



Lymph node metastasis in oesophageal cancer – what we (do not) know?

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Although many aspects of the treatment of oesophageal cancer remain controversial, one of them is beyond doubt: prognosis in this disease is still poor, with overall 5-year survival slightly over 10% (1). One of the most important issues determining prognosis is metastatic spread in the lymphatic system. The mechanism of this spread is poorly understood, as is the role of lymphadenectomy. Whilst there are ongoing discussions on the impact of lymph node dissection on survival, it is generally agreed that lymphadenectomy enables accurate staging and, therefore, is important for prognostic purposes. However, high quality scientific data regarding many factors related to this issue are scarce.

Relative rarity of oesophageal cancer is the reason for difficulties in setting well-designed studies on prognostic factors in a single institution. Practically, the only way to overcome this problem is the creation of large, international databases, collecting prospectively important clinical data.

One of such projects is the Worldwide Esophageal Cancer Collaboration (WECC) (2). On the basis of clinico-pathological data collected within this project, Rice *et al.* performed an interesting analysis, published in the January issue of the *Annals of Surgery* (3). The authors have used modern mathematical models to find associations between the number of metastatic nodes and several variables related to the patient, the cancer and the method of treatment, and to define the extent of lymph node dissection necessary to precisely determine the pN status. They analyzed data

of 5806 patients collected in the WECC database, using the advanced machine learning method, Random Forest technique, designed especially for analysis of complex nonlinear relationships between multiple variables (4). It is a kind of advanced decision-tree analyses, in which the variable that is most related to a particular outcome is optimally split to improve prediction. Next, a series of consecutive splits of this and other variables is used to create a tree. The analysis was performed in two steps: first, with 31 clinico-pathological variables, 1,000 random bootstrap classification trees were generated. In the second step, the ‘forest’ created was used to determine the importance of variables and their relationships regarding outcome (3).

Despite this advanced statistical modelling, the conclusions from this analysis were not surprising. The authors have found that depth of invasion into the oesophageal wall, the length of invaded oesophagus and grade were associated with an increasing number of positive nodes—the results that merely confirm previously published evidence. A logical consequence of this is the finding that, as far as accurate nodal staging is concerned, for advanced, high-grade cancers fewer nodes need to be dissected to adequately determine N status, whilst for less advanced, low-grade tumours a higher number of lymph nodes should be removed.

It should be noted, that impact of lymph node dissection on survival was not the objective of this analysis. However, from the practical point of view, the therapeutic aspect

of lymphadenectomy should not be missed. Almhanna *et al.* analysed a group of 635 patients with oesophageal cancer and found that removal of 13–20 lymph nodes was associated with longer survival, as opposed to a lower number of nodes dissected (5). Similarly, Schwarz *et al.* in a study including 5,620 concluded, that removal of >30 lymph nodes is an independent prognostic factor for survival (6); in a study of Peyre *et al.* this cut-off number was 23 nodes (7).

Although it may seem obvious that extensive, three-field lymphadenectomy may enable complete resection, it should be kept in mind that such extensive dissection is associated with increased risk of adverse effects, including serious complications. Particularly, devascularisation of the airway is of concern. Maruyama *et al.* have found that removal of >60 lymph nodes during oesophagectomy increases the risk of tracheal fistula (8). Where the borderline between an attempt to perform oncologically complete resection and potentially dangerous devascularisation of mediastinal structures, remains an unanswered question.

A promising alternative may be the concept of the sentinel lymph node as, theoretically, it may enable sparing the unnecessary dissection, whilst maintaining the completeness of resection. This technique may also improve staging by identification of crucial target groups of lymph nodes (9). Whether the idea of the sentinel lymph node will be proven effective in oesophageal cancer, is also a matter of future investigations.

The study of Rice *et al.* did not include patients who underwent multimodal therapy, and therefore it does not provide information regarding this very important group of patients with oesophageal cancer. As there is convincing evidence showing survival benefit from trimodal therapy, except the early cancers (10), it is unlikely that primary surgery will be offered to many patients with more advanced oesophageal cancer—most of them are probably candidates for trimodal therapy.

Another important question is how meticulous is the pathological assessment of resected lymph nodes. Of course, if the standard hematoxylin-eosin stain light-microscopy is used, single clusters of malignant cells and micrometastasis are likely to be missed. Among prognostic factors, the role of micrometastasis should not be omitted. Reportedly, they are independent prognostic factors for shorter survival, both for squamous cell cancer and adenocarcinoma (11–13).

In the struggle to improve the still unsatisfactory results of treatment of oesophageal cancer, a combination of new, diagnostic modalities and advanced statistical analyses of international databases is necessary. The study of Rice *et al.*

is an excellent example of the latter.

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