Endoscopic resection and the T category: Baby steps toward risk stratification

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In the 1991 movie *What About Bob?*, the psychiatrist character played by Richard Dreyfus is ironically driven catatonic by to an “inherited” patient played by Bill Murray. By being crazy and fun, the Murray character was able to take control away from the pathologic narcissist played by Dreyfus. To advance the management of esophageal cancer, you have to be crazy (think minimally invasive esophagectomy, endoscopic mucosal resection and robotically assisted minimally invasive esophagectomy) but also have fun (collaborate) to gain control of this pathology. Patients with early-stage esophageal adenocarcinoma (EAC) provide a particular clinical challenge. We perform an esophagectomy and accept a high perioperative morbidity and mortality risk. We perform an endoscopic mucosal resection and worry that we are undertreating. Are we between a rock and a hard place? No; clinical management is slowly evolving, but molecular translational efforts need to contribute to progress.

In this issue of the *Journal*, Weksler and colleagues¹ take baby steps toward a better understanding of how best to proceed with management of superficial EAC. Risk stratification models have been proposed earlier,² but Weksler and colleagues¹ developed an algorithm based on a retrospective review from the National Cancer Database. Advantages of their study: a large database. Limitations? Missing data, an inability to review the pathology slides, lack of esophagectomy data, and nodal understaging. This is still, however, a step forward. EAC is an uncommon cancer and thus a challenge to study. Validation of a prognostic risk stratification system may be impossible. But as the alternative is worse—patients die—we need to keep taking small steps forward.

What limits progress? We still have a major knowledge gap: a robust molecular profile for nodal involvement. From a small, albeit multi-institutional, series of T1 tumors, we know lymphovascular involvement, differentiation and tumor size can be used to provide a scoring system to predict nodal involvement.² Identification of positive nodes

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Central Message

Optimal risk stratification for esophageal adenocarcinoma T1 tumors should include molecular profiling.

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with molecular techniques has been applied to more common thoracic malignancies, such as non-small cell lung cancer,³ and microRNA arrays have been used to identify 3 microRNAs associated with EAC nodal positivity.⁴ Additional applications of gene profiling from large series can sort out the miscreant early cancers,⁵⁻⁷ whereas some investigators report a single molecular marker to distinguish a bad phenotype.⁸ Of course, these are likely not disparate features; rather, they all need to be wrapped into the negative performance profile (risk of nodal involvement, risk of recurrence), and certainly some variables may be surrogates for others. It is complicated, because not all tumor gene expression at the RNA level translates into actionable items to address.

How do baby steps add up to a giant step forward when studying an uncommon cancer? Bioinformatics, publicly available data, and old-fashioned pathology are the requisite tools. Collaboration with respect to resources and cases will allow testing of cases and validation of proposed risk stratification systems. Focus on the profile and collaborate as teams. Baby steps are small but forward steps for advancement.

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