Editorial Commentary

Squamous cell carcinoma and adenocarcinoma of the esophagus: same organ, different disease

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Researchers and practitioners continue to group esophageal cancer as one disease process on the basis of the organ of presentation: the esophagus. However, over time, esophageal cancer has been separated into two distinct entities—adenocarcinoma and squamous cell carcinoma (SCC)—on the basis of histologic subtype. Disease presentation, patient demographic characteristics, response to treatment, and outcomes differ by subtype (1). Recently, molecular analysis from The Cancer Genome Atlas showed key differences between the subtypes—namely, SCC resembles head and neck cancers, and esophageal adenocarcinoma has chromosomal instability and resembles gastric cancer (2). Therefore, when comparing the two histologic subtypes of esophageal cancer, these important differences must be taken into account.

The recent study by Xi *et al.*, "Multi-institutional analysis of recurrence and survival after neoadjuvant chemoradiotherapy of esophageal cancer—impact of histology on recurrence patterns and outcomes," in the *Annals of Surgery* attempts to provide further evidence that histologic subtype is a major factor that affects recurrence and survival in esophageal cancer (3). In their retrospective review, the authors include data from three institutions on two continents, in order to include a sufficient number of patients with the subtype predominant in North America (adenocarcinoma) and the subtype predominant in Asia (SCC). While such efforts are commendable, they also predispose the study to major biases. Specifically, the patients with SCC were younger, more likely to be women, more likely to have upper or middle tumors, and more likely to have advanced-clinical-stage, node-positive disease. In addition, treatment strategies differed by subtype. Compared with patients with adenocarcinoma, patients with SCC were more likely to receive a lower radiation dose (median, 40.0 *vs.* 50.4 Gy) and less likely to receive induction chemotherapy. Unfortunately, the dropout rate of patients who initially started on neoadjuvant chemoradiotherapy with the intent of undergoing surgery but did not make it to surgery was not included.

The authors rightfully excluded patients who had macroscopically incomplete resection after neoadjuvant chemotherapy. However, it appears the authors included patients with R0 as well as R1 resection. Although data from one of the institutions included in the study suggest that microscopically positive circumferential margins may not have an effect on recurrence or survival (4), such a finding is contrary to those of other studies, which have shown that R1 resection is associated with inferior survival and recurrence outcomes (5). Furthermore, the authors did not include the number of patients who had an R1 resection and whether R1 resection numbers differed between the adenocarcinoma cohort and the SCC cohort.

As mentioned above, the treatments administered differed by histologic subtype; response to treatment did as well. The rate of pathologic complete response (pCR), a surrogate for better survival, was 30.3% (271 of 895 patients) in this study, with a significantly higher rate among patients with SCC (44.9%) than among patients with adenocarcinoma (25.9%) (P<0.001). On multivariate analysis that adjusted for demographic, cancer, and treatment variables and

considered the subtypes separately, patients with a pCR had better survival than those without a pCR (hazard ratio, 2.57 for SCC *vs.* 2.417 for adenocarcinoma) (1) (pCR was the only variable that was associated with recurrence-free survival for both histologic subtypes). Other trials have also revealed a difference in response to neoadjuvant treatment on the basis of histologic subtype. In the practice-changing CROSS trial, 29% of patients had a pCR, with a significantly higher rate among patients with SCC (49%) than among patients with adenocarcinoma (23%) (P=0.008) (1). In a recent study of patients treated with trimodality therapy for SCC at our institution—where surgery is favored for patients with residual disease after neoadjuvant chemoradiotherapy—47% were found to have a pCR (6).

Interestingly, Xi *et al.* note no differences in recurrence patterns between the two subtypes among patients with a pCR. However, among patients without a pCR, rates of locoregional recurrence [16.7% (SCC) *vs.* 6.3% (adenocarcinoma); P<0.001] and distant recurrence [32.5% (adenocarcinoma) *vs.* 17.5% (SCC); P=0.002] diverged. In our experience, recurrence patterns among patients with a pCR differed by subtype: patients with adenocarcinoma with a pCR were more likely to have distant recurrence, whereas patients with SCC with a pCR were more likely to have locoregional recurrence. In addition, we found similar recurrence patterns between patients with and without a pCR (7). Recurrence patterns by pCR differed between the Xi *et al*. study and our experience for main reasons including different practice patterns, differences in neoadjuvant and adjuvant therapy, and differences between overall disease patterns in the East and West.

The authors note that patients with adenocarcinoma were more likely to have recurrent disease (43.2% *vs.* 34.3%; P=0.023) and to receive salvage therapy (74.4% *vs.* 57.7%; P=0.005), compared with patients with SCC. The main reason patients with SCC did not receive salvage therapy, according to the authors, was poor performance status. However, even before initial treatment, ECOG performance status differed by subtype, with more patients in the SCC cohort having an ECOG score of 1 to 2 (51.7% *vs.* 41.3%; P=0.008). Additionally, it is difficult to ascertain the practice patterns between the three institutions with regard to salvage treatment, as there is no mention of the criteria for treatment of recurrent disease and what salvage therapies patients received.

Last, the authors report no differences in overall survival or recurrence-free survival between histological subtypes. Once again, this analysis is limited by factors responsible for bias in the study, and it is advisable not to make too much of such findings. The patient populations were different—patients with SCC were sicker, were more likely to have upper or middle esophageal cancer, and received different neoadjuvant treatment.

Overall, while the study by Xi *et al*. attempts to shed light on some crucial aspects of the care of patients with esophageal cancer by focusing on histologic subtype, the inherent biases introduced by the study design make any comparisons difficult to analyze. It could be said that comparing esophageal SCC and esophageal adenocarcinoma is like comparing apples and oranges and that the only common factor between these two entities is the organ of presentation. As we move forward as practitioners and researchers in the design of future trials, genomic analyses, and potential targeted treatments, we should think of esophageal SCC and esophageal adenocarcinoma as two different diseases.

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