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Commentary: Signet ring cell: One bad apple spoils the bunch!

Andrew Tang, MD, MS, and Siva Raja, MD, PhD

The presence of signet ring features in esophageal adenocarcinoma has always been a harbinger of a worse prognosis in a disease with an often bad prognosis. Corsini and colleagues provide us unique insight into signet ring cell adenocarcinomas based on their vast esophageal cancer database. Through diligent review of historic pathology slides spanning across 2 decades, they demonstrate in this issue of the *Journal* that even small percentages of signet ring cell histology portend a worse prognosis in esophageal cancer survival.¹

The World Health Organization has specified that signet ring cell adenocarcinomas only qualify as such when they contain >50% signet ring features. Several studies have demonstrated that patients with signet ring cell histology have worse response to chemoradiation, greater likelihood of positive surgical margins, and ultimately worse survival.²⁻⁶ However, this is the first study to evaluate survival by breaking down the percentage of signet ring cell histology. Although the tumors with signet ring features had worse complete tumor response, the authors did not find that the degree of signet ring percentage correlated with the degree of tumor response. Similarly, greater percentages of signet ring cell histology did not translate into worse survival compared with lower percentages of signet ring features. Based on conventional wisdom one would have expected to see a difference. This finding could be related to the overall small study cohort, as it may be underpowered to detect survival differences between the varying degrees of signet ring features. Alternatively, this finding could be due to sampling error, as the percentage of signet ring cells was based on

Andrew Tang, MD, MS (left), and Siva Raja, MD, PhD (right)

CENTRAL MESSAGE

Any degree of signet ring features on pretreatment biopsy portends worse prognosis, making it the proverbial bad apple that spoils the bunch.

endoscopic biopsies. The authors of this study were unable to assess the post-treatment specimens for the percentage of signet ring morphology, as many of them had lost their signet ring features. This is a new phenomenon indeed, as it has not been our experience to see regression of signet ring cells with a complete response. While the jury may still be out on the correlation between percentage of cells with signet ring features and prognosis, there no doubt from this study, and others, that it has a worse prognosis.²

Given the worse prognosis of any amount of signet ring features, this study makes the case to use this threshold rather than the >50% rule. Maybe we should treat the signet ring cell as the proverbial rotten apple that spoils the bunch.

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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

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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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