). In 2014, Shin *et al.* (12) reported a series with six N2 single station cases accidentally found at pathologic examination. Overall survival at 5 years was 50%.

Unfortunately, only few retrospective data are available about correct approach to these patients at the moment. To date, NCCN guidelines (1) report that N2 <3 cm single station disease is not a contraindication to surgery if planned in a multi therapy project. However further data are needed to understand the best approach.

Staging recommendations

Based on the above considerations, clinical nodal staging further becomes a key point in patient selection for carinal resection. The most of Authors agree that accurate complete invasive staging of mediastinum nodes is mandatory in case of nodal enlargement at CT scan or suspicious uptake at PET/CT scan. Mediastinoscopy used to be the most successful and diffuse approach to mediastinal nodes allowing to reach bilateral stations, especially non-

subcarinal nodes. However, mediastinoscopy implicates tissue dissection that leads to airway devascularization and determines, in a short period, tissue scarring and reduced tracheal mobility at the moment of anastomosis procedure. To avoid these difficulties some authors suggest that mediastinal staging should be performed at the same time of planned surgery. For the same reasons mediastinoscopy repeated during patient restaging after induction therapy should be avoided (18).

Nowadays, endobronchial ultrasound (EBUS) presents more advantages than mediastinoscopy. Mainly, it allows to reach also subcarinal stations and, adopting a trans esophageal approach, stations number 8 and 9. Moreover, it can be repeated without risk of tissue devascularization or scarring (19).

In case of induction therapy, restaging is mandatory since nodal residual disease is considered a contraindication to surgery by the most of authors. Histopathologic diagnosis is needed since imaging findings are not sufficient to confirm negative nodal status. This argument is based on the high false-negative rate (about 25%) at CT evaluation of the mediastinum in central tumors (20). In turn, PET supplies further metabolic information, but there are opposing data about its use (21). However, we report a recent paper by Cetinkaya *et al.* (22) that confirmed the high diagnostic accuracy rate of EBUS in nodal restaging after induction therapy but also a remarkable low sensitivity, inducing to the conclusion that mediastinoscopy should be considered in case of negative N2 at restaging after induction therapy, particularly if imaging findings are suspicious. Their conclusions underline that more data are needed to better define correct restaging procedures in patients referred to carinal resection.

Conclusions

General oncological indications for pneumonectomy in malignant tumors involving carina and/or distal trachea (T3/T4), should be mainly arranged according to N stage. Carinal resection and reconstruction is feasible in select N0/N1 patients, with acceptable mortality and morbidity rates.

Surgery in multistation N2 cases is questionable, and in the most of cases mediastinal nodal involvement is a strong contraindication. In selected cases with excellent performance status, induction therapy should be considered and surgery should be planned when complete mediastinal disease regression has been achieved. Otherwise, long-term

survival is poor and in addition perioperative morbidity is high.

N2 single station is not a contraindication to surgery in itself. Long-term survival is better than multistation cases and similar to occult cases, but poorer than N0/N1. Chemotherapy should be considered in a multimodal approach and should probably be administered after surgery in order to reduce the incidence of severe perioperative complications.

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