# The role of surgery for marginally operable tumours (stage IIIBT4)

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## Introduction

Despite continuous progress, non small-cell lung cancer (NSCLC) remains a therapeutic challenge, where feasibility of curative surgical resection is limited to a few patients. The poor prognosis that is associated with locally advanced NSCLC is in part due to its inoperability, and most patients will die with intrathoracic disease, despite radical thoracic irradiation and/or systemic chemotherapy [1]. In this subset of patients, prospective studies have demonstrated a poor local control achieved by thoracic irradiation (less than 20% at 2 years) and a high rate of distant failure (more than 50% at 2 years) in patients treated with chemotherapy alone or associated with radiotherapy [2]. Patients with stage IIIB disease are considered inoperable and are usually treated with chemoradiotherapy [3]. An analysis of the sites of relapse has shown that locoregional failure is the major stumbling block in these patients because chemotherapy dramatically decreases the rate of distant metastasis [4]. These results underscored the need to overcome persistent viable tumour cells after chemoradiotherapy. Since then, several teams have investigated surgery after induction therapy as a possible alternative means of improving locoregional control of locally advanced disease [5–8]. The anatomical surgical landmark has been established by the International Staging System for lung cancer between stages IIIA and IIIB [9]. Clearly, this frontier does not reflect reality, since patients at stage IIIA are daily excluded from surgery by surgeons, while in some situations, stage IIIB disease is considered for resection [8].

Stage IIIB disease is currently considered unresectable. Nevertheless, selected patients can be proposed for extended resections after induction treatments. The surgical approach to this group of patients leads to a subdivision of stage IIIB into three subgroups, depending on the possibilities of resection: (i) ' nodal' IIIB, where N3 disease is associated with T1, T2, or T3; (ii) ' mediastinal' T4, in which mediastinal organs or vertebral bodies are invaded; (iii) presence of malignant pleural or pericardial effusion.

## 'Nodal' IIIB

Nodal stage IIIB is reputed to have a bad prognosis and is considered unresectable by almost every author. Naruke and colleagues reported a 5-year survival rate of 0% in 55 patients with N3 disease [10]. However, a phase II study conducted by the Southwest Oncology Group included 27 NSCLC patients with N3 involvement [5]. Among them, 14 (52%) underwent a surgical resection after induction chemoradiation. Eberhardt and colleagues reported the results of a series of 42 stage IIIB NSCLC treated by chemotherapy, then chemoradiotherapy, followed by surgery [11]. Among 23 patients with N3 disease, 18 underwent a pathological staging, with a mediastinal complete response rate of 72%. 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]. Such a mediastinal dissection results in a devascularisation of the mediastinal structures, mainly the bronchial stump, and combined with the harmful effects of pre-operative radiotherapy and possibly chemotherapy can induce an increased risk of defects in bronchial healing, resulting in bronchial fistula [11–13]. For this reason, most authors propose preventive strategies using different techniques [11, 14]. Following experimental findings in lung transplantation experience, preventive bronchial omentoplasty was successfully used in patients operated after induction chemoradiation [8,15,16]. Hata and his colleagues from Japan reported a 60% 2–year survival in 9 patients after surgical resection of N3 involvement via midline sternotomy [17]. Therefore the anatomical situation of the lymph node metastases and their volume do not, theoretically, constitute absolute criteria of inoperability. On the other hand, it seems unreasonable to propose this kind of operation to patients in whom a bulky involvement has extended beyond the capsule and invades the mediastinal fat (this neoplastic mediastinitis can be detected easily by mediastinoscopy).

## 'Mediastinal' T4

Several co-operative groups reported on the technical resectability of T4 tumours. In 1995, a South West Oncology Group trial reported by Albain and colleagues showed better median survival for stage IIIB than IIIA patients respectively, after chemoradiotherapy followed by surgery [5]. In this series, included stage IIIB patients were mainly T4N0 tumours, and had a better prognosis than N2 involvements, which were the majority in the IIIA cohort of patients. Obviously, nodal invasion compromises long-term survival because of high potential of metastatic spread. Regarding, T4 descriptors, as re-defined in the last issue of the International Staging System, a selection of patients can be proposed for radical surgery, including invasion of superior vena cava, or great mediastinal vessels in some situations, left atrial involvement in a few patients, tracheal and carinal involvement in most of the cases, and satellite nodules. In case of frank invasion of the heart, in particular at ventricular level, oesophageal involvement, malignant pericardial or pleural effusion patients must be considered as definitively unresectable. Vertebral invasion becomes a controversial issue, since several series of surgical resections with encouraging results have been published in recent years [18,19]. The significance of surgical treatment for T4 lung cancer has been studied by numerous authors, particularly in Japan. Sakurada and colleagues found 50% and 38% 5-year survival rates after resection for lung cancer invading the left atrium and major vessels, respectively [20]. In the same paper, patients with carinal and/or tracheal resection achieved 22% long-term survival to their patients, while no survivors at 5 years were found after vertebral resection. The only significant prognostic factor they identified was the completeness of resection ($P < 0.05$). Similarly, Shirakusa and colleagues reviewed their experience in extended operations for T4 lung carcinoma [21]. Interestingly, the results were found far better in the last period of their study (from 1992 to 1997), with a 3-year survival rate of 25%, compared with the 7% observed in the former period (1978–89), showing an increasing experience in the management of patient' s care. In this study oesophageal invasion was clearly identified as the worst prognostic factor. Authors emphasised the prognostic value of nodal status with median survivals of 25.5 and 14 months in N0-1 and N2-3 diseases respectively. These data were confirmed by Takuashi and colleagues, who analysed the prognostic factors for 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 [22]. According to the principle that the tumour debulking induced by neo-adjuvant treatments can render resectable some locally advanced non-small cell lung tumours in selected patients, chemotherapy, or chemoradiotherapy was proposed as induction pre-operative strategy in stages IIIB patients. Rendina and colleagues reported a dramatic downstaging in their patients after chemotherapy alone in a series of 57 patients with T4 tumours, including tracheal, superior vena cava, left atrial, or vertebral involvement [23]. Major complications were observed in 16% of the patients, including two cases of bronchopleural fistula.

Regarding the T4 descriptors from the International Staging System separately, some of them, invading 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 tumours from the lower lobe developed around the inferior pulmonary vein can extend in the atrial wall of the heart. In some patients a left atrial resection can be performed, either by the means of direct clamping and suture, or stapling, of the left atrium, or patch-replacement of the atrial wall (pericardial or prosthetic patch), with or without extracorporeal circulation. Klepetko and colleagues reported a series of 7 patients operated for lung tumours invading thoracic aorta [24]. In this Austrian study surgical resection was performed using extracorporeal bypass, without any mortality. The 4-year survival rate was 25%. Thoracic aorta can be resected either by lateral clamping or complete interruption of the descending aorta, which needs to use a by-pass during the step of resection and prosthetic reconstruction. Tsuchiya and colleagues reported also a series of 7 patients with invasion of the thoracic aorta [25]. Fukuse and colleagues reported a series of 42 patients operated upon for lung cancer invading the left atrium or great vessels [26]. The left atrium was resected in 14 patients, great arteries in 15, and superior vena cava in 14. A complete resection could be achieved in only 15 patients of the whole series. Mortality rate of was low (2.4%), regarding the complexity of the procedures. Overall 3-year survival was 17%. Again, low stages in nodal status were associated with a better survival ($P = 0.0013$) and great vessel invasions were found to be of better prognosis than

atrial involvements ($P = 0.036$). Great arteries include the sub-clavian artery, which can be invaded in the cases of apical chest tumours. Sometimes vascular resection and/or reconstruction are needed to achieve an *en bloc* resection of these anterior extending Pancoast' s tumours [27]. An anterior cervico-thoracic incision such as the transmanubrial approach gives an outstanding access to the supraclavicular area, as well as the upper anterior mediastinum [28].

## Superior vena cava

Invasion of the superior vena cava by a T4 tumour coming from the right upper lobe led surgical teams to attempting lobectomies or pneumonectomies extended to the vena cava [29]. Different aspects of this topic are controversial. In fact, direct extension to the vessel by the tumour itself is a rare situation. Usually a vena cava resection is needed by extension of a bulky disease, in which the nodal disease actually is the most component, and by consequence the tumour remains difficult to classify, between N2 or T4. One could discuss the rationale of resecting a superior vena cava for bulky N2 disease, regarding the high potential of metastatic spreading 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 many patients described in the literature. Looking at the anatomy and the diameter of a normal superior vena cava, it seems unlikely that a partial resection could allow a complete tumour resection including an adequate security margin of normal tissue around the tumoural extension, without reducing the internal lumen of the vessel, with a high risk of massive thrombosis in this low-pressure flow system. 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 needed. Indeed a unilateral revascularisation increases the risk of upper limb thrombophlebitis. However, unilateral or bilateral revascularisation remains a controversial issue, as well as the need for the duration of postoperative anticoagulation therapy. In addition, high rates of postoperative morbidity jeopardise the outcome expected with these attractive procedures. Several published series suggest that lung carcinomas invading the superior vena cava can be managed surgically with acceptable long-term outcomes. Therefore, in a paper by Spaggiari and colleagues, a complete resection with grafting was performed in only 7 patients out of a series of 25 superior vena cava resections for lung cancer, while tangential resection was performed in 12 patients [30]. Five patients (20%) had incomplete resections. Postoperative complications occurred in 36% of patients and mortality was 12%. Despite these disappointing immediate results, long-term outcome was encouraging, since overall calculated 5-year survival was 29%. A multi-centre international review of prosthetic replacement after superior vena cava resection for NSCLC in 28 patients, in which N2 involvement was present in 50% of the patients, showed the same rates of postoperative morbidity and mortality (39% and 14%, respectively) [31]. The overall survival rate at 5 years was only 15%, however, probably reflecting the adverse impact of mediastinal lymph node metastases. Thomas and colleagues reported on 15 patients who underwent radical resection, with concomitant vascular reconstruction for lung cancer invading the superior vena cava [32]. Two of these patients presented with superior vena cava (SVC) syndrome. Direct extension to the superior vena cava by the tumour itself (T4) was found in 11 patients. There was one postoperative death, and non-lethal morbidity was reported in 2% of the patients. The overall survival rate at 5 years was 24%.

## Carina, trachea

A bronchial carcinoma of the right lung extended to the lower part of the thoracic trachea, and/or the tracheal carina can be resected in selected patients. Although this kind of resection is technically feasible, true indications are fairly rare, because the oncological safety margin demands resection of healthy tissue beyond the dysplastic zone, which often surrounds the actual tumour. In these cases a right pneumonectomy is enlarged to the tracheal bifurcation and the airway is reconstructed by 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. Indeed Tsuchiya and colleagues reported only 13 complete resections in a series of 20 carinal resections [33]. Resection was performed according to the sleeve-resection procedure with end-to-end re-implantation of the contralateral bronchus onto the trachea. These operations, necessarily combined

with mediastinal lymph node dissection, carried an additional risk of morbidity, especially poor bronchial healing or even esophageal necrosis caused by the devascularisation it induces. The hospital mortality is high, from 10 to 30% [34]. Despite a high rate of post-operative morbidity (10 to 30%), including bronchial dehiscences, long-term survivals have been achieved in 15 to 23% of the cases [33,34]. Various surgical techniques of carinal resection have been summarised by Mitchell and his colleagues, who reviewed the clinical experience at Massachusets General Hospital during the past decades [35]. The largest series in the world shows a very high rate of postoperative complications (39%) and an operative mortality of 13%. Anastomotic complications (dehiscence or stenosis), who occurred in 17% of the cases, were found as predictor of operative mortality ($P=0.04$). Yatsuyanagi and colleagues focused their study on anastomotic complications after bronchoplastic procedures [36]. Out of 47 cases, anastomotic dehiscence or stenosis were both observed in 8.5%. Neither the operative procedure, nor the suture material was found as predictor of airway complications. The only predictive technical factors were a positive resection margin ($P<0.01$) and pre-operative chemotherapy ($P<0.05$). Nodal involvement at postoperative pathological examination (pN0-1/N2) was the only clinical predictor of bronchial complications. Because of anatomic considerations, right lung carcinomas can extend both to the superior vena cava and the tracheal bifurcation. These situations need a combined tracheal sleeve and superior vena cava resection. Such complex operations are associated with a high risk of mortality and major morbidity (50%) [37]. Moreover, as demonstrated by Sakurada and colleagues in a review on 114 patients who underwent surgery for T4 lung cancer, the presence of more than one factor of T4 (i.e. superior vena cava plus trachea) in the same patients jeopardises long-term survival ($P<0.01$) compared with one T4 factor only [20].

## Vertebral body

Non–small cell lung cancers invading the thoracic inlet can easily involve spinal structures because of their particular anatomic situation. For this reason, most of the tumours invading the spine are located in the superior sulcus, although vertebral extension can be observed in tumours more caudally situated. Initial local control as a result of the first treatment provides the only possibility of survival for patients with superior sulcus tumours [38]. The best local control for resectable tumours is achieved by surgical operation, provided the resection is complete and respecting oncological principles [39]. Since the first descriptions of surgical resection in Pancoast tumours, several limitations to surgical resection have been successively surpassed [40,41]. Paulson, in his classic article from 1975, identified contra-indications to surgical intervention, which included invasion of the vertebrae [42]. Tumours involving the transverse process or the lateral part of the vertebral body could be resected through an enlarged posterolateral thoracotomy [43]. However, direct major invasion of the vertebral body remained an absolute contra-indication to surgical repair, until the first report in 1996 of a successful total vertebrectomy for *en bloc* resection of lung cancer invading the spine [44]. Among the factors that determine outcome in patients with superior sulcus tumours treated by multi-modal approach at the University of Texas MD Anderson Cancer Center, surgical treatment was found to be a significant predictor ($P<0.01$), while vertebral body involvement remained marginally significant ($P=0.05$) [45]. 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 [18]. Their surgical technique consisted of dissecting the vertebral body through normal-appearing bone and removing the remaining portion of grossly normal vertebral body with a high-speed burr resection. Preliminary results on 17 patients (median follow-up = 25 months) showed no postoperative lethality, consistent morbidity, tumour recurrences in half of the patients, and a 2-year survival rate of 80% for completely resected patients. In the same way, at l' Institut Mutualiste Montsouris, an *en bloc* technique of resection was developed, in an attempt to respect oncological principles, by means of a no-touch resectional attempt. Variations in techniques between both institutions probably reflect philosophical differences between orthopaedic surgeons, who are involved at Montsouris, and neurosurgeons at MD Anderson [19]. Nevertheless, despite these variations, results are quite similar, since updated data from 32 patients showed a complete resection rate of 88%, with a 3% rate of postoperative mortality. Severe morbidity was observed in a third of patients (32%). Five-year survival rates were 24% and 40% for the entire series and completely resected T4 patients, respectively. These completely resected T4 patients had a median survival of 44 months. It is important to notice that 24 out of 32 patients received induction treatments: 17 were treated by induction chemotherapy (vinorelbine/cisplatin, 2 cycles); 5 patients

received concomitant chemoradiotherapy (42 gray-bifractionated radiation therapy, concurrent cisplatin, 5-fluorouracil, and vinblastine, 2 cycles); and 2 patients received only pre-operative radiotherapy. These results can be compared with those reported by the team of University of Texas MD Anderson Cancer Center, which observed an overall actuarial survival at 2 years of 54% [18]. In completely resected T4 patients ($n=11$), the median survival was found to be 25 months. Disease-free-survival rates at 2 years of this aggressive strategy compared favourably with the results achieved by non-surgical treatments. In the same institution, Komaki and colleagues found a 15% local control rate at 2 years in Pancoast tumours with vertebral involvement [38].

## Multi-modal approach

Several studies have demonstrated the feasibility of surgical resection after induction chemoradiotherapy in patients with stage IIIB NSCLC [5,11]. Stamatis and colleagues reported a complete resection rate of 48% after bifractionated radiotherapy associated with chemotherapy given pre-operatively in 56 patients with stage IIIB disease [46]. The 5-year survival rate in completely resected patients was 43%, while overall 5-year survival of the entire series was 26%. At Montsouris, surgical resection after induction chemoradiotherapy achieved an encouraging 28% long-term survival for patients with stage IIIB disease in whom chemoradiotherapy alone failed to control disease [8]. Tumour response was observed in 73% of the patients and complete resection could be achieved in 58%. Interestingly the survival according to 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 patients.

Thus, patients with stage IIIB NSCLC can be subdivided into 2 main groups: those in whom surgery may be possible and those in whom it is not. In highly selected patients, a surgical resection can be performed in this category of locally advanced NSCLC. However, these patients with locally advanced disease have a high potential of metastatic spread. Surgery after induction was reported to be feasible and complete resection possible in more than 50% of patients [5,6,8]. Such an aggressive surgery is part of a combined multidisciplinary treatment strategy, but a remaining question is the relevance of proposing surgery to non-responders [47]. In the tumour-node-metastasis (TNM) International Staging System T4 tumours are currently classified as ' unresectable locally advanced' stage IIIB. Nevertheless, the fact that surgical intervention makes it possible to achieve complete remission and to spare patients with residual disease after chemoradiotherapy argues for changes in the TNM classification. A subclassification of T4 tumours as ' potentially resectable' T4-1 and ' definitively non-resectable' T4-2 has been proposed [48]. Moreover, the prognostic influence of nodal downstaging after induction therapy would suggest to modify the current NSCLC staging system, in attempting to better define therapeutic subgroups [8,49,50].

In conclusion, surgery remains a valuable curative procedure for lung carcinomas, and must be considered as an option in any patient in whom it appears feasible, including marginally resectable T4 tumours, associated with N0 or N1 nodal involvement.

## Conflict of interest statement

None declared.

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