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.

References

1. Nafteux PR, Lerut TE, Villeneuve PJ, Dhaenens JM, De Hertogh G, Moons J, et al. Signet ring cells in esophageal and gastroesophageal junction carcinomas have a more aggressive biological behavior. *Ann Surg*. 2014;260:1023-9.
2. Corsini EM, Foo WC, Mitchell KG, Zhou N, Maru DM, Ajani JA, et al. Esophageal adenocarcinoma with any component of signet ring cells portends poor prognosis and response to neoadjuvant therapy. *J Thorac Cardiovasc Surg*. 2021;162:1404-12.e2.
3. Signet Ring Cell Carcinoma in Esophageal Adenocarcinoma (SRCC). ClinicalTrials.gov identifier: NCT01824966; 2013. Available at: <https://clinicaltrials.gov/ct2/show/NCT01824966>. Accessed September 2, 2020.

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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.

From the Division of Cardiothoracic Surgery, University of California San Diego, La Jolla, Calif.

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Address for reprints: Mark Onaitis, MD, Division of Cardiothoracic Surgery, University of California San Diego, 9300 Campus Point Dr #7892, La Jolla, CA 92037-7892 (E-mail: monaitis@health.ucsd.edu).

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Josh Boys, MD, and Mark Onaitis, MD

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

pretreatment sample and esophagectomy specimen from 0% to 100%. Pathology reports without the term “signet” were designated “usual type.” Of 819 patients, 106 (13%) were SRC type and did not differ from the usual type in regards to comorbidities, stage, or pretreatment tumor size. The median percent of SRC pretreatment was 20% with median SRC response of 0% (interquartile range, 1-10). SRC tumors were less likely to have a complete pathologic response post-treatment and more likely to have minimal response to chemotherapy, but this did not significantly correlate to the percent of pretreatment SRC. Median survival for the “usual type” adenocarcinoma was 59 months compared with 29 months with any percent of SRC, and SRC was independently associated with worse overall survival. Survival by percent of SRC was 31 months for 1% to 10%, 29 months for 11% to 49%, and 21 months for >50% and was not significantly different between groups or proportionally reflective of worse survival.

The authors are to be congratulated for performing a retrospective study of this magnitude. Limitations of this study that may be addressed in future trials include, first, the small sample size of SRC. Perhaps a multicenter study in the future could help. Also, no pathologic overread of the “usual type” was done, and no inter- or intrareader variability of specimens was read. Because pretreatment biopsies are small and because histologic percentages may

change with treatment, how to use the information clinically is still a question at present. Even with these limitations, this paper challenges our current classification of signet ring as based on >50% SRC in the specimen by showing evidence that any percent of SRC confers a worse prognosis.⁵ It is interesting that the median residual SRC after neoadjuvant treatment appears good at 0%, but those patients still had less common pathologic complete response and worse survival. The paper highlights the need to further investigate this subgroup from the bench to bedside and start documenting the amount of SRC in our specimens at our own institutions.

References

1. Van Hagen P, Hulshof MCCM, Van Lanschot JJB, Steyerberg EW, van Berge Henegouwen MI, Wijnhoven BP, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med*. 2012;366:2074-84.
2. Yendamuri S, Huang M, Malhotra U, Warren GW, Bogner PN, Nwogu CE, et al. Prognostic implications of signet ring cell histology in esophageal adenocarcinoma. *Cancer*. 2013;119:3156-61.
3. Patel VR, Hofstetter WL, Correa AM, Agarwal A, Rashid A, Bhutani MS, et al. Signet ring cells in esophageal adenocarcinoma predict poor response to preoperative chemoradiation. *Ann Thorac Surg*. 2014;98:1064-71.
4. Corsini EM, Foo WC, Mitchell KG, Zhou N, Maru DM, Ajani JA, et al. Esophageal adenocarcinoma with any component of signet ring cells portends poor prognosis and response to neoadjuvant therapy. *J Thorac Cardiovasc Surg*. 2021;162:1404-12.e2.
5. Watanabe H. The World Health Organization's histologic classification of gastrointestinal tumors. *Cancer*. 1990;66:2162-7.