Editorial

Cancer of the esophagus and esophagogastric junction: an 8th edition staging primer

Claire L. Donohoe, Alexander W. Phillips

Northern Oesophagogastric Cancer Unit, Royal Victoria Infirmary, Newcastle upon Tyne, UK

Correspondence to: Alexander W. Phillips. Northern Oesophagogastric Unit, Royal Victoria Infirmary, Newcastle upon Tyne, UK.
Email: awphillips@doctors.net.uk.

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The latest edition of the AJCC/UICC cancer staging manual (8th edition) (1,2), has several important implications for physicians involved in treating patients with cancers of the esophagus and esophagogastric junction within the multidisciplinary setting. The latest staging system employs data driven techniques (3) for the analysis of a far greater number of patients (22,654 *vs.* 4,627 patients) than preceding edition (4) and provides several insights into the biology of this cancer. It also sets the agenda for future clinical research.

New clinical and post neoadjuvant pathologic staging systems

The first key change is the recognition of the difference in outcomes between clinical staging (cTNM) and pathological staging, whether it be with (ypTNM) or without (pTNM) neoadjuvant therapy. This analysis reveals that current staging methodologies (from high volume, expert centres) results in the under staging of early cancers and over staging of advanced cancers—as demonstrated in the survival curves of the clinical stage groups. There appears to be a bias towards the selection of certain categories by clinicians during the clinical staging process e.g., T3N1—with fewer staging groups of different prognosis recorded for patients in the World Esophageal Cancer Collaboration (WECC) database and fewer patients within some stage groups. Importantly, there were too few patients with clinically predicted T1–3N3 disease to analyse the prognosis of these groups for squamous cell carcinoma (SCC) and too few to assess the impact of N3 disease in adenocarcinoma.

The relative contribution of various staging investigations, as well as geographical or centre interactions are not described and may have an important impact on the interpretation of how clinical staging data are applied to patients at the time of treatment decision making. For example, with squamous tumours, clinical staging was unable to distinguish between node positive and node negative tumours for patients with cT1 and cT2 tumours and for adenocarcinomas, nodal involvement could be distinguished. Is this due to tumour biology or centre/geographical differences in the clinical staging processes?

Nodal involvement and outcome

The impact of nodal involvement was seen across all staging categories [clinical (c), pathologic (p) and post neoadjuvant pathologic (yp)]. Patients with pT4N+ disease of any T stage with N3 disease, have equivalent prognosis as patients with metastatic disease and are denoted as stage IVa. The present data also confirm that patients with N3 disease following neoadjuvant treatment i.e., those not down staged, have survival comparable to metastatic disease. Even in clinical staging, where the stage for locally advanced tumours is more likely to be over staged, patients with cT3N2 disease had as equivalently poor prognosis as

patients with M1 disease.

Whether lack of disease response can be accurately determined post neoadjuvant treatment and whether esophagectomy impacts on overall survival in instances where there is no change in nodal response from neoadjuvant treatment, are important clinical questions. Furthermore, acknowledging the poor outcomes for many patients receiving neoadjuvant treatment raises the requirement for consideration for additional neoadjuvant or adjuvant treatments in non-responders.

"Watch and wait" approach to complete response following neoadjuvant therapy

Since N stage rather than T stage is the key determinant of outcome following neoadjuvant treatment, accurate assessment of N stage is the key determinant of decisions affecting long-term survival. Surgery as needed in patients with a complete response to neoadjuvant treatment, as planned in the SANO (5) and Esostrate-Prodige 32 studies (6), therefore, mandates accurate assessment of nodal involvement. Data from this analysis, shows that survival in patients who initially had locally advanced disease but who have complete response or disease localised to the esophageal wall is still not equivalent to that of early tumours and, at best, equates to an approximately 60% 5-year survival. The "watch and wait" approach to treatment derives from experience with rectal cancer treated with neoadjuvant chemoradiation. However, in a recent series of 129 rectal cancer complete responders, patients on a "watch and wait" protocol had a 3-year disease-free survival of 88% (7), implying that this paradigm may not be applicable to esophagogastric cancers.

Even if pathologic response could be accurately determined pre-operatively, and current data suggest this is not the case (8,9), surgery may still be an important factor in disease control. In fact, given the poor long-term outcomes, trials of further adjuvant treatment even in complete responders will probably also be required to augment response and further improve long-term survival.

cT2N0 disease

Due to limitations with modern staging with endoscopic ultrasound (EUS) and computed tomography-positron emission tomography (CT-PET) patients with cT2N0 disease are under staged in approximately half of cases and over staged in about one quarter of tumours in this group (10,11). Although included in many trials of neoadjuvant treatment, whether neoadjuvant treatment brings benefit to patients with this clinical stage is questionable (12-14). The French FFCD 9901 trial randomly assigned 195 patients with early tumours (cT1,2Nany or cT3N0) to pre-operative 5-FU and cisplatin and concurrent 45 Gy radiotherapy (RT), versus surgery alone (15). The trial was stopped early as the planned enrolment would not show a significant benefit in favour of one arm over the other. In addition, a multi-centre European collaboration including 355 patients with cT2N0 disease and propensity matching showed no benefit to multimodal therapy compared with surgery alone (16).

The latest consensus on clinical staging omits grade from assignment to stage groups. The data driven analysis, however, indicates that discriminating outcomes for cT2N0 tumours is aided by differentiation with G1 tumours having a better prognosis than G2 or G3 for both histologic subtypes and may be a useful discriminator in clinical practice (17).

Conclusions

The expanded TNM system should allow for improved prognostication in patients with esophageal cancer. There have been a number of suggestions for other parameters which could be involved in disease staging- such as lymph node ratio (18), lymphovascular and perineural invasion (19) that have noticeably not been included. It may be that as more evidence is acquired such information can be utilised in future editions, however doing so may lead to a potentially unwieldy system that is no longer user friendly.

The latest staging system for esophageal and esophagogastric cancer is certainly superior to previous incarnations. It has been a result of a collegial drive to provide more robust data for clinicians dealing with esophageal cancer. Conclusions have been derived from analysing data from a large number of patients from different geographical centres using data-driven approaches rather than hypothesis driven modelling.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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