The role of surgery in non-small-cell lung cancers

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Introduction

About 40% of patients with non-small-cell lung cancer (NSCLC) present with stage IV disease, while resectable early stages I–II and marginally resectable locally advanced stage III each represent one-third of the patients, respectively. The anatomical surgical landmark has been paradigmatically established by the international staging system between stages IIIA and IIIB [1]. Clearly, this frontier does not reflect reality, since patients with stage IIIA disease are daily excluded from surgery by surgeons, while in some situations, stage IIIB disease is considered for resection [2].

Surgery in stage I–II disease

Surgical resection remains the treatment of choice for stages I and II provided the general and respiratory conditions allow the patient to undergo the planned surgical procedure. According to clinical and surgical findings, various resections can be performed in lung tumors: right or left pneumonectomy, upper, middle or lower right lobectomy, and upper or lower left lobectomy. On the right side, bilobectomies can also be performed, either upper, middle or lower, and middle bilobectomies. Anatomically, right upper and middle lobes have a common venous drainage via an upper pulmonary vein, whereas at the bronchial level, a common trunk, the intermediate bronchus, serves both middle and lower lobes. Resections less than lobectomy, such as anatomical segmentectomy or wedge resection, must be reserved for compromised patients. Indeed, a randomized study conducted by the North American Lung Cancer Study Group established clearly that lobectomy associated with lymph node dissection is the gold standard for localized NSCLC, since more limited resections were followed by a three times higher local recurrence rate [3].

A particular presentation concerns stages IIB, T3N0M0 tumors. The descriptor T3 indicates either an endobronchial tumor, involving the main bronchus close to the carina, without invading it, or a tumor invading the parietal wall of the thorax. In this specific condition, an en bloc resection is required, removing together a lobe or more and a costal flap, ideally without opening the tumor block [4]. An initial thoracoscopic exploration can be required to assess adequately actual invasion of the parietal wall, which is frequently suggested but not proven by imaging methods, including computed tomography scan and magnetic resonance imaging. Chest wall reconstruction after en bloc resection can be performed using various prosthetic techniques such as polytetrafluoroethylene (PTFE) patch, metallic plates or others. Apical chest tumors invading the superior sulcus can also be resected by an en bloc resection removing the upper lobe and the first ribs together, using different approaches. The classical posterolateral approach described by Paulson is frequently performed after preoperative thoracic radiotherapy [5]. Sometimes, nervous roots (C7 or C8) must be sacrificed, leading to radicular sequellae. Anterior apical tumors but also posterior Pancoast’s tumors can be removed using an anterior cervicothoracic approach, allowing subclavian vascular resections, venous, arterial or both, with anatomic or prosthetic reconstruction, by the means of PTFE ring-reinforced grafts [6]. Published series show 30% overall 5-year survival rates in T3N0M0 (stage IIB) NSCLC [7].

Surgery in stage III disease

The outcome of locally advanced stage IIIA NSCLC is mainly related to N2 mediastinal nodal disease. In fact, N2 involvement of lymphatic structures is an heterogeneous disease, as shown by Martini and Flehinger [8], who identified two subcategories of patients: those in which mediastinal disease could be histologically documented before surgical treatment, considered as ‘clinical N2’, and those in whom N2 was found at surgery, so-called ‘minimal N2’. A clear prognostic difference between the two subcategories was confirmed in a large retrospective study of 702 patients with N2 NSCLC, treated by surgery with or without induction chemotherapy (P<0.0001) [9]. Obviously the best surgical staging procedure for identifying clinical N2 disease is mediastinoscopy. However, the areas accessible through cervical mediastinoscopy are limited to anterior paratracheal left and right nodal levels, excluding in particular the aorto-pulmonary window, which can only be explored through a left thoracoscopy. Owing to the poor prognosis of clinical N2, induction treatments have been tried in multiple studies, with controversial results in terms of survival. Two small randomized studies demonstrated a clear advantage in favor of induction chemotherapy followed by surgery compared with surgery alone in N2 patients [10, 11]. The low statistical power and particularly poor outcome in the surgical arm in both studies jeopardized their impact on clinical practice. Nevertheless, bad results in the surgical arm can be easily explained by a selection bias of N2 patients, since...
only ‘clinical N2’ patients were enrolled in these trials, from which ‘minimal N2’ patients of better prognosis were excluded. Moreover, these results were not confirmed for stage IIIA NSCLC in a large European trial examining the same question, in which 373 patients have been randomized [12]. Another retrospective study of >700 patients with resected N2 NSCLC showed that those treated preoperatively achieved a significantly better survival than patients who did not receive induction chemotherapy [9].

The role of surgical resection in locally advanced-stage NSCLC is currently being tested in clinical trials. According to the principle that tumor debulking by neo-adjuvant treatments can render some locally advanced tumors in selected patients resectable, chemotherapy or chemoradiotherapy was proposed as induction preoperative treatment in stage IIIA and IIB patients. A randomized study by the North American Intergroup attempted to assess the relevance of surgical resection in stage IIIA NSCLC with N2 disease [13]. This trial, INT 0139 (RTOG 9309), asked the surgical question on a very homogeneous group of T1–3/N2 disease. Interestingly, half of the patients (46%) were downstaged to N0, and for those patients median survival was 37 months. These results emphasize the hypothesis that the absence of tumor in mediastinal nodes at surgery is the strongest predictor of long-term survival. Previous studies have reported that the mediastinal lymph node status after induction treatment had a prognostic significance for patients treated with post-induction surgery. In a study including 42 stage IIIA N2 patients treated with multimodality therapy, Choi et al. [14] reported that the degree of lymph node downstaging was translated into a survival benefit, since the 5-year overall survival was 79%, 42% and 18% for postoperative tumor stage 0/I, II and III, respectively. On the other hand, the absence of mediastinal lymph node involvement after induction therapy for stage III patients is always associated with a long-term survival of >30% after surgery, whatever the initial T stage. In a retrospective study with >700 N2 patients with completely resected disease, nodal clearance after induction chemotherapy induced far better survival than observed in the entire group of patients with clinical N2 disease [9]. These findings were confirmed by Betticher et al. [15], who showed that mediastinal downstaging is the most powerful positive prognostic factor for survival (P<0.0001). A prospective approach for future clinical practice could suggest reserving surgery only for patients who respond at the mediastinal level after induction treatment. Patients with negative positron emission tomography (PET) scan results after induction treatment could be offered surgery, provided predictive value of PET could be confirmed in this post-induction situation.

Moreover, it has been proven that complete resection increases disease-free survival, and therefore probably can improve a patient’s quality of life.

Stage IIB includes T4 tumors with invasion of mediastinal organs. Surgical resections have been described for T4 tumors involving heart, great vessels, trachea, carina or vertebral bodies [16]. Left atrial invasion of the heart can be observed when a very proximal perivenous tumor mass extends in the wall of the atrium. Tsuchiya et al. [17] reported a 22% 5-year survival rate in a series of 44 patients after left atrium resection. Owing to involvement of the thoracic aorta or aortic arch vessels, T4 tumors have been resected in some very selected cases with the use of cardiopulmonary bypass [18, 19]. Superior vena cava invaded by NSCLC can be resected either partially or completely [20]. Reported results of this type of resection showed a 15% 5-year survival rate in a multicenter retrospective study [21].

Although resection of lung cancers involving or invading the carina or lower trachea 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 tumor. Indeed, Tsuchiya et al. [22] reported only 13 complete resections in a series of 20 carinal interventions. Resection is 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, carry an additional risk of morbidity, especially poor bronchial healing or even esophageal necrosis due to devascularization. Hospital mortality is high, ranging from 10% to 30% [23].

Vertebral body involvement has long been considered an insurmountable obstacle to curative resection [23, 24], but recent progress in spinal surgery has opened new possibilities [25, 26]. Two-stage surgery allows en bloc partial or complete resection of the vertebral body (or bodies) together with the lung resection needed. An overall 5-year estimated survival of 25% was found in the series of 26 patients with apical NSCLC invading the spine, operated on at the Institut Montsouris in France [27]. These outstanding procedures, requiring the participation of highly specialized spinal surgeons, are currently in development and address the issue of induction (chemo- and/or radiotherapy) strategies.

In conclusion, surgery remains a valuable curative procedure for NSCLC and must be considered as an option in any patient in which it appears feasible.

References