Three Angels are Dancing on the Head of the Esophageal Cancer Pin, but Shouldn't We Not Topple One or Two?

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The burden of esophageal cancer (EC) is great around the globe.^{1,2} Although adenocarcinoma is on the rise in the West, squamous cell carcinoma of the esophagus is rampant in the endemic areas.³ Even when EC is localized, it presents numerous challenges for the patients, their family, and the team of caretakers. Therapies are often associated with considerable morbidities and lifestyle alterations that are often quite uncomfortable. Localized EC is best treated after a multidisciplinary evaluation and discussions at a high-volume center. Patients with stage II or III EC are often offered a combination of chemotherapy, radiation, and/or surgery based on comorbid conditions, resectability, and geographical distribution of EC. There is well-established evidence to recommend definitive chemoradiation^{4,5} or chemoradiation followed by surgery,^{5,6} but the data is less convincing for chemotherapy followed by surgery (and more so for chemotherapy postsurgery).^{7,8} Surgery alone for clinical stage II or III EC, irrespective of histology (squamous cell carcinoma or adenocarcinoma), universally leads to poor outcome,⁹ and this strategy should be abandoned if facilities exist to deliver effective radiation therapy and chemotherapy.

In this issue of the *Annals of Surgical Oncology*, two reports from Japan present three approaches to localized, predominantly squamous cell EC (Watanabe et al. and Okumura et al.). Watanabe et al. conducted a prospective single arm study in 55 localized EC patients. These patients received a Japanese modification of docetaxel, cisplatin, and fluorouracil (DCF) systemic chemotherapy followed

by surgery. This was a well-executed trial, as 50 patients could undergo surgery. Pathologic complete response was observed in 12 % of ECs but the 2-year disease-free survival for patients was only 56 %; these results are concerning. The authors provided no hypothesis or sample size justification, noting that the multivariate analysis suggested response to therapy was an independent prognosticator. This study builds on prior Japanese experience and could be pursued further in a phase III setting. However, it has limitations because it is a single arm and single institution study; therefore, we suggest that the authors exercise caution before committing to a large investment of resources in a randomized study. There may be more fruitful ways to tackle this question.

The Okumura et al. report is puzzling and filled with shortcomings. First, the authors claim that the role of preoperative chemoradiation remains controversial and they support this notion by citing their own <50 patients randomized trial,¹⁰ but they do not acknowledge the Chemoradiotherapy Oesophageal Cancer Surgical Study (CROSS) trial results and the National Comprehensive Cancer Network (NCCN) recommendations.^{5,6} This sets the stage for their current report in which the authors retrospectively compared two treatments of 50 patients in a nonrandomized fashion. They provide no sample size justification or concrete hypothesis for their research trajectory. However, there does appear to be some structure to treatment selection. There were 30 patients who had three or fewer “malignant” nodes by clinical stage (and cT3 or cT4 primary) who were taken straight to surgery, but 20 patients who had more than three malignant nodes by clinical staging received cisplatin/fluorouracil (FU) and 40 Gy of radiation followed by surgery. The authors then compared the outcome of these two groups and found no difference in overall survival. These conclusions are difficult to interpret. Not only do the authors not acknowledge

the current literature, but they also compare outcomes of two nonrandomized populations and make a conclusion that is not supported by their results.

Which angels must we topple? Clearly, surgery first for clinical stage II or III should be discouraged, and we would also discourage chemotherapy as preoperative therapy because of the low level of effectiveness compared with that produced by preoperative chemoradiation.

In conclusion, Watanabe et al. made balanced choices and may be able to advance research in squamous cell EC. Okumura et al., on the other hand, present a confusing picture that leaves us confused. More research should be done to characterize the molecular biology (including immune biology) of squamous cell EC. Unless we apply more resources to learn the molecular underpinnings of EC (by identifying high-risk groups, refining early detection strategies, identifying novel targets, and individualizing therapy), we will collectively be remiss and unsuccessful in our attempts to significantly improve the lives of our patients with EC.

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