Editorial Commentary

Is persistent intestinal metaplasia a prognostic factor after definitive chemoradiation in patients with esophageal adenocarcinoma?

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Barrett's esophagus (BE) is defined as the replacement of the normal esophageal squamous epithelium with columnar epithelium. This process is also known as intestinal metaplasia and is a relatively common disease with a reported incidence ranging from 1.6% to 6.8% (1-3). The true incidence of BE may be even higher as studies limited to symptomatic patients will not demonstrate the true prevalence of the disease. The natural history of BE is thought to follow a sequence of events that starts with non-dysplastic metaplasia and progresses to low-grade dysplasia (LGD), high-grade dysplasia (HGD) and finally to early esophageal adenocarcinoma (EAC). BE with HGD carries a 50 to 100 times increased risk for development of EAC and it is estimated that 1 out of 200 patients with BE will develop esophageal cancer throughout their lifetime (4). Other studies have also suggested that the absolute risk of carcinogenic progression from BE to EAC is low (~0.5%) (5). Because of the risk for progression of the disease it is recommended that BE patients undergo lifelong surveillance endoscopies and serial four-quadrant biopsies (6).

The development of endoscopic ablation and resection techniques including photodynamic therapy (PDT), cryotherapy, radiofrequency ablation (RFA) and endoscopic mucosal resection (EMR), have provided noninvasive therapeutic options for management of metaplastic and dysplastic esophageal mucosa. BE with HGD previously was an indication for esophagectomy due to the risk of progression to EAC, however the introduction of endoscopic modalities have largely swayed the treatment algorithm of BE with HGD towards endoscopic therapies. However, the natural history and prognostic value of residual or new Barrett's in the setting of post-treatment esophageal carcinoma is largely unknown. The study by Amlashi *et al.* aims to evaluate the outcomes of EAC patients after bimodality therapy (BMT) focusing on the effect that post-treatment BE has on overall survival (OS) and local recurrence free survival (LRFS). The study attempts to address the prognostic value and management of BE with or without dysplasia in patients who have undergone BMT for esophageal EAC. This interesting study has several significant limitations that stem from the retrospective nature of the data.

Patients were retrospectively evaluated from a single institution database between 2002 and 2015. Patients were included if they demonstrated Siewert type I and II EAC and underwent BMT with at least 2 endoscopic evaluations with biopsies in the follow up period. Median Follow up was 37 months. The study included 228 patients: 98 with BE and 130 without BE after treatment. Prior to treatment 68 (29.8%) patients were diagnosed with BE in addition to EAC. Clinical staging prior to BMT according to the 7th edition of the American Joint Committee on Cancer Staging Manual, demonstrated 6.1% stage I (14/228), 81% stage II–III (185/228), 10% stage IV (23/228) and 2.6% unknown stage (6/228) patients. Twenty-four patients underwent salvage esophagectomy. Of note, explanation

was not provided as to why esophagectomy was or was not offered to selected patients.

One of the conclusions drawn from the data indicated that endoscopic intervention for BE was not associated with decreased risk for local recurrence or death. The authors recognize that the numbers were very small (11 patients underwent endoscopic intervention) and that the power needed to detect a difference was not achieved. Further they acknowledge that there was no identifiable guideline as to why only 11 patients underwent an intervention; there was no standardization of treatment in these cases. The decision making that led to salvage esophagectomy is also not discussed.

The second conclusion was that after mean follow up of 37 months after BMT there was no difference in recurrence or survival rates between patients with BE and without BE. Again, the small numbers and retrospective study design contribute to the difficulty in performing a complete evaluation that could answer the clinical question completely. In this group of esophageal cancer patients one may not expect that the presence or absence of BE would have an effect on recurrence or OS and that the true driver of survival rates would be the presence of carcinoma in the final specimen. The fact that there is no pathologic specimen makes it impossible to determine persistence (pathologically incomplete response to BMT) from recurrence. It is reasonable to surmise that persistence and recurrence would likely be driven by the characteristics of the original tumor and its response to BMT, not the presence or absence of BE. Furthermore, the majority (~95%) of EAC cases are diagnosed without a prior diagnosis of BE and BE as an isolated diagnosis, has never been shown to be predictive of survival (7,8).

As expected, 91% of patients in the cohort were stage II–III. It may have been informative, if possible, to differentiate stage II and III patients instead of combining them together in a group that accounts for 81% of the cohort. The breadth of disease and prognostic implications of this segment of the cohort covers a diverse range. For example, the clinical staging of T2N0 disease is particularly troublesome given the diagnostic inaccuracies inherent in clinical staging of these patients (9). The poor accuracy of clinical staging for stage II tumors was likely the impetus for grouping the stages together, although as many as 25% of these patients are likely down staged after pathologic staging based on resection specimens (10). However, the majority of patients in this study did not go on to surgery.

The explanation as to why the early stage esophageal cancer patients did not undergo resection is unclear and some explanation would provide context as to the group of patients that are undergoing evaluation. If the patients had too high a perioperative risk due to comorbidities we may expect that their chronic conditions as well as the esophageal cancer would dictate their survival instead of the presence or absence of BE.

One of the major limitations of this study is the lack of pathologic staging given that most patients did not undergo esophagectomy. The inability to definitively identify complete responders with a pathologic specimen makes differentiation of local recurrence and persistent disease problematic. Several studies have demonstrated the inadequacy of using post BMT endoscopic biopsies as a measure of complete response. Sarkaria *et al.* demonstrated that in a group of 118 patients with normal biopsies after treatment, 69% had residual disease on the pathological assessment after resection (11). As quoted in the manuscript, Ajani *et al.* evaluated 322 EAC patients treated with BMT and demonstrated that 79% were thought to be complete responders based on endoscopic biopsy when, in fact, only 21.7% had a complete response when the esophagus was resected and evaluated (12). We can assume that within the cohort of 228 patients evaluated in this study there are a significant number of patients who have residual cancer, representing the most likely driver of their survival.

In conclusion this study attempts to evaluate the effect that BE has on outcomes in patients with EAC who have undergone BMT. The current study would benefit from a more detailed description of the patient staging, more insight into the decision making as to the reasoning and selection for surgical resection, and standardization of the decision-making regarding interventions in patients with BE prior to analyzing the outcomes. While an interesting study hypothesis, the lack of pathologic staging and the unclear comparisons between what likely represent different and distinct populations of patients are significant limitations of this retrospective study that make any meaningful conclusions from the data difficult to infer or support. Regardless, the authors should be congratulated for initiating the dialogue on this subject and providing a framework for future evaluation.

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