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DISEASES OF THE ESOPHAGUS

Editorial

New methodology, tools, and protocolized analysis are needed to advance individualized treatment paradigms in esophageal cancer

Outcome prediction tools have the potential to provide clinicians and patients with practical decision aids in the diagnosis of cancer. Esophageal cancer often involves a multimodal approach. Ultimately, improvements in the reliability to predict pathologic stage based on clinical datasets are likely to be dependent on the feasibility to normalize and apply the currently available data while bringing to the clinical arena novel genetic and molecular assays. For now, pathologic complete response (pCR) is an often-used surrogate of response to combined modality therapy and a predictor of disease outcome.

To that end, we commend the authors of 'Clinical Tools Do Not Predict Pathologic Compete Response in Patients with Esophageal Squamous Cell Cancer Treated with Definitive Chemo-radiotherapy' in this current issue of *Diseases of the Esophagus*, for their timely and concise presentation of a dataset from a large tertiary cancer center. Acknowledged within their manuscript are the inherent limitations of their available data: a retrospective data set collected over 14 years at a single institution during which there was a shift in the demographics of squamous cell (SCC) esophageal cancer treatment patterns. However, their framing of the literature, relevant data that demonstrates congruency with prior publications, and isolation of the SCC histology sums to solidify the dilemma that practitioners currently face when managing esophageal cancer. The currently employed clinical assays and our understanding of their results does not provide adequate information to identify, or reasonably predict, patients that have achieved a pCR following receipt of chemoradiotherapy (CRT) prior to formal resection and en bloc pathologic examination.

Normalized definitions of terms pertinent to statistical analysis will aid in the ongoing movement toward database and predictive analysis for individualized patient treatment. The authors' definition of pCR included patients with residual nodal disease. Using recursive partitioning analysis, the authors previously demonstrated that SCC patients with fewer than four positive lymph nodes following CRT, their outcome was equivalent to those patients without any positive nodes.[1] However, their definition of pCR may not be currently employed by all members of the community. Perhaps a robust discussion and prospective analysis on this topic would aid in consensus and allow appropriate comparison across different analyses.

Positron emission tomography standard uptake value (PET-SUV) continues to lack uniformity in quantification and radiographic technicalities across institutions and instruments. Concordant with findings in several other publications, the authors found that PET-SUV change, between pretreatment and 2 weeks post-treatment, and the isolated post-treatment SUV were significantly associated with pCR ($P < 0.01$ and $P < 0.001$, respectively). Omloo *et al*. reported a review of 31 total studies reviewing analysis of absolute SUV and SUV change in response to some form of CRT.[2] While not every study positively identified these values as predictive of survival, this may be due to several factors. Reviewed carefully within the analysis, there was significant heterogeneity between studies – notably involving the parameters and protocols used in the actual performance of the PET, the timing of the exam in relationship to treatment, and their definitions of response. Many of the reviewed studies were retrospective and analyzed relatively small numbers of patients. However, several prospective studies involving early analysis of PET, after 2 weeks of CRT,[3,4] were powerful predictors of outcome. The optimal timing, along with standardization of PET administration, should be prospectively analyzed on an appropriately powered in separate analysis for SCC *and* adenocarcinoma.

Separately, it is important to recognize the authors' appropriately limited and directed use of post-treatment endoscopic modalities. As noted by the authors, endoscopic ultrasound (EUS) has been demonstrated to be relatively unhelpful in predicting residual disease, with an accuracy of 26–50%.[5] Puzzling endoscopic data were demonstrated in the authors' data, with post-treatment endoscopy showing persistent disease in significant percentage of patients with a pCR and demonstrating no disease in over half of the patients with residual disease (Table 2).[6–8] Similarly, analysis in patients receiving isolated esophagectomy reveals similar, if less striking, concerning discrepancies between clinical endo-

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scopic staging and pathologic. The consistent reports of inaccurate clinical staging[9–11] could explain the authors' finding of a higher rate of pCR in stage III patients compared with stage II – these stages were based on clinical staging, which is relatively inaccurate when compared with pathologic data.

Accurate clinical nodal staging continues to be a challenge. A recently compiled predictive tool specifically addresses the question of an individual's likelihood of nodal involvement based on clinical data specifically, finding endoscopic tumor length (dichotomized at 2 cm) to be the most prognostic of available data.[12]

Similarly, as described by the authors, no single currently available exam is available to reliably determine whether a patient has achieved a pCR following CRT. However, for any patient, there is an abundance of individualized complementary prognostic information. Using the available institutional and administrative databases, multiple groups have used a combination of radiographic, clinical, demographic, pathologic data, and potentially genetic information, to construct predictive models to determine: likelihood of pCR,[13] pathologic lymph node involvement based on clinical data,[12] benefit of neoadjuvant CRT[14] (http://skynet.ohsu.edu/nomograms/), definitive CRT,[15] tumor radiosensitivity based on a gene expression signature,[16,17] and identify those most likely to suffer perioperative morbidity and mortality.[18]

Accurate identification of those patients that will benefit from, and tolerate without significant complication, aggressive treatment, while sparing nonresponders the risks associated with trimodality treatment, will depend on novel utilization of existing prognostic information and the development of additional assays.

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