At any stage, lung cancer is a potentially systemic disease. Stage IIIA (N2) disease typifies this assertion. However, it encompasses a complex area characterised by much confusion and controversy, because data derived from a particular historical subgroup of IIIA (N2) often are inappropriately applied to another current subgroup. The basics of its treatment include the need for chemotherapy, preceding or following an effective loco-regional treatment. The choice of the optimal loco-regional treatment, however, is all the more debated that the present systemic treatment is still poor.

From a very pragmatic point of view, this stage may be divided in three main categories: unresectable, potentially resectable and finally resected N2 tumours. At a glance, the delineation of the first category seems fairly subjective, since the definition of resectability relies on the surgeon’s experience and skill. In fact, most lung cancer clinicians can agree on what constitutes an unresectable N2 disease when any combination of some of the following characteristics exists: bulky, extranodal, fixed, multi-station, nodal disease. The prognostic bounders of the two other categories are obscure since they are moving continuously according to new investigational technological inputs. Indeed, the last category, finally resected N2 disease, results currently from incidental findings at thoracotomy or on the final pathological examination of the surgical specimen despite careful pre-treatment staging, including routine computed tomography (CT) scan and positron emission tomography (PET) and selective mediastinoscopy. Adding trans-oesophageal (EUS) and/or trans-bronchial (EBUS) ultrasound fine-needle aspiration to the work-up has the potential to reduce dramatically the portion of patients with unexpected N2 involvement at surgery [1], as well as to improve the overall prognosis of this ‘false negative’ category after surgery due to the well-known Will Rogers’ stage migration phenomenon [2]. Accordingly, routine application of such extensive staging will also change the blurry shape of the so-called minimal N2 disease, offering new insights on the place of first-line surgery.

The paper from the Leuven Lung Cancer Study Group [3] deals with the intermediate category. It consists of the meticulous retrospective evaluation of a prospective homogeneous surgical cohort of N2 non-small-cell lung cancer (NSCLC) patients considered as resectable at baseline. The authors should be commended for having provided data that help to assess the quality of lymphadenectomy — information currently unavailable in publications on the topic. It shows that in appropriately selected stage IIIA-N2 patients operated on after induction chemotherapy in a high-volume and experienced centre, surgery is feasible, safe and can result in an impressive number of patients with complete resection and a substantial 33% 5-year survival. Two phase II studies with intent-to-treat reporting and reliable long-term follow-up have pointed out remarkably similar 5-year survival rates of 36% [4] and 34% [5]. However, whether this approach is superior to radical modern thoracic radiotherapy techniques remains controversial. Lessons learned from four randomised trials [6—9], involving more than 900 patients with stage IIIA-N2 lung cancer, summarise in a better local control of the disease, but a modest and insignificant overall survival benefit for patients undergoing surgery compared with radiotherapy as loco-regional treatment after induction chemotherapy. Since these trials were diverse in terms of the interventions and populations, they are not suitable for pooled analysis. Unplanned post hoc analyses of subgroups of the above-mentioned phase II and phase III studies, when done, show similar findings as those from the Leuven group: the best survival figures are seen in patients in whom a complete resection has been achieved, a pneumonectomy has been avoided, a mediastinal nodal down-staging has been obtained or a single-station residual N2 disease was found. These findings also are relevant, but echo the hypothesis of the role of induction treatment as to select ‘winners’ [10]. Furthermore, as they were all defined postoperatively, they do not help in identifying those new patients who are most likely to benefit from multimodality strategies including radical surgery.

To date, multimodality treatment strategies with or without surgery are valuable options for potentially resectable stage IIIA-N2 disease. None could be claimed as a standard on evidence-based clues. Preference is to be given to the safest approach, which differs among national health systems, and in a given country, may vary among geographical areas. Improvements in dose-localisation techniques, and their diffusion, will certainly allow high-dose irradiation with near-surgical precision in patients with low-burden N2.
involvement while sparing of normal lung tissue and other radio-sensitive organs. To date, in the ‘real life’, continuous educational efforts towards standardising surgical practices and evaluating the quality of surgery [11] are similarly relevant ways to be pursued.

For the purposes of generating rational treatment guidelines, the TNM (tumour, node, metastases) classification is revised regularly, as it is in 2009 [12]. To achieve uniformity, the International Association for the Study of Lung Cancer also proposes a new lymph node map as well as a method of grouping lymph node stations into ‘zones’ for the purposes of future survival analyses [13]. However, these anatomical descriptors reflect only in part the biological heterogeneity of tumours. Recently, histology of NSCLC has been re-visited with the adjunct of anti-angiogenesis agents for which patients are required to have a non-squamous subtype [14]. Moreover, some biological predictive markers have been correlated with an improved response to epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors [15], or to tumour sensitivity to adjuvant platinum-based chemotherapy [16], prefiguring new exciting paradigms in the treatment of NSCLC with individualised tailored approaches. Certainly, the identification of similar predictors relating to tumour sensitivity to adjuvant platinum-based chemotherapy and radiotherapy (CT/RT) vs. CT/RT followed by surgical resection for stage II A (pN2 non-small cell lung cancer): outcomes update of North American Intergroup 0139 (RTOG 9309) [abstract]. J Clin Oncol 2005;23(Suppl.):7014.


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