Commentary: Making the Grade: Prognostic, Therapeutic and Staging Implications of Tumor Differentiation in Esophageal Adenocarcinoma

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Central Message:

Given its prognostic significance after neoadjuvant chemoradiation therapy, esophageal adenocarcinoma tumor differentiation has important implications for the future of both staging and treatment.

Central Figure Legend:

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In this issue of the Journal, McKay and colleagues performed a multi-institutional retrospective review of 550 patients with esophageal adenocarcinoma who underwent esophagectomy within 12 weeks after completing neoadjuvant therapy. As compared with patients with well or moderately differentiated tumors, patients with poorly differentiated tumors were more likely to have residual nodal disease and to have worse overall and disease-free survival, even among those patients who had a pathologic complete response (pCR) \(^1\). The World Esophageal Cancer Collaboration did not include grade in the clinical staging of T3 or T4 adenocarcinomas in the 8th edition. As such, the authors identified a knowledge gap regarding the impact of grade on prognosis after neoadjuvant therapy that could serve as the basis for future trials on perioperative systemic therapy and for modifications to subsequent editions of the American Joint Committee on Cancer (AJCC) Staging Manual. Several salient points deserve mention.

First, tumor grade is indicative of a more aggressive malignancy. Indeed, the 5-year overall survival rate was significantly lower (p=0.0021) in poorly differentiated (40.2%) than
well/moderately differentiated tumors (55.2%). While there was no difference in overall pCR rates based on tumor differentiation in the current study, the nature of the residual disease was distinct. In particular, poorly differentiated tumors were more likely to have residual nodal disease (58%) than well/moderately differentiated tumors (42.6%). This finding is particularly important since residual nodal disease is one of the most important prognostic factors for patients who received neoadjuvant therapy and identifies a group of patients who may benefit from adjuvant therapy. Previous studies have also demonstrated the aggressive nature of poorly differentiated tumors, noting a higher rate of nodal metastases than well/moderately differentiated tumors.

Second, this study is a sobering reminder that pCR is not synonymous with cure - 31% of the total cohort of pCR patients developed locoregional or distant recurrence, similar to the rates in other studies (20% and 40%) 

Though it did not reach statistical significance (p = 0.065), there was a trend towards a higher rate of recurrence among patients with poorly differentiated tumors (34.4%), as compared with well/moderately differentiated tumors (27.1%). The finding of an association between differentiation and recurrence is corroborated by a single institution study which demonstrated that poorly differentiated tumors are independently associated with recurrence (Hazard Ration 2.39; 95% confidence interval, 1.16 – 4.93).

Based on the results of Checkmate 577, the current standard of care after neoadjuvant therapy is immunotherapy for patients with (any) residual disease and surveillance for patients with a pCR. However, based on the available evidence, perhaps all patients with poorly differentiated tumors could benefit from adjuvant immunotherapy (independently of pathologic response rate). Further study is needed.
Finally, though it is included in the AJCC 8th edition for staging T3 squamous cell carcinomas, tumor differentiation is not included in the staging of T3 adenocarcinomas. However, based on the sum of the evidence, consideration should be given to including grade in future AJCC staging editions on esophageal adenocarcinoma.
References


