
Discussion
Dr Steven G. Swisher (Houston, Tex). This study reviews the outcome of an uncommon subset of patients with esophageal cancer: those patients with clinical T2N0 tumors as defined by EUS. The authors make the observation that this group of patients seem to be difficult to accurately stage by EUS, with only 7 of 53 patients (13%) actually having a pathologic T2N0 tumor. Some 55% of the EUS-staged patients were overstaged and 32% were understaged, making proper treatment decisions difficult. The authors then evaluate the outcome of these patients and suggest that the optimal treatment for these patients is surgery first with postoperative chemoradiation reserved for those patients who have been understaged.

The article is to be commended for attempting to address an uncommon group of patients for whom little data are available and treatment decisions have not been defined. There are, however, several limitations to this study. It is retrospective and nonrandomized, and because of this, it is subject to bias and selection. This study was performed over a long period of time (20 years), with a small number of heterogeneous patients who were treated with several different treatment strategies. Because of these inherent limitations, accurate treatment assessments and recommendations are difficult to make even when performed with the aid of sophisticated statistical analyses.

I have several questions for the author. First, the accuracy of EUS staging for T2 esophageal cancers is much lower than that reported by recent groups who have used new EUS probes that operate at a higher frequency (15-20 MHz), as opposed to the 7.5 MHz described here, in which the esophageal wall can be visualized as a series of 7 or 9 layers. Would the use of these more accurate EUS miniprobes eliminate some of the staging inaccuracies reported in this study?

Dr Rice. No doubt the limitation of staging is ultrasound technology. As we look at the study period, we find that staging accuracy did not get any better over time, although we do use the 12-MHz probe to look within the wall and the 7.5-MHz probe to look distantly. The problem with adding more and more layers is that you have, of course, more and more interfaces to deal with. So, although increasing technology may seem attractive, it could add more areas for error.

Dr Swisher. Second, I believe that you would agree it is difficult to come up with absolute conclusions about treatment because this is a small, retrospective, nonrandomized study performed over a 20-year time period. How did the authors select the 7 patients treated with postoperative adjuvant treatment? Was the decision made because of age or performance status or because of a feeling by the surgeon that the tumor was at high risk for recurrence?

Dr Rice. There were 8 patients over approximately 18 years who received induction chemoradiation therapy, and, yes, they probably were treated a little earlier in the series; now, we would never consider anyone with disease confined to the wall for induction therapy. Certainly in these 8 patients, there is a small amount of induction toxicity and many tumor deaths, suggesting inaccuracy in staging. That is the best we could do. I agree it is a small number, but you must realize that it took us nearly 20 years to accumulate this experience; at our institution, where we perform 80 to 100 resections a year, that is only 2 patients per year.

Dr Swisher. Third, why do the authors think that their induction therapy experience was associated with such a poor outcome in their study? At MD Anderson we reviewed 21 patients who were treated with preoperative chemoradiation and had EUS-defined T2N0 tumors. They were treated with induction chemoradiation since 1997, and their overall survival is 67% at 3 years rather than the 13% 3-year survival reported by this study. Was the increased toxicity reported by your group caused by the hyperfractionated radiation therapy and paclitaxel that were used?

Dr Rice. Only 1 of 7 deaths was due to toxicity; 6 were due to recurrent cancer.

Dr Mark J. Krasna (Baltimore, Md). Tom, as always, I compliment you and your group for helping to elucidate all of the fine intricacies in the management of esophageal cancer, the stage-specific approach.

I will just reiterate what we just heard from Dr Swisher, that to make any kind of conclusion based on 7 of 53 patients would be inappropriate when we walk out of this room, but we appreciate the chance to discuss it. I do advise more than anything to caution against what I now have heard several times as a tendency among thoracic surgeons to adopt a postoperative adjuvant therapy approach in dealing with patients with any stage of esophageal cancer. To my knowledge, there are only 2 positive trials that would support that approach. One is a Chinese trial of adjuvant radiation therapy alone for patients with esophageal cancer. The only other data that are available that are either prospective or randomized are the results of the Gastric Cancer Study, which included patients who had total gastrectomies with D1, D2 resections, radical lymphadenectomies, and most of them splenectomies. So, again, I would just caution, although I know your experience is excellent, to generalize this, that people not walk out
of the room thinking that there is a proven role for adjuvant radiation or chemoradiation for esophageal cancer.

**Dr Rice.** Can I turn that back to you? Where is the evidence for the benefit of induction therapy? As surgeons, I would plead with you to do the operation first whenever possible. Then at least you know the pathologic stage and can decide how to treat your patient. If you are using induction chemoradiation therapy, two thirds of your patients will not respond. That is as bad as giving them postoperative adjuvant therapy based on matched data or some questionable phase III data. But I stand, as you stand, with no phase III study to help us. So, as a surgeon, take the cancer out first. You’ll be happy. At least you will know the pathologic stage.

**Dr Krasna.** Just to clarify, I do think that there are 3 phase III trials out there, including the first one that was presented from the group in Michigan, as well as the Walsh study and recently the Intergroup trial (CALGB 9781). Although all were small and some were questionable in terms of the long-term 5-year survival, especially for the Michigan trial, 2 of those 4 clearly showed a significant advantage in 5-year survival, not just 1-, 2-, and 3-year survivals, with trimodality therapy over surgery alone.

**Dr Rice.** But two thirds of your patients are getting therapy they will not benefit from: toxic high-dose therapy.

**Dr Krasna.** In 2 of those trials, that’s correct. One of the trials was a stage-specific approach.

**Dr Steven DeMeester** (Los Angeles, Calif). I’m glad to see that your study is echoing some of the data we have presented as well, that patients, regardless of the size of the tumor (even in our experience, T3 tumors that are N0), have an excellent survival. I think that’s an important message, that the lymph node status is much more important than the size of the tumor.

I am a bit surprised how 10% of patients could be overstaged when they had only high-grade dysplasia. Did those patients have a biopsy that showed cancer, leading to the EUS that gave you the misreading, or did they never have a biopsy of cancer? The question is, how did that happen?

**Dr Rice.** That is only 3 patients.

**Dr DeMeester.** That’s 10% though.

**Dr Rice.** It’s 10%, and they did have a mass in a segment of high-grade dysplasia, but the biopsy was read as invasive cancer.

**Dr Antoon Lerut** (Leuven, Belgium). You didn’t say anything about the lymph node ratio. How many lymph nodes were involved and what was the ratio? Is the burden of lymph node involvement comparable to what you find in the patients with T3? Would the lymph node ratio be helpful in discriminating whether you would see that as an indication for adjuvant chemo/chemoradiotherapy?

**Dr Rice.** Once we find N1 disease postoperatively, we try to administer postoperative adjuvant therapy. There is no doubt that in our experience if a patient has 1 or 2 positive nodes, he or she does better than if 3 or more positive nodes are present, but that survival advantage is 10% versus 24% at 5 years. Still, if you want to leave those patients with low lymph node burden unprotected, then that would be a way to direct your postoperative adjuvant therapy.

**Dr Joe B. Putnam Jr** (Nashville, Tenn). I have no conflicts. Tom, I appreciated the information that you presented here today and the lively discussion that has ensued.

As noted by the discussants, there are significant differences in survival that have been noted between single institutions. On the basis of multiple single-institution studies, we have created paradigms of cancer treatment, and there is a significant lack of multi-institutional trials in the prospective fashions. We have been successful in some phase II studies, and phase III studies have not been adequately subscribed to by our surgeons, medical oncologists, and radiation oncologists in a way that would allow rapid accrual, completion, and timely publication of the results. I would like your opinion as to the strategies that we can use to develop these multi-institutional trials to answer these significant problems, these significant questions that we have as surgeons and members of multidisciplinary teams in the treatment of our patients with esophageal cancer.

**Dr Rice.** For a phase III multi-institutional study, you obviously have to use high-volume centers. So, the first step is to get these centers to agree to participate. I believe that including low-volume centers will eliminate any survival advantage through increased operative or treatment mortality. The big boys have to get together.