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Commentary: Lowering the threshold rings in a new harbinger

Dustin K. Lieu, BS, and Anthony W. Kim, MD

Dustin K. Lieu, BS, and Anthony W. Kim, MD

Signet ring cell (SRC) esophageal adenocarcinomas represent a subset of malignancy that exhibit particularly aggressive behavior and are associated with poor prognoses relative to non-SRC esophageal adenocarcinomas.¹ In their study, Corsini and colleagues² challenge the existing binary definition of SRC esophageal adenocarcinoma by providing evidence to support that tumors with any number of SRCs, including those with $\leq 50\%$, portend the same poor prognosis associated with classically termed SRC esophageal adenocarcinomas with $>50\%$ SRCs.

Performing a retrospective analysis, the authors identified 819 patients who underwent esophagectomy following neoadjuvant chemoradiation therapy for esophageal adenocarcinoma over a 12-year period at their institution. Of these patients, 106 were noted to have varying degrees of SRCs on pretreatment biopsy. Tumors were characterized further according to the percentage of SRCs based on a review of available specimens by an esophageal pathologist and were recategorized into 3 groups based on pretreatment SRC proportions. On multivariable analysis, the authors found that the presence of SRCs in any amount was an independent predictor of worse overall survival. Interestingly, however, there was no statistically significant relationship between the percentage of pretreatment SRC and overall

CENTRAL MESSAGE

The $>50\%$ threshold defining signet ring cell (SRC) esophageal adenocarcinoma deserves a re-examination and discussion, as the mere presence of any SRCs may actually be clinically significant.

survival within the 3 SRC patient subcategorizations. Similarly, tumors with any proportion of SRC cells were noted to have lower pathologic complete response rates compared with non-SRC esophageal adenocarcinomas, with no significant trend associated with tumor regression grade among the 3 SRC cohorts.

The authors indicate that their study was limited by a sample size that may have been underpowered to detect differences within the spectrum of SRC esophageal adenocarcinomas. While possibly true and valid, it also is possible that even with greater numbers the lack of differences would still persist, owing to the ostensibly binary outcome associated with the simple presence of SRCs as their study implies. Alternative formats or clinical trials to evaluate the issue of whether the mere presence of SRCs is a determinant of survival could reduce variability in tumor sampling and assessment.³ However, at the expense of putting forth a circular argument, the utility of controlling for these issues may be unnecessary if, quite simply, the identification of any SRCs is found to have a prognostic value equal to that of a greater threshold percentage of SRCs such as 50%. Furthermore, the current threshold for defining

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SRC adenocarcinomas is founded in historical data and consensus regarding poorly differentiated adenocarcinomas of the digestive tract, in general, and, therefore, it lends itself to a re-examination. In this manner, the distillation of a tremendous experience by the authors, and one that only a few individual surgeons or institutions will experience, into a practical argument is what makes this current study meaningful and clinically useful.

In the context of the optimal multimodality treatment strategy for patients with SRC esophageal adenocarcinoma having yet to be defined definitively, this study unveils a specific group of patients that may be overlooked. Those patients with any SRCs but who fall short of the 50% threshold may expand the cohort from which a greater understanding of SRC esophageal adenocarcinomas can be

gleaned. In contrast to the current dichotomous classification system, this study suggests that the threshold for defining an SRC adenocarcinoma could be lowered, such that a single SRC very well could serve as a harbinger for certain esophageal adenocarcinomas.

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Commentary: You can't hit what you can't see: Esophageal adenocarcinoma with signet ring cells

Josh Boys, MD, and Mark Onaitis, MD

For almost the last 20 years, the CROSS (Chemoradiotherapy for Oesophageal Cancer followed by Surgery Study) protocol of concurrent neoadjuvant chemoradiation for esophageal adenocarcinoma has been one of the biggest steps forward for improving survival.¹ Shortly after the CROSS trial, we began to better understand the poor outcomes associated with esophageal signet ring cell (SRC) adenocarcinoma compared with non-SRC adenocarcinoma.^{2,3} However, more study of signet ring patients is necessary to elucidate prognosis.

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CENTRAL MESSAGE

Presence of signet ring cells is increasingly seen as a negative prognostic factor in esophageal adenocarcinoma. The present study improves understanding but also raises new questions.

In the current study by Corsini and colleagues⁴ they hypothesize that the amount of SRC found on pretreatment biopsies would proportionally and inversely correlate to the rate of complete pathologic response and overall survival after multimodality treatment with the CROSS protocol and esophagectomy from 2006 to 2018 at a single institution. They were careful to identify any patients with “signet” in the pathology report and re-review it with an esophageal pathologist. They scored SRC in each