Pulmonary metastasectomy and the use of molecular and radiological markers: is this a way to reduce unavailing surgery?

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Pulmonary metastasectomy is now one of the commonest thoracic operations and is a major part of a Thoracic Department’s workload. The report by Schweiger et al. [1] in this issue of EJCTS provides a comprehensive update concerning biological and radiological markers. They note that these are not routinely used and propose that more information is needed in order to treat patients with pulmonary metastases adequately.

The review from colleagues in Vienna is timely. Confidence in knowing which patients can gain benefit from pulmonary metastasectomy has been shaken by a recent analysis by colleagues from Switzerland concerning the most common application of metastasectomy in colorectal cancer [2]. The selection of patients for pulmonary metastasectomy has relied predominately on preoperative factors known to be associated with longer survival: fewer metastases, a longer elapsed time since the primary operation and raised carcinoembryonic antigen (CEA). The significance of these features has been confirmed in a meta-analysis of studies published since 2001 including 2925 patients [2]. This analysis argues for stringent selection. Based on state-of-the-art statistical methods and large numbers of patients, the metastasectomy failure (i.e. early recurrence) was seen to double for each of these three preoperative factors [2].

The Swiss analysis [2] confirms the importance of the most familiar of the biological markers, CEA. Elevated CEA nearly doubles the likelihood of failure of metastasectomy due to early recurrence [hazard ratio (HR) = 1.91, 95% confidence interval (CI) 1.57–2.32]. The principal application of serum markers is in monitoring the treatment response of cancers [3], but earlier detection is pointless unless we can use the information for patient benefit. In the early years of hepatic resection for metastases [4], a CEA assay was proposed for surveillance: its elevation triggered a ‘second-look’ laparotomy for exploration of the colonic anastomosis, lymph nodes, the retroperitoneum and mobilization of the liver with the intent of removing any further cancer discovered. Effectiveness was tested in a randomized controlled trial. Patients were randomly assigned to have CEA elevation concealed or revealed to the surgeon. Patients whose CEA elevation was not disclosed survived longer than those who had it revealed [HR = 0.85, 95% CI 0.62–1.13, not significant] [5].

It is seductive to think that the more we know about the biology of a cancer the better we can select patients for further treatment. In the hands of thoracic surgeons this further surgery is pulmonary metastasectomy. Sophisticated research is being done with this objective. Cancer biologists in Santiago de Compostela, Spain, have identified genes related to cell movement, adhesion, cell death and proliferation in circulating colorectal cancer cells [6]. From Chicago, there is a study on specific microRNAs in resected pulmonary metastases and their correlations with high and low rates of progression [7]. Casting something of a shadow on this optimism is a study from London which reports heterogeneity in different metastases from the same kidney cancer. The authors conclude that heterogeneity can lead to underestimation of the tumor genomics landscape portrayed from single tumor-biopsy samples and may present major challenges to personalized-medicine and biomarker development [8]. Cancer biology is already very complicated and, so far, it appears to be only at an exploratory stage. It is well short of guiding us towards better targeting of our surgical skills. Markers might lead us to identify otherwise occult cancer, but it does not automatically follow that further surgery on metastatic cancer will be of benefit.

Historically each successive refinement of cancer investigation and imaging has had the effect of identifying subsets of patients that are literally beyond the reach of surgery: the disease is too diffuse or too extensive. Once that is known, these patients can be spared operations that cannot help them. In lung cancer that was the intention of the introduction of mediastinoscopy (and subsequent methods of mediastinal staging), routine computerized tomographic scanning and later, positron emission tomography. These methods are now used in the routine work up for thoracic oncological surgery and they have successively reduced the number of patients who undergo unavailing surgery. That necessarily reduces the number of operations we do, but it is undeniably a better outcome for patients than to undergo operations than cannot help and can only harm. Take the well-known example of CEA: when subjected to a randomized trial, the marker detected cancer progression, but the further surgery it prompted did not benefit the patient but unquestionably added hospitalization and suffering in their last months and years.
The leaders of the European Society of Thoracic Surgeons Lung Metastasectomy Project concluded ‘in the absence of a randomized controlled trial looking at the effectiveness of pulmonary metastasectomy on survival and quality of life, it is unlikely that the current practice will ever be influenced. Only one such trial is known to us’ [9]. The trial referred to is Pulmonary Metastasectomy in Colorectal Cancer (PulMiCC) (http://www.rbht.nhs.uk/research/cteu/projects/respiratory-disease/pulmicc/) and is now recruiting patients in England, Serbia and Italy with 160 patients enrolled. We need evidence of effectiveness which in this instance is best obtained by a randomized controlled trial. Sophisticated cancer biology may then allow us to individualize that evidence in the best interest of patients—but we need the evidence of effectiveness first.

When circulating tumour markers [5] or the studies of the genetic makeup of the cancer [6, 7] alert us to a greater likelihood of blood born dissemination, how should we as surgeons, use this information? [3] Should we pursue the escaping cancer with further surgery? It seems to us self-evident that we should have a more evidence-based reason than that ‘pulmonary metastasectomy is nowadays a common practice in thoracic surgery’ [1]. On the basis of existing evidence, it is our contention that we cannot reliably distinguish between the effect of the surgery itself and a non-causative association between surgery and longer survival. Patients who have slowly progressing disease, and have some years to live irrespective of treatment, provide more opportunities for further surgery and live through more treatment episodes rather than being alive because of them [10]. Alongside the laudable progress in the knowledge of the biology of the cancer we need well-designed trials to establish whether that knowledge can be translated into patient benefit.

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REFERENCES