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Small-cell lung cancer: local therapy for a systemic disease?

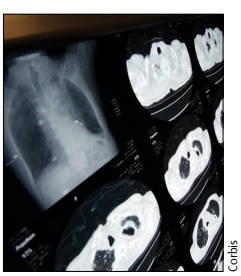
In *The Lancet*, Ben Slotman and colleagues report the results of a phase 3 trial of thoracic radiotherapy for small-cell lung cancer.[1] The trial is the most recent in a long line of studies showing that local radiotherapy benefits patients with small-cell lung cancer, a disease characterised by a bulky intrathoracic mass at presentation, a high propensity for metastasis, and high chemosensitivity, but with a poor prognosis.[2]

Combination of different modalities of cancer treatment offers several advantages. Reduction of the bulk of the tumour will increase blood flow and oxygenation to the tumour. The absence of overlapping toxic effects enables full effective doses of each treatment modality to be maintained, important for surmounting resistance to any one modality. Pignon and colleagues[3] described a 5% benefit in survival at 3 years when thoracic radiotherapy was added to induction chemotherapy for patients with limited stage disease. The benefit did not become apparent until about a year after randomisation.

De Ruysscher and co-workers confirmed a postulated interaction between chest irradiation and chemotherapy by showing better long-term survival if the overall treatment time for radiotherapy was shorter than 30 days.[4] This approach requires concomitant administration of both treatments and accelerated fractionation of radiotherapy. Furthermore, combined treatment modalities enable the eradication of micrometastatic disease in pharmacological sanctuaries—eg, the brain. A reduction in the incidence of symptomatic brain metastases and a 6% benefit in overall survival at 3 years were reported with the sequential addition of prophylactic cranial irradiation in responding patients with stage 1–3 disease.[5] The European Organisation for Research and Treatment of Cancer reported a doubling of 1-year survival with cranial irradiation in responding patients with extensive stage disease without a deleterious effect on overall health status.[6]

It took several decades and the pooling of data from hundreds of patients to obtain these results, but combined chemotherapy and prophylactic cranial irradiation are now considered the standard of care in many clinical guidelines.[7] The next logical step was to irradiate the tumour bulk in patients with clinically evident metastases. Slotman and colleagues[1] randomly assigned nearly 500 patients responding to first-line chemotherapy to either standard follow-up or thoracic irradiation consisting of ten fractions of 3 Gy. All patients underwent prophylactic cranial irradiation and no serious toxic effects were reported. Similar to early stage disease, the survival curves separated only at nine months after randomisation, favouring the thoracic radiotherapy group by 18 months. At 2 years, overall survival was 13% in the group of patients receiving thoracic radiotherapy versus 3% without radiotherapy; the number needed to treat for one more patient to survive for 2 years was 10·6. Presumably, the competing risk of death caused by extrathoracic metastatic disease that is refractory to chemotherapy becomes less important than the risk caused by uncontrolled disease at the primary site in unirradiated patients at 2 years. Hence, there is an ongoing need for development of novel drugs targeted against molecular alterations in small-cell lung cancer.[8]

The rationale for Slotman and colleagues' study was sound: intrathoracic progression was common in a previous trial of prophylactic cranial irradiation for patients



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with stage 4 disease.[6] Irradiation (or resection) of sites of residual disease after treatment with chemotherapy or targeted drugs is increasingly done, although without a strong evidence base, for various metastatic cancers.[9,10] Refreshingly, the radiotherapy in Slotman and colleagues' study was not technically complex and it would be easy to provide at low cost in even the most modestly resourced radiotherapy departments.

Should Slotman and colleagues' results therefore require oncologists to consider thoracic radiotherapy in all responders with extensive disease, as recommended by the authors? Only for selected patients. For example, would thoracic radiotherapy be appropriate in a responder who still has large volume liver metastases and minimal intrathoracic disease burden? Should we bring forward thoracic radiotherapy and administer it at an accelerated schedule and during chemotherapy? The trial's primary aim was to detect a difference in survival of 10% at 12 months, which the study did not do (HR 0·84, 95% CI 0·69–1·01), yet the delayed survival benefit was consistent with a previous practice-changing meta-analysis.[3] Information about patient-related outcomes would have helped to formulate answers to research questions, but the investigators did not report such outcomes. We await the results of a similar US trial in which patients with metastatic small-cell lung cancer are randomly assigned to prophylactic cranial irradiation with or without consolidative extracranial radiotherapy to locoregional and residual metastases.[11]

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JPvM was involved in the early stages of the trial discussed in this Comment while working at Ghent University Hospital in 2009–12, but did not personally enrol any patients. We declare no competing interests.

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Biodegradable stents: the golden future of angioplasty?

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Key steps in the biodegradable stent revolution, including the first-in-man results of magnesium[1,2] and poly-L-lactide (PLLA) stents,[3,4] have been reported in *The Lancet*. With more than 60 000 Absorb bioresorbable vascular scaffolds implanted in the past 3 years, a randomised comparison of metallic and fully bioabsorbable stents, both eluting the antiproliferative drug everolimus, is now presented by Patrick Serruys and colleagues.[5] The ABSORB II trial had a 2:1 single-masked design and a small sample population of 501 patients, with sophisticated coprimary endpoints of nitrate-induced vasomotion and changes in minimum lumen diameter (in-stent late loss) at 3 years. The results, presented are limited to secondary outcomes after 1 year of clinical follow-up, but address what matters most to patients and physicians—symptoms and adverse events—and include an elaborate analysis of procedural results including data from quantitative coronary angiography and intravascular ultrasound.

In ABSORB II, the Absorb bioresorbable scaffold and the Xience metallic stent were associated with very low and similar mortality, and target lesion revascularisation, at 1 year: the composite of cardiac death, target-vessel myocardial infarction, and clinically indicated target-lesion revascularisation occurred in 16 (5%) patients in the Absorb group *vs* five (3%) patients in the Xience group (difference 1·80%, 95% CI −2·48 to 5·16); and 1-year probable or definite stent thrombosis was recorded in three (0·9%) patients versus no patients (0·91%,