EDITORIAL

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Oesophageal cancer: location, location, location

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The three most important factors in determining the desirability of a property are location, location, location.
— Harold Samuel, Baron of Wych Cross (1912–1987)

At the request of the American Joint Committee on Cancer (AJCC), non-anatomic (non-TNM) classifications were evaluated and important classifications incorporated into staging recommendations for oesophageal cancer in the 7th edition of the Cancer Staging Manual [1]. Cancer location, histopathological cell type and histological grade were demonstrated to enhance cancer staging [2]. Adenocarcinoma location was overwhelmingly in the lower thoracic oesophagus (96%), and thus the influence of cancer location on adenocarcinoma staging could not be evaluated [2, 3]. However, location was an important classification for squamous cell cancer. Distribution of squamous cell cancer location in worldwide data was upper thoracic (10%), middle thoracic (58%) and lower thoracic (32%) [3]. Only addition of histological grade to TNM improved staging of squamous cell cancers confined to the mucosa and submucosa (pT1). However, a complex interplay of cancer location and histological grade added to staging of pT2-T3N0M0 squamous cell cancer, such that four combinations were identified (Fig. 1). These ranged from lower thoracic well-differentiated (G1) squamous cell cancers (stage IB), which had the best survival, to middle and upper thoracic moderately differentiated to poorly differentiated (G2–G3) squamous cell cancers (stage IIB), which had the worst survival. G2–G3 lower thoracic squamous cell cancers and G1 upper and middle thoracic squamous cell cancers were grouped together (stage IIA), with intermediate survival. Non-anatomical classifications, including cancer location, did not influence staging of advanced squamous cell oesophageal cancer (T4 and N+) [1, 3].

Shi *et al.* [4] present their single-institution experience, analysing the importance of cancer location in squamous cell cancer. Prompted by the famous real estate quote, we reviewed their data and analysis (cancer location), the Asian experience (geographic location) and timing of this publication (temporal location).

CANCER LOCATION

Shi *et al.* retrospectively reviewed 2015 patients undergoing oesophagectomy from January 1984 to December 1995. Nine hundred and eighty-eight met inclusion criteria, which included (i) thoracic oesophagus squamous cell cancer, (ii) oesophagectomy only, without neoadjuvant or adjuvant therapy, (iii) R0 resection, (iv) 12 or more regional lymph nodes resected, (v) complete records and (vi) 10-year follow-up. Surgical inclusion criteria assured curative resection with adequate lymphadenectomy and thus a study group of well-classified pN patients underwent oesophagectomy alone. The size of Shi *et al.*'s study group is repeatedly decreased by exclusions and appropriate confinement of cancer location to patients with pT2-T3N0M0 cancers; pT2N0M0 patients comprise 64% of the study group and 31% of oesophagectomy patients.

However, an unusual study interval and need for 10-year follow-up are peculiar inclusion criteria. These patients had oesophagectomy from 20 to 30 years ago, raising questions about transferability of this experience to the 21st century and 7th edition staging. The need for 10-year follow-up, not possible for most oesophageal cancer patients because of high early cancer-related mortality, is unnecessary because actuarial methods permit follow-up variation, and even short follow-up of more recent operations informs the early portion of the distribution of times until death.

Distribution of cancer location in this series was upper (2%), middle (78%) and lower (20%)—notably fewer cancers at extremes of cancer location and an overwhelming predominance in the middle thoracic oesophagus, a different distribution from that used to develop 7th edition staging. Distribution of grade was G1 (39%), G2 (49%) and G3 (12%), dissimilar from more evenly distributed 7th edition data of G1 (46%), G2 (33%) and G3 (21%). Importantly, interplay of cancer location and histological grade may result in further magnification of these dissimilarities and thus limit comparisons.

Analytic techniques used to assess survival differences consisted of multiple stratifications of the data and applications of log-rank testing. Significant classifications were next identified through repeated Cox proportional hazard analyses. Repetitive use of these techniques was employed in an attempt to confirm previously identified pTNM subsets and nonanatomical classifications with significant survival differences. This piecemeal strategy is suboptimal for exploring complex interactions among classifications because investigation of one variable is not adjusted for any other. Multiple applications of tests also increase the probability of identifying chance associations. It is a doubtful patchwork strategy for constructing optimal stage groupings, as accomplished using the random forest machine learning technique [5].
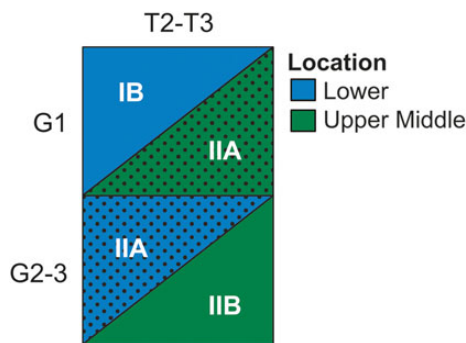
Figure 1: Stage groupings for pT2-T3N0M0 oesophageal squamous cell carcinoma by cancer location and histological grade (G). G1 is well-differentiated histological grade, and G2–3 is moderately and poorly differentiated. Dots indicate shared stage grouping IIA.

Analysis for the entire group did not identify cancer location as important in staging, but cancer location was significant in pT2-T3N0M0 patients. Although the analysis detected survival differences among all three cancer locations, it was incapable of exploring monotonicity, distinctness and homogeneity of stage groupings (as can be achieved using random forest analyses) and thus was unable to recognize the importance of combining upper and middle thoracic cancer locations for optimal staging of pT2-T3N0M0 squamous cell cancers. Although repeated analysis confirmed differences among the three stage subgroupings, this analysis was unable to confirm optimal combinations of cancer location and histological grade to produce best stage groupings. Significant differences exist between Shi *et al.*'s data and analyses used to construct the 7th edition, leading to questions about comparability.

GEOGRAPHIC LOCATION

There have been small single-institution Asian reviews of 7th edition staging of squamous cell cancer that failed to identify the importance of cancer location [6–8]. These studies share data and analysis problems [9]. The authors choose to explain these shortcomings by presumed special differences in Asians with oesophageal cancer. Shi *et al.* perpetuate the misconception that 'Eastern patients are known to differ biologically from esophageal cancer patients in Western countries'; however, this statement is supported only by one-sided views of the experience. Random forest analysis of the only available worldwide data did not detect a difference between East and West in survival and staging after oesophagectomy for squamous cell cancers [2, 3].

TEMPORAL LOCATION

There is ongoing debate concerning components of staging. The Union for International Cancer Control's (UICC) historical position has been promotion of anatomical stage groupings based on TNM classifications alone. The AJCC 7th edition charge resulted in adding non-anatomical classifications in determination of stage groupings. This disharmony led to confusion, frustration and dissatisfaction with the AJCC 7th edition. Thus, AJCC is refocusing the goals of

the 8th edition. Stage groupings will be TNM-based. Additional prognostic factors will be added as necessary. This importantly relegates stage groupings to coarse treatment stratifications for patient cohorts, leaving individual patient treatment decisions and prognostication to be based on anatomical TNM factors and important patient, non-anatomical cancer and treatment factors [9]. Delay in performing this analysis and its publication more than 5 years after introduction of the 7th edition staging recommendations may render Shi *et al.*'s literature contribution of historical interest only. Timing of this publication is crucial to its value in the staging debate.

LOCATION, LOCATION, LOCATION: THE 7TH EDITION AND BEYOND

The 7th edition oesophageal cancer staging was the first attempt at data-driven oesophageal cancer staging for the AJCC and UICC Cancer Staging Manuals. It used worldwide data from multiple locations. Histopathological cell type, histological grade and cancer location augmented TNM classification in stage groupings. However, sophisticated analysis demonstrated cancer location had a very limited role only for pT2-T3N0M0 squamous cell cancers, which was also importantly modified by dichotomized histological grade.

Continued challenges of oesophageal cancer staging by the analysis of single-institution experiences are expected as the 8th edition further refines oesophageal cancer staging, using expanded worldwide data and refined random forest analysis to meet present day staging goals. It is unfortunate that these efforts will be directed at testing evolving staging recommendations rather than assisting in their fundamental construction.

Although a consideration in oesophageal cancer, 'location, location, location' is far from the most important factor.

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