The surgeon and the oncologist in non-small cell lung cancer (NSCLC)

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A strict collaboration is necessary between the oncologist and the surgeon, both must know the respective problematic competences and must contribute together to all phases of clinical management of patients affected by NSCLC.

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Lung cancer is the leading cause of cancer death in many countries. Despite major efforts to reduce smoking rates, lung cancer continues to claim more lives than the next three major cancers combined. Over the past 10 years, in the Western World the incidence of lung cancer in men has begun to decline but in women it is expected that lung cancer will continue to rise. Moreover, the number of patients affected by lung cancer continues to increase in developing countries and up to 50% of new lung cancer cases occur in former smokers and those who have never smoked [1]. Despite the recent developments in the care of this disease and in the field of cancer research, the prognosis for patients with lung cancer remains dismal, with an overall five-year survival rate of 14% [2]. The poor results have encouraged the attempt to associate all available therapeutic arms: at present all curable tumors (except for the stage Ia) are treated by surgery and systemic chemotherapy. Therefore, a strict collaboration is necessary between the oncologist and the surgeon. It is very important to perform an accurate loco-regional staging to assess the gold-standard treatment and the resectability of the neoplasia. Indeed an incomplete resection is not useful in NSCLC. The methods in Clinical staging widely vary. The basic chest X-ray can show a paradox of the emidiaphragm – generally due to unresectable T4 tumors and/or bulky N2–N3 disease. The CT-scan is fundamental to define the clinical staging (TNM) of the tumor: it allows to evaluate the exact local extension of the primary tumor (T factor) and it can determine the lymph-node involvement (N factor) based on their size (even if the use of a cut-off of 10–15 mm for normal nodes provided sensitivity and specificity for detecting nodal metastases of only 40% to 70%) [3–4]. The Nuclear Magnetic Resonance (NMR) is useful to obtain specific information about the involvement of great vessels, diaphragm and chest wall. The Positron-emission tomography (PET) is emerging as an important non-invasive test for mediastinal assessment: it is significantly better than CT-scan for the detection of N1 or N2/N3 disease and it can prevent non-therapeutic thoracotomy. However, a positive PET for mediastinal nodes must be confirmed by tissue acquisition, because positive predictive value is only 56% [5]. Bronchoscopy, with Trans Bronchial Needle Aspiration (TBNA), or mediastinoscopy are considered the gold standard for invasive mediastinal lymph-node evaluation. Video-assisted thoracic surgery (VATS) and anterior mediastinotomy are the procedures of choice for invasive mediastinal evaluation in the aorto-pulmonary (A-P) window. Moreover, VATS is complementary to cervical mediastinoscopy because it helps to stage the lymph nodes in the A-P window (#5, 6), as well as the para-esophageal (#8) and the pulmonary ligament (#9) lymph nodes. VATS is also extremely useful to exclude malignant pleural effusions in otherwise operable patients. This examination can be done in the operating room immediately prior to formal thoracotomy [6]. Surgery remains the best treatment modality for potential cure in patients with NSCLC. Surgical resection is the primary therapy for stage I/II NSCLC. Reported survival data range between 24% and 30% for stage-IIB patients and approximately between 61% and 79% for stage IIA patients, with distant metastasis being the dominant form of relapse after surgical resection. There is a strong rationale that supports the concept of the addition of systemic therapy to surgery either preoperatively or postoperatively even in patients with early-stage disease. Randomised trials of adjuvant chemotherapy show an absolute survival benefit of 12–15% for patients receiving postoperative chemotherapy and these results suggest that adjuvant platinum-based chemotherapy may become the new standard of care in resected stages IB-II NSCLC [7–8]. The addition of chemotherapy to local treatments such as radiation or surgery is now considered the standard of care in the Western World for patients with stage III [1]. Stage III comprises a fairly heterogeneous group of tumors and the optimal approach is still debated in these subgroups. In the IIIA (T3N1) group the role of surgery is clearer and these patients should undergo adjuvant chemotherapy if they have a good performance status (PS). Radiotherapy should be added only when the surgeon feels that resection margins were unusually close [9]. The disappointing
survival rates with surgery alone in N2 disease histologically proved before the surgery (stage IIIA), have led to evaluate the efficacy of multimodality approach including the induction treatment with preoperative chemotherapy, in order to early treat the micrometastatic disease, to reduce the intrathoracic tumor size thus improving resectability and, as shown in several phase-II trials and some phase-III trials, to ensure almost complete dose delivery of chemotherapy. Only few, small randomized phase-III studies of neoadjuvant chemotherapy in stage IIIA (N2) disease have been published. The oft-quoted Rosell et al. [10–11] and Roth et al. [12–13] studies provided data supporting neoadjuvant chemotherapy followed by surgery for selected patients with IIIA NSCLC. Although other studies did not demonstrate a benefit with neoadjuvant treatment for IIIA (N2) disease [14–15] this approach has however gained wide acceptance. T4 tumors can be divided in potentially resectable T4 (satellite nodule tumor, invasion of superior vena cava, carina, lower trachea, left atrium, and vertebrae) and definitely non-resectable T4 (malignant pleural or pericardial effusion, invasion of esophagus) [16]. The patients with T4 tracheal invasion or T4 pulmonary metastases showed a significantly better prognosis than that of the patients with T4 extrapulmonary invasion [17], and in these patients a neoadjuvant chemotherapy is put forward. With the aim to improve the local control and resectability, preoperative radiation in addition to chemotherapy has been introduced in the neoadjuvant treatment setting for stage III disease. The feasibility of this approach has been assessed in several phase-II trials [18] but there are not randomized studies supporting neoadjuvant chemo-radiotherapy. At this moment, good results are obtained in the complex management of Pancoast tumor, using a multimodality approach, involving chemo-radiotherapy and surgical resection [19]. Some important clinical questions are still open regarding the surgical management of patients with NSCLC. There is emerging evidence that there may be a role for sublobar resection (segmentectomy or even wedge resection) for small stage I tumors [20], but there are not yet prospective randomized data available about this. Currently, to perform a lobectomy or a larger procedure, is still considered as the gold standard, even for limited lung cancer [21]. Some studies showed that performing a full mediastinal lymph node dissection in stage I may improve pathologic staging, but there

Figure 1. NSCLC T2 N2. Three CT-scans show the primitive neoplasm (a), aorto-pulmonary window pathologic lymph-nodes (b) and intraparenchimal pathologic lymph-nodes (c), respectively. The same CT-scans after neoadjuvant chemotherapy clearly show the pathologic tissue volume reduction in all districts (d, e, f).
isn’t proven therapeutic improvement over a systematic sampling [22]. In stage II and IIIA a complete mediastinal lymph node dissection allows to identify significantly more levels of N disease and it is associated with improved survival when compared with systematic sampling even if the survival advantage is limited to the patients with tumors on the right lung [23]. For surgically resected early-stage lung cancer two definitive paradigm-shifting studies clearly showed that surgery following adjuvant chemotherapy could prolong the survival and improve the cure in NSCLC with 12% and 15% improvements in long-term survival [7–8]. The question of whether and/or when perform surgery in stage IIIA (N2) disease is not clear yet. For example poor PS patients with N2 disease are not eligible for induction chemotherapy followed by a major operative procedure and patients with N2 ‘bulky’ disease should be treated by definitive chemo-radiotherapy (for these patients a very poor survival rate is reported regardless which treatments they receive). Preoperative chemotherapy alone generally is tolerated better than combined chemo-radiation; therefore preoperative chemo-radiation should be proposed only for more extensive N2 nodal involvement (larger nodes unlikely achieve a complete resection with clear margins) and for patients with at least a good PS. Surgical resection can achieve clear margins when maximal diameter of involved mediastinal lymph nodes is less than 1.5–2 cm and these patients can be operated after chemotherapy alone. After neoadjuvant therapy the patients should be evaluated again and if there is no disease progression should be candidate to a complete surgical resection [9] (Figure 1). The most common procedure performed for a T4 tumor involving the tracheal carina is the right carinal pneumonectomy; the reported 5-year survival rate of 51% and 32% respectively for T4 N0 and T4 N1 patients (but

**Figure 2.** Right tracheal sleeve pneumonectomy in NSCLC of right main bronchus infiltrating tracheal carina. (a) Endoscopic view; (b) Operation scheme; (c) Operative field after removal of right lung and tracheal carina; the tracheal tract (*) and the left main bronchus (**) before the anastomosis (inside the bronchus there is the tube for high frequency jet ventilation); (d) Anastomosis completed.

**Figure 3.** (a) CT scan: the neoplasm interests the pulmonary artery and infiltrates the origin of left upper lobar bronchus with consensual atelectasis. The broncho-vascular reconstruction technique allows to make a radical resection and to avoid pneumonectomy; (b) Intraoperative view demonstrating the removal of the left upper lobe with bronchial sleeve resection and reconstruction; (c) After bronchial reconstruction the vascular anastomosis is carried out.
12% only for T4 N2/N3 patients) [24] and the acceptable mortality and morbidity rates with skill surgical management suggest the feasibility of curative surgical procedure (Figure 2). The induction therapy represents a potential risk factor for the carinal reconstruction anastomosis, while a postoperative adjuvant therapy can be consider. Patients with T4 tumors with mediastinal involvement, who don’t have lymph-node involvement, are uncommon. When carefully staged and selected, however, some patients appear to benefit by adding resection as part of the treatment, compared to chemo-radiotherapy alone. Patients with T4 disease must be accurately selected by resectability and PS: definitely resectable patients should be first operated and then treated by adjuvant chemotherapy; resectable patients with poor PS should undergo definitive chemo-radiotherapy; patients not surely resectable with good PS could undergo neoadjuvant chemo-radiotherapy and after a re-evaluation could be operated on. Neoadjuvant chemo- (radio-)therapy can increase operative morbidity and mortality. Even if in some studies surgical morbidity or mortality after neoadjuvant chemotherapy were not observed [25], in an Intergroup trial, testing the value of surgical resection after combination chemo-radiotherapy in patients with stage IIIA N2, the treatment-related death rate in the surgical arm was 7% (mainly in patients undergoing right pneumonectomy) versus 1.6% in the non-surgical arm [26]. In a study of the Memorial Sloan-Kettering group [27] the right pneumonectomy after neoadjuvant chemotherapy showed a 24% postoperative mortality rate. These data suggest the need for a careful selection of the patients considering either the main prognostic factors either the PS. Is it correct, for example, to suggest a neoadjuvant chemotherapy for a patient with minimal N2 disease but with a poor PS? On the other hand, the surgeons have a series of technical arrangements to avoid an aggressive resection with higher mortality and morbidity, using a reconstructive procedure (e.g. bronchial and/or arterial sleeve resections) [28] (Figure 3).

The professional treatment of NSCLC is then multidisciplinary. The recent studies demonstrate the better results obtained with the association of more weapons (surgery, chemotherapy and radiotherapy) in the war against the NSCLC. Oncologist and surgeon must work synergically giving the respective competences: the oncologist must globally evaluate the patient, judging their capacity to tolerate both pharmacological and radiological treatments, the surgeon must establish the resectability of the tumor. The availability of a multidisciplinary specialized and qualified team is therefore necessary in every hospital for an optimal cure of patients affected by NSCLC.

disclosures
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references


