response using clinical investigation, the wait and see approach can result in missing the so-called curable window. Therefore, in patients with ESCC and acceptable surgical risk, we strongly recommend esophagectomy, even in a case of complete clinical response. We are impatiently awaiting the important results of the Neoadjuvant Chemoradiotherapy for Esophageal Squamous Cell Carcinoma versus Definitive Chemoradiotherapy with Salvage Surgery as Needed trial ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT04460352) identifier: NCT04460352), which addresses this issue and we encourage centers from all over the world to actively participate.

See Article page 1632.

Commentary: The Hydra: Residual esophageal squamous cell tumor after neoadjuvant chemoradiotherapy

Jules Lin, MD

In this issue of the *Journal*, Tang and colleagues¹ describe characteristics of residual esophageal squamous cell carcinoma (ESCC) after neoadjuvant chemoradiotherapy (nCRT) at the time of esophagectomy. They conclude that residual tumors may be difficult to identify on endoscopic biopsy because of the small amount of viable tumor cells in the superficial layers. The results are of interest especially as debate continues on whether patients with ESCC with a complete clinical response after nCRT can be managed with surveillance.

The pathologic complete response in the CROSS (49%) and NEOCRTEC5010 studies (43.2%) was higher than the 26.2% rate in the current study.^{2,3} One possible explanation is that only patients with more advanced T3-4a disease were

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Hercules and his nephew Iolaus attacking the multi-headed Hydra using sword and fire (engraving by Cornelis Cort/Wikimedia Commons).

CENTRAL MESSAGE

Results of this study suggest that residual ESCC may be difficult to detect after neoadjuvant therapy because of only small amounts of viable tumor in the superficial layers.

included in the current study. Is it possible that patients with more superficial disease are more likely to have a complete response and less likely to have hidden disease deeper in the esophageal wall? In addition, there were substantial differences between the clinical T stage and the pretreatment prepT stage, the original tumor depth based on pathologic evidence of tumor regression. It is unclear if this is due to inadequate clinical staging, because many patients did not undergo endoscopic ultrasound, or difficulty determining the prepT stage due to treatment-related changes.

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Disclosures: The author reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

Received for publication Oct 11, 2020; revisions received Oct 11, 2020; accepted for publication Oct 14, 2020; available ahead of print Oct 17, 2020.

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J Thorac Cardiovasc Surg 2021;162:1643-4
0022-5223/\$36.00

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<https://doi.org/10.1016/j.jtcvs.2020.10.044>

Overall, the findings are consistent with previous studies. Chao and colleagues⁴ found that 45.6% of patients with a clinical complete response had residual cancer hidden underneath a cancer-free mucosal layer. In a similar study, only 58% of patients with a near complete pathological response had residual tumor in the mucosa, and the rate of identifying residual disease was only 65% after including submucosal involvement.⁵ Although complete pathologic response was lower with neoadjuvant chemotherapy alone at 14.1%, Hashimoto and colleagues⁶ found that 38% of nonresponders with ESCC had no residual tumor in the mucosal layer. In addition, Chao and colleagues⁷ found that most patients with ESCC with false-negative biopsy results after nCRT had mucosal or submucosal involvement on final pathology. This suggests that even when present, small amounts of residual mucosal or submucosal tumor cells may be difficult to detect on standard endoscopic biopsies.

The results of the current study demonstrate the distribution of residual disease in the esophageal wall. The response to treatment in the various layers may be due to tumor heterogeneity and differences in the microenvironment affecting blood flow, oxygen levels, and immune response leading to localized differences in chemoresistance.⁸ In addition, a subset of patients with a complete response within the primary esophageal tumor had positive lymph nodes highlighting the complexities of detecting residual ESCC after neoadjuvant therapy.

Although a complete pathologic response is possible after neoadjuvant therapy, like the Hydra, esophageal cancer can be persistent. If you cut 1 head off, 2 grow back. Until we are able to reliably determine a complete response based

on imaging, biopsies, and other biomarkers, the surgeon, like Hercules, should continue using a multidisciplinary approach attacking the Hydra with not only the sword, but fire, with neoadjuvant therapy followed by esophagectomy.

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