

## Treatment of Clinical T2N0M0 Esophageal Cancer

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There are now three randomized controlled trials showing benefit to preoperative chemoradiation for patients with locally advanced esophageal carcinoma. Although these trials are in the minority, with a total of nine published trials, meta-analyses have also shown that survival advantages are imparted to those undergoing treatment plus surgery rather than surgery alone. However, one of the main issues with applying those results to clinical practice is identifying which patients actually derive benefit. The standard, accepted approach would be to extend the same selection criteria used in the randomized studies to our clinical practices. All three of the positive trials included cT2N0M0 patients in the selection criteria, but the actual representation within those trials is an unknown (there were 3 patients in the CALGB 9781 trial, and the other two do not specify). It is unclear, based on the data presented in the randomized trials and in the article by Hardacker et al.<sup>1</sup> that patients presenting with cT2N0M0 disease derive any benefit from preoperative therapies.

There is also ample published evidence that the clinical diagnosis of intermediate-stage thoracic esophageal cancer is rife with inaccuracy. In fact, we have just presented an abstract to the American Association for Thoracic Surgery (2014) validating the findings of the study by Hardacker et al. The Esophageal Cancer Study Group's (ECSG) review of 767 patients treated in 16 centers of excellence between 2000 and 2012 showed that only 14 % of the diagnoses with a clinical stage of T2N0M0 were actually pathologically correct.<sup>2</sup> The fact that 44 % were understaged and that 38 % had nodal disease seemingly reinforces the notion that preoperative therapy is the

treatment of choice in this cohort of patients. Similar to the Hardacker article, the ECSG study showed equally poor staging accuracy when the inclusion was limited to patients from 2008 to 2012, thus indicating that this is not an issue that has been overcome by recent advances in staging.

Whereas I am in agreement that preoperative therapy is potentially more favorable than adjuvant therapy, there has yet to be any convincing evidence that it is necessary or that we are able to accurately stratify patients who would benefit. In as far as we are understaging patients, we are also overstaging. The Hardacker group indicated that they observed a 43 % overstaging incidence, and this is entirely consistent with the ECSG data (42 %) and previous data published by authors cited within the Hardacker article (e.g., Rice, Kountourakis, Stiles, and Crabtree). More specifically, a policy of preoperative chemoradiotherapy for cT2N0M0 patients will result in delivering potentially unnecessary therapy to more than half of the patients treated.

With reference to therapeutic benefit, the data presented by the ECSG were stratified, and treatments were compared. About half of the patients received preoperative therapy (chemotherapy or chemoradiation), and the other half received surgery alone. There were no differences in survival. Of course, a strategy of up-front surgery also allowed for adjuvant therapy. As the Hardacker group reported, there are potential predictors of more advanced disease. They report that poor differentiation can be a sign of potential understaging. In the ECSG study, lymphovascular invasion (LVI) and tumor length were strong predictors of nodal involvement, with inflection points at 2 and 3.5 cm. Perhaps we should be reserving preoperative therapy for patients who have known nodal involvement or who are at such high risk for it that the option is more favorable than the potential of adjuvant therapy.

Although a randomized trial may be the best type of data to potentially resolve this debate, any trial that attempts to randomize with such poor staging as to be incorrect more

than 85 % of the time will be overcome with inequities and errors. Ultimately, the methods used to stage esophageal cancer patients need to improve. Our current recommendation is that any patient with a tumor that appears potentially resectable by endoscopic resection should undergo an attempt. The information gathered from the histologic analysis will reduce potential overstaging in a significant proportion of this patient cohort. Endoscopic ultrasonography (EUS), although inaccurate for depth, should not be discarded, as it is extremely useful for identifying nodal disease that goes undetected by imaging. Fine-needle aspiration via EUS is the optimal minimally invasive histologic confirmation of stage. Multivariable analysis and clinical nomograms may also be useful; stratifying patients into high versus low risk for nodal disease on the basis of pretreatment clinical variables is an adjunct to invasive staging. At this point, I am reserving

preoperative therapy for patients with longer tumors (greater than 3.5 cm), those with LVI, or both. We are awaiting further data from the ECSG group on PET SUVmax and tumor differentiation.

I applaud the Indiana group for publishing their experience with this cohort of patients. The more the word gets out, the more likely we are to find a solution.

## REFERENCES

1. Hardacker, Ceppa, Okereke, et al. Treatment of clinical T2N0M0 esophageal cancer. *Ann Surg Oncol*. In press.
2. The Esophageal Cancer Study Group. Surgery alone or preoperative therapy in cT2N0 esophageal cancer? A multi-institutional study on staging deficiencies, treatment patterns, and outcomes in cT2N0 esophageal cancer. AATS abstract 2014. Presented 4/28/2014, Toronto.