

Novel treatment options in early-stage non-small-cell lung cancer

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1. Introduction

Early-stage lung cancer refers to patients presenting with clinical stages I and II non-small-cell lung cancer (NSCLC) according to the TNM classification. They represent approximately 20–25% of incident cancer cases in most population-based cancer registries, and radical surgical resection is considered the treatment of choice in operable and fit patients [1]. Although no prospective, randomised trial exists to compare surgery versus radiotherapy in the treatment of early-stage NSCLC, surgical resection has traditionally been considered the treatment of choice. Markedly improved survival rates are reported in surgical series in comparison to patients who did not undergo surgical resection for a variety of reasons [2]. This abstract will address some of the challenges of novel treatment options in these patients.

With low-dose computed tomography (CT) scan screening becoming the new standard of early detection of lung cancer, physicians and surgeons will be confronted with an increase in T1a lung cancer, disguised as non-calcified nodules. Although it is tempting to proceed to a parenchyma-sparing resection for issues of functional operability, the risk of local recurrence and inadequate intraoperative lymph-node staging should not be neglected. Whether some of these lesions can be treated by so-called sublobar resection – consisting of either anatomical segmentectomy or wedge excision – is currently the subject of intensive investigation by appropriate randomised trials. For a limited resection to be oncologically valid, a precise pre- and intraoperative diagnosis is imperative. In terms of preoperative diagnosis, specific criteria on chest CT as percentage ground-glass opacity (GGO), tumour shadow disappearance rate and histogram analysis have been shown to have a high predictive value^[3]. Three similar trials – JCOG 0802 in Japan, CALGB 140503 in North America and IEO S638/311 in Italy – are currently enrolling patients, and collaboration is highly regarded [4,5].

More tailored, personalised surgical therapy has recently been introduced. Quality-of-life parameters and surgical quality indicators become increasingly important to deter-

mine the short-term and long-term impact of a surgical procedure. International databases currently collect extensive surgical data, allowing more precise calculation of mortality and morbidity according to predefined risk factors. Centralisation of care has been shown to improve results [6].

Functionally inoperable patients are nowadays proposed stereotactic ablative body radiotherapy (SABR), in which hypofractionated doses are administered over a short period of time [7,8]. Although lung-cancer-specific time-to-event outcome data seem very promising, unusual late toxicity is increasingly being reported, and there is concern regarding the inclusion of variable fractions of non-pathologically proven non-calcified nodules [9]. Clearly, before extrapolating these results to functionally operable patients, large randomised trials with an unequivocal non-inferiority design should be carried out [10]. Other radiotherapeutic techniques in development to improve local control with minimal pulmonary toxicity are the application of different breath control devices and the introduction of hadron/proton therapy.

Radiofrequency ablation is another way of tackling pulmonary masses and nodules whereby a transthoracic radioprobe is inserted under CT guidance, allowing for a subsequent 'cooking' with electromagnetic energy. The technique is well known in the treatment of primary liver cancer and metastases, and several uncontrolled series have been reported in a mixed series of patients with primary lung cancer and lung metastases [11]. However, the technique lacks standardisation and long-term results, but is promising for centres which cannot afford SABR. There are currently no ongoing randomised trials [12]. An endobronchial application is certainly promising.

Adjuvant chemotherapy is the present standard of care in completely resected stages pII and III NSCLC, albeit toxicity is considerable and the observed improvement in outcome modest. Patient selection using molecular and biological biomarkers and signatures is likely to increase the fraction of patients benefiting from it. The large BIO-IALT study has described a number of prognostic and predictive factors, although recent reports challenge the accuracy of the

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techniques used [13,14]. One of the most critical issues regarding tumour biomarkers concerns methodology. Techniques for carrying out the test, the reagents used, methods used to score/quantify the results, the analysis and interpretation of the results are all critical yet prone to variability and error. Some are more subjective than others; many are simple and readily available, others are complex, expensive and less accessible. Complexity does not guarantee accuracy, greater reliability or relevance. In terms of biomarker testing of tumour samples, the handling and processing of the tissues prior to testing is of critical importance yet difficult to standardise, but these factors are often ignored or overlooked [15].

Biomarkers might be selected for patients preferably treated with agents targeted at hallmark pathways of oncogenesis: e.g. sustained proliferation, angiogenesis and avoiding immune destruction. Trials investigating the efficacy of adjuvant epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors, vascular endothelial growth factor (VEGF) inhibitors or vaccines against melanoma antigen (MAGE) are currently ongoing, and their results are expected to alter clinical practice [16,17].

Although neoadjuvant chemotherapy is better tolerated and its added value to outcome is similar to that of adjuvant, its widespread use suffers from a low rate of pathological remission, which is a precondition for a lesser resection to be carried out. Window-of-opportunity trials with neoadjuvant targeted agents and biological imaging are promising [18]. They have so far not been conducted in a biomarker-selected population.

The role of postoperative radiotherapy is currently limited to non-radically resected cases, although there are uncontrolled observations of its efficacy in subgroups of completely resected patients. In the ongoing randomised LUNGART trial, its role is explored in patients with clinical or pathological N2 disease [19].

An important handicap in present-day patient selection is the inaccuracy of clinical staging. Half or more of clinically staged patients are up- or down-staged at surgery [20]. Positron emission tomography–CT (PET–CT) scan and minimally invasive mediastinal ultrasound techniques are expected to improve on this figure and result in a stage shift.

Conflict of interest statement

None declared.

REFERENCES

- [1] Crinò L, Weder W, van Meerbeeck J, Felip E. Early stage and locally advanced (non-metastatic) non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010;21(Suppl. 5):103–15.
- [2] Reif MS, Socinski MA, Rivera MP. Evidence-based medicine in the treatment of non-small-cell lung cancer. *Clin Chest Med* 2000;21:107–20. ix.
- [3] Ikeda K, Awai K, Mori T, et al. Differential diagnosis of ground-glass opacity nodules: CT number analysis by three-dimensional computerized quantification. *Chest* 2007;132:984–90.
- [4] Van Schil PE, Asamura H, Rusch VW, et al. Surgical implications of the new IASLC/ATS/ERS adenocarcinoma classification. *Eur Respir J* 2012;39:478–86.
- [5] Anonymous. Comparison of different types of surgery in treating patients with stage IA non-small cell lung cancer. <http://www.clinicaltrials.gov/ct2/show/NCT00499330> [accessed 22.05.13].
- [6] von Meyenfeldt EM, Gooiker GA, van Gijn W, et al. The relationship between volume or surgeon specialty and outcome in the surgical treatment of lung cancer: a systematic review and meta-analysis. *J Thorac Oncol* 2012;7:1170–8.
- [7] Palma D, Lagerwaard F, Rodrigues G, Haasbeek C, Senan S. Curative treatment of Stage I non-small-cell lung cancer in patients with severe COPD: stereotactic radiotherapy outcomes and systematic review. *Int J Radiat Oncol Biol Phys* 2012;82:1149–56.
- [8] De Ruyscher D, Faivre-Finn C, Nestle U, et al. European Organisation for Research and Treatment of Cancer recommendations for planning and delivery of high-dose, high-precision radiotherapy for lung cancer. *J Clin Oncol* 2010;28:5301–10.
- [9] Ball D. Extracranial stereotactic body radiotherapy for stage I non-small cell lung cancer: still investigational or standard of care? *J Thorac Oncol* 2008;3:1209–10.
- [10] Anonymous. Surgery with or without internal radiation therapy compared with stereotactic body radiation therapy in treating patients with high-risk stage I non-small cell lung cancer. Available from: <http://www.clinicaltrials.gov/ct2/show/NCT01336894> [accessed 22.05.13].
- [11] de Baère T, Palussière J, Aupérin A, et al. Midterm local efficacy and survival after radiofrequency ablation of lung tumors with minimum follow-up of 1 year: prospective evaluation. *Radiology* 2006;240:587–96.
- [12] Bilal H, Mahmood S, Rajashanker B, Shah R. Is radiofrequency ablation more effective than stereotactic ablative radiotherapy in patients with early stage medically inoperable non-small cell lung cancer? *Interact Cardiovasc Thorac Surg* 2012;15:258–65.
- [13] Olaussen KA, Dunant A, Fouret P, et al. DNA repair by ERCC1 in non-small-cell lung cancer and cisplatin-based adjuvant chemotherapy. *N Engl J Med* 2006;355:983–91.
- [14] Friboulet L, Olaussen KA, Pignon JP, et al. ERCC1 isoform expression and DNA repair in non-small-cell lung cancer. *N Engl J Med* 2013;368:1101–10.
- [15] Kerr KM. Personalized medicine for lung cancer: new challenges for pathology. *Histopathology* 2012;60:531–46.
- [16] Anonymous. Chemotherapy With or without bevacizumab in treating patients with stage IB, stage II, or stage IIIA non-small lung cancer that was removed by surgery. Available from: <http://clinicaltrials.gov/ct2/show/NCT00324805> [accessed 22.05.13].
- [17] Anonymous. GSK1572932A antigen-specific cancer immunotherapeutic as adjuvant therapy in patients with non-small cell lung cancer. Available from: <http://clinicaltrials.gov/ct2/show/NCT00480025> [accessed 22.05.13].
- [18] Schaake EE, Kappers I, Codrington HE, et al. Tumor response and toxicity of neoadjuvant erlotinib in patients with early-stage non-small-cell lung cancer. *J Clin Oncol* 2012;30:2731–8.
- [19] Anonymous. Radiation therapy in treating patients with non-small cell lung cancer that has been completely removed by surgery. Available from: <http://clinicaltrials.gov/ct2/show/NCT00410683> [accessed 22.05.13].
- [20] Van Meerbeeck JP, Nicholson M, Gilligan D, et al. Adjuvant or neoadjuvant chemotherapy in early-stage non-small cell lung cancer (NSCLC): how would staging affect the patients treated? *J Clin Oncol* 2008(26 Suppl.) [abstract 7509].