Chairperson's Introduction

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The optimal treatment for patients with stage III non-small cell lung cancer (NSCLC) remains a challenge for clinical oncologists. Much of the controversy comes from the inappropriate distinction of the different subsets of this heterogeneous group of patients, ranging from (1) unforeseen N2 i.e. only detected at the time of surgery, to (2) preoperatively detected but potentially resectable N2, to (3) bulky unresectable N2, and, finally, to (4) patients with N3 lymph node involvement.

For that reason, accurate staging and assessment of resectability is of paramount importance, both at the time of diagnosis and after induction treatment. With all the modern tools available for this purpose – such as computed tomography (CT), positron-emission tomography (PET), integrated PET-CT, oesophageal or endobronchial ultrasound (EUS/EBUS) guided needle aspiration, mediastinoscopy and thoracoscopy – this has become a truly multidisciplinary process.

For patients with intra-operatively detected N2, there is little doubt that complete resection followed by cisplatin-based chemotherapy is the best strategy, while the value of postoperative radiotherapy remains unclear.

Likewise, for patients with bulky unresectable N2 or N3, it is clear that a combination of chemotherapy and radiotherapy is to be preferred. Surgery has no role here, as demonstrated in a recently reported European randomised trial (EORTC08941). This important study must be understood in its appropriate context of patients with *unresectable* IIIA-N2 disease: induction chemotherapy did not convert unresectable disease into resectable – as illustrated by the 50% incomplete resection rate in the surgery arm – and, not unexpectedly, did not result in better outcomes with surgery in comparison with radiotherapy, with a 15% survival at 5 years in both arms. Of note, surgery provided better local control (32% locoregional failure) than radiotherapy (55%).

For chemoradiotherapy approaches, a concurrent use of both treatments is more effective than a sequential use, but some patients are not suitable for the more toxic concurrent approach, because of co-morbidity or tumour spread requiring too large irradiation volumes. Several recent advances in radiotherapy contribute to potential further improvement: 3D conformal radiotherapy, stereotactic radiotherapy, gating techniques, and intensity modulated radiotherapy. All these approaches try to deliver a higher biologic dose without an increasing severe toxicity. As many patients still develop metastatic relapse after a concurrent approach, optimisation of the systemic part of the treatment is an urgent need. Chemotherapy in this radical setting is preferentially cisplatin-based; an individual-patient-based meta-analysis in advanced NSCLC recently convincingly demonstrated that cisplatin is a more active drug than carboplatin in this tumour. Full dose cisplatin and etoposide can be delivered safely concurrently with radiation, and there is ample historical experience with this combination. More recent cytotoxic agents such as gemcitabine, taxanes, or vinorelbine cannot be given in systemic doses in concurrent schedules, which led to questions on use of induction chemotherapy before, or consolidation chemotherapy after the concurrent schedule. Moreover, the advent of agents targeting the Epidermal Growth Factor Receptor (EGFR) or the Vascular Endothelial Growth Factor (VEGF), and their successful use in well selected patients with advanced NSCLC, has opened a great potential to test these agents in combination with chemoradiation, in an attempt to further improve treatment outcomes.

Patients with potentially resectable N2 were studied in several prospective studies with dedicated assessment of resectability. These series on induction treatment followed by attempted complete resection in general report similar 5-year survival rates of about 30%. Even if non randomised, many were well designed prospective trials, with intent-to-treat reporting and reliable long-term follow-up. In the randomised US Intergroup 0139 trial, chemoradiotherapy up to 45 Gy, randomly followed by either surgical resection or additional radiotherapy to a radical dose, was compared. Progression-free survival was significantly better in the surgical arm ($P = 0.017$), and the rate of

locoregional recurrence was significantly lower. Overall survival curves were overlapping for 2 years, but then separated, favouring surgical combined modality treatment with a 5-year survival of 27.2% versus 20.3% in the other arm, a 7% difference, but not reaching significance ($P = 0.10$). In an exploratory analysis – comparing patients undergoing lobectomy with a matched group treated by chemoradiotherapy – there was a significant survival advantage for the surgical group (5-year survival of 36% versus 18%, $P = 0.002$). The rationale of this approach is to provide surgery as the best local treatment for resectable NSCLC and improve outcome by induction therapy to manage distant micro-metastasis.

In conclusion, there is no generalised recommendation for the same multimodality treatment in each patient with stage III NSCLC. Chemotherapy, radiotherapy, surgery and targeted agents all are valuable components when making the choice of an optimal therapeutic approach for each individual patient with stage III NSCLC. In an era where we become convinced that customised treatment is the way forward for patients with advanced NSCLC, it would be a dangerous mistake to think that one single approach can be the best for each patient with stage III NSCLC. Dedicated staging and assessment of resectability are important tools in the customisation of treatment in this setting.

Conflict of interest statement

None declared.