

The role of surgery in the treatment of stage IIIB non-small cell lung cancer

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Patients with T4 and/or N3 disease are generally considered as unresectable [1]. Nevertheless, selected patients have been proposed for surgical challenge, despite this bad reputation. According to the most recently revised staging system for lung cancer, T4 disease includes three subcategories of patients: separate satellite nodules in the same lobe, malignant effusion, and direct invasion of adjacent structures. Patients in the latter subcategory, provided the T4 tumor is not associated with a mediastinal N2 nodal involvement, have been proposed for extended resections, either as a primary treatment, or after induction [2,3]. The N3 involvement, or contralateral lymph nodes within the mediastinum, which is by definition contraindication for surgical dissection through conventional approaches, has been explored in extended resections using bilateral approaches. Patients with malignant pleural effusion ("wet IIIB") are definitely unresectable.

Separate satellite nodules

A satellite pulmonary nodule in the same lobe should not be staged as IIIB non-small cell lung cancer. In a case-control study comparing T4 lesions from a satellite nodule with T4 from local invasion, those patients with T4-satellite non-small cell lung cancer who underwent complete resection had a similar survival rate to patients with stage IB and stage IIA lesions, significantly better than patients with T4-invasion ($p=0.016$) [4]. Resection should be considered in patients with T4-satellite N0M0 lesions.

Nodal stage IIIB disease (mediastinal N3)

Nodal stage IIIB is reputed to carry a poor prognosis and is considered unresectable by almost all authors. Naruke et al. reported a five-year survival rate of 0% in 55 patients with N3 disease [5]. However, a phase II study conducted by the Southwest Oncology Group

included 27 NSCLC patients with biopsy proved N3 involvement [6]. Among them, 14 (52%) underwent a surgical resection after induction chemoradiation. Induction was two cycles of cisplatin and etoposide plus concurrent chest RT to 45 Gy. Resection was attempted if there was a response or the disease stabilised. There was no difference in survival ($P=0.81$) between stage IIIA (N2) versus stage IIIB. The strongest predictor of long-term survival after thoracotomy was the absence of a tumor in the mediastinal nodes at surgery (median survivals, 30 v 10 months; 3-year survival rates, 44% vs. 18%; $P=0.0005$). Stamatis et al. reported on the results of a series of 42 stage IIIB NSCLC patients treated by chemotherapy, then chemoradiotherapy, followed by surgery [7]. Among 23 patients with N3 disease, 18 underwent a pathological staging, with a 72% rate of mediastinal complete response. In addition, an extensive bilateral lymphadenectomy can be performed through an anterior midline sternotomy, possibly extending as far as the cervical areas in the case of supraclavicular N3 [8]. Hata and his colleagues from Japan reported a 60% five-year survival rate in 8 patients with N3 involvement after complete surgical resection via midline sternotomy [9]. These authors concluded in 1997 that their systematic mediastinal dissection beyond the anatomical difficulties would bring better prognoses in patients with pN2–3 disease. A detailed analysis suggested that bilateral mediastinal lymphadenectomy was significant and beneficial for the left lung cancer patients with N3 but controversial for the right [10]. The same group of investigators reported in 2006 the results from a series of 44 patients with left upper lobe cancer who underwent extended radical mediastinal nodal dissection bilaterally approached through median sternotomy [11]. Multivariate analysis demonstrated that aortic nodal involvement (stations 5–6) was a significant predictive factor for metastases in the mediastinal lymph node which cannot be dissected through a left thoracotomy (stations 1–2, 3R, 4R). Whether bilateral dissection has a beneficial effect

on prognosis remains controversial, according to the authors' conclusions.

T4 direct invasion of adjacent structures

Technical resectability of some categories of T4 tumors has been reported by several groups. As early as 1995, a South West Oncology Group trial reported by Albain et al. showed better median survival for stage IIb than IIIa patients respectively, after chemoradiotherapy followed by surgery [6]. In this trial, the stage IIb patients included were mainly T4N0 tumors, of better prognosis than N2 involvements that were the majority in the IIIa cohort of patients. Obviously nodal invasion compromises long-term survival due to the high potential of metastatic spreading. The significance of surgical treatment for T4 lung cancer has been studied by numerous authors, particularly in Japan. For instance, Sakurada and his colleagues found 50% and 38% five-year survival rates after resection for lung cancer invading the left atrium and major vessels, respectively [12]. In the same paper carinal and/or tracheal resection was associated with 22% long-term survival, while no survivors at 5 years were found after vertebral resection. The only significant prognostic factor identified was the completeness of resection ($p < 0.05$). In the same way, Shirakusa and coll. reported on their experience in extended operations for T4 lung carcinoma [13]. Interestingly the results were found to be far better in the last period of their study (from 1992 to 1997), with a 3-year survival rate of 25%, compared to the 7% observed in the former period (1978–1989), showing increased experience in the management of patient's care. In this study oesophageal invasion was clearly identified as the worst prognostic factor. Authors emphasized the prognostic value of nodal status with median survivals of 25.5 and 14 months in N0–1 and N2–3 diseases respectively. This data was confirmed by Takuhashi et al., who analysed the prognostic factors of extended resection for lung cancer invading mediastinal organs. Complete resection ($p < 0.0001$), N status ($p < 0.05$), and histology ($p < 0.02$) were significant factors affecting survival [14]. According to the principle that tumor debulking induced by neo-adjuvant treatments can render some locally advanced non-small cell lung tumors resectable in selected patients, chemotherapy, or chemoradiotherapy was proposed as induction pre-operative strategy in stage IIb patients. Rendina et al. reported a dramatic downstaging in their patients after chemotherapy in a series of 57 patients with T4 tumors, including

tracheal, superior vena cava, left atrial, or vertebral involvement [15]. Major complications were observed in 16% of the patients, including two cases of bronchopleural fistula.

When regarding the T4 descriptors from the International Staging System separately, some of them, particularly the invasion of mediastinal organs, have been considered as potentially resectable by several groups. Consistent series of extended resections have been published in these different situations.

Left atrium and great arteries

Proximal tumors from the lower lobe developed around the inferior pulmonary vein can extend until the atrial wall of the heart. In some patients a left atrial resection can be performed, either by direct clamping and suture, or stapling, of the left atrium, or patch-replacement of the atrial wall (pericardial or prosthetic patch) [16–18]. Klepetko and coll. reported a series of 7 patients, operated on for lung tumors invading thoracic aorta [19]. In this Austrian study, surgical resection was performed using extracorporeal bypass, without any mortality. A four-year survival rate was found to be 25%. Similar procedures were reported by de Perrot et al., emphasizing the role of cardiopulmonary bypass in helping resection of lung carcinomas invading aortic arch or left atrium, but also for carinal resections [20]. Thoracic aorta can be resected either by lateral clamping or complete interruption of the descending aorta, which requires a by-pass during the step of resection and prosthetic reconstruction. Tsuchiya and coll. also reported a series of 7 patients with invasion of the thoracic aorta [17]. Fukuse and coll. reported a series of 42 patients operated upon for lung cancer invading left atrium or great vessels [18]. Left atrium was resected in 14 patients, great arteries in 15, and superior vena cava in fourteen. A complete resection could be achieved in only 15 patients of the whole series. Mortality rate was low (2.4%), with regards the complexity of the procedures. Overall 3-year survival was found to be 17%. Again low stages in nodal status were associated with increased survival ($p = 0.0013$), and invasions of great vessels were found to be of better prognosis than atrial involvements ($p = 0.036$).

Superior Vena Cava

Invasion of the superior vena cava by a T4 tumor in the right upper lobe led surgical teams to attempt lobectomies or pneumonectomies extended to the vena cava [21]. Different aspects of this topic are controversial. In fact direct extension to the vessel by

the tumor mass itself is a rare situation. A vena cava resection is usually needed as a result of extension from bulky disease, in which the nodal disease is the greatest component, and by consequence the tumor remains difficult to classify, between N2 or T4. One could discuss the rationale of resecting a superior vena cava for bulky N2 disease and the high potential of metastatic spread of this category, and the poor prognosis. Nevertheless, as far as the technical aspect is concerned, different techniques were described to achieve a complete resection. Lateral clamping of the superior vena cava followed by direct continuous suture has been used in a lot of cases described in the literature. In attempting to avoid thrombotic complications due to iatrogenic surgical stenosis, reconstruction has been proposed by using pericardial or prosthetic patch, to restore the diameter of the vessel. The best technique to reconstruct an anatomic vena caval system is the total replacement of the vessel by a prosthetic ring-reinforced tube, implanted in the right atrium of the heart, bilaterally if required. A high rate of postoperative morbidity jeopardizes the outcome to be expected by these attractive procedures. A multicentric international review of prosthetic replacement after superior vena cava resection for non small cell lung cancer in 28 patients, in which N2 involvement was present in 50% of the cases, showed significative rates of postoperative morbidity and mortality (39 and 14%, respectively). But overall the 5-year probability of survival was only 15% [22].

Carina, trachea

A bronchial carcinoma from the right lung extended to the lower part of the thoracic trachea, and/or the tracheal carina can be resected in selected patients [23,24]. In these cases a right pneumonectomy is enlarged to the tracheal bifurcation and the airway is reconstructed by the means of an end-to-end anastomosis between the thoracic trachea and the main left bronchus. These "sleeve" pneumonectomies have been performed by several teams since more than 25 years. Despite a high rate of post-operative morbidity (10 to 30%), including bronchial dehiscences, patients experiencing long-term survivals have been achieved in 15 to 23% of the cases. Various surgical techniques of carinal resection have been summarized by Mitchell and his colleagues, who reviewed the clinical experience at Massachusetts General Hospital over the past decades [25]. The largest series in the world shows a high rate of postoperative complications (39%) and

an operative mortality of 13%. Anastomotic complications (dehiscence or stenosis), which occurred in 17% of the cases, were found to be predictors of operative mortality ($p=0.04$). Yatsuyanagi and coll. focused their study on anastomotic complications after bronchoplastic procedures [26]. Out of 47 cases, anastomotic dehiscence or stenosis were observed in 8.5% and 8.5%, respectively. Neither the operative procedure, nor the suture materials were found as predictors of airway complications. The only predictive technical factors were a positive resection margin ($p<0.01$) and preoperative chemotherapy ($p<0.05$). Nodal involvement at postoperative pathological examination ($pN0-1/N2$) was the only clinical predictors of bronchial complications. Macchiarini and his colleagues tried to focus their purpose on perioperative management of operable lung cancer invading the tracheobronchial bifurcation [27]. The technique used for ventilation, and controlled fluid perfusion allowed these authors to achieve a 4% thirty-day mortality rate, despite preoperative chemoradiation. Regnard et al. reviewed a retrospective series of carinal resections for lung carcinoma [28]. At multivariate analysis, only nodal status (N0, N1 versus N2; $p=0.0046$) had a significant impact on long-term survival.

Vertebral body

Non-small cell lung cancers invading the thoracic inlet can easily penetrate spinal structures because of their particular anatomic situation. For this reason, most tumors which invade the spine are located in the superior sulcus, although vertebral extension can be observed in tumors more caudally situated. Initial local control as a result of the first treatment provides the only possibility of survival for patients with superior sulcus tumors [29]. The best local control for resectable tumors is achieved by surgical operation, provided the resection is complete and respecting oncologic principles [30]. Since the first descriptions of surgical resection in Pancoast tumors, several limitations to surgical resection have been successively surpassed. Paulson, in his classic article from 1975, identified contraindications to surgical intervention, including the invasion of the vertebrae [31]. Tumors involving the transverse process or the lateral part of the vertebral body could be resected through an enlarged posterolateral thoracotomy [32]. However, direct major invasion of the vertebral body remained an absolute contraindication to surgical repair until the first report in 1996 of a successful total vertebrectomy for en bloc resection of lung cancer invading the spine [33]. Among the factors

which determine outcome in patients with superior sulcus tumors treated by multimodal approach at the University of Texas MD Anderson Cancer Center, surgical treatment was found as a significant predictor ($p < 0.01$), while vertebral body involvement remained marginally significant ($p = 0.05$) [34]. At the same institution, a multidisciplinary team of neurosurgeons and thoracic surgeons attempted to achieve a locoregional control, i.e. a negative surgical margin of all areas including the involved vertebrae [35]. Preliminary results on 17 patients (median follow-up = 25 months) showed no postoperative lethality, consistent morbidity, tumor recurrences in half of the cases, and a 2-year survival rate of 80% for completely resected patients. In the same way, an en-bloc technique of resection was developed in Europe, attempting to respect oncologic principles, by means of a no touch resectional attempt [36]. Variations in techniques between both institutions most likely reflect philosophic differences between orthopaedics and neurosurgeons. Nevertheless despite these variations, the results are quite similar. Interestingly, patients without recurrence at two years also remained free of disease at 5 years. More recently, a Japanese team reported a 68% five-year survival rate after complete resection with en bloc partial vertebrectomy following induction chemoradiotherapy (50 Gy) [37].

Multimodal approach in stage IIIB

Several studies have demonstrated the feasibility of surgical resection after induction chemoradiotherapy in patients with stage IIIB non-small cell lung cancer [38–40]. Stamatis and colleagues reported a complete resection rate of 48% after bifractionated radiotherapy associated with chemotherapy given preoperatively in 56 patients with stage IIIB disease [7]. Forty three percent of the patients who could be completely resected survived 5 years, while overall 5-year survival of the entire series was 26%. In our study, an encouraging 28% achieved long-term survival following surgical resection in patients with stage IIIB disease in whom induction chemoradiotherapy alone failed to control the disease [8]. Tumor response was observed in 73% of the cases and complete resection could be performed in 58%. Interestingly, survival according to the mediastinal lymph node status after induction treatment was significantly different between N0–1 and N2–3 ($p = 0.03$). Nodal downstaging after induction treatment seems to be a good prognosticator of long-term outcome. Poor results obtained after surgery in the absence of nodal downstaging raises the

issue of the relevance of extended surgical resection in these cases.

Conclusion

The role of surgery in locally advanced non-small cell lung cancer remains under investigation. Clearly surgical resection is an efficient salvage procedure for selected stage IIIB patients who are partial responders to chemotherapy or chemoradiation and have no mediastinal lymph node involvement at the time of surgery. Altogether, available data suggests that post-induction TN status is more accurate than pretreatment TN status, to guide the indications of surgery for patients with locally advanced NSCLC. Several questions remain to be answered: What is the best preoperative strategy to increase the rate of mediastinal lymph node downstaging? How can multimodality treatment-induced toxicity be lessened? Faced with such toxicity, should surgery be performed in patients presenting a complete response and how can they be identified preoperatively?

In addition, the staging system for lung cancer must be adjusted according to progress in surgical techniques, allowing extended resections in the context of multimodality treatments, and particularly taking into account the concept of potentially resectable versus definitively nonresectable advanced tumors [41].

Conflict of interest statement

None declared.

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