Preoperative Therapy in Esophageal Cancer: Controversy and Consensus

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By David H. Ilson, MD, PhD [1]

Dr. Krasna has written an overview of multimodality therapy in esophageal cancer, with a particular focus on aspects related to staging and surgical care. The optimal management of locally advanced esophageal cancer remains a subject of controversy and active debate. However, there is now a clear consensus that surgery alone is inadequate therapy for patients with T3 or node-positive disease.

Staging of Esophageal Cancer
For locally advanced esophageal cancer, staging for the purpose of planning appropriate therapy has included endoscopy with biopsy and endoscopic ultrasound (EUS), CT scan of the chest and abdomen, and more recently positron emission tomography (PET) scanning. Clinical staging has proven increasingly accurate and has led to less use of invasive surgical staging methods, such as thoracoscopy or laparoscopy. There is a 70% to 80% concordance of EUS with pathologic tumor staging. PET scanning has the ability to identify nearly 15% of patients with stage IV distant metastases not revealed on conventional CT scans. With the more recent advent of EUS and fine needle aspiration (FNA) of suspect local regional nodal disease, nodal staging accuracy by EUS/FNA now exceeds 90%.

A recent cost/benefit analysis suggested that the most cost-effective staging strategy, as well as the one with the best yield, combined EUS/FNA with PET scanning.[1] Once the presence of a T3 lesion is established (with or without confirmation of nodal disease with EUS/FNA) and PET scanning has assessed for distant metastases, a decision to proceed with a combined-modality therapy approach can usually be made. The contribution of surgical staging is likely to add little benefit, when one factors in the added cost as well as the exposure of patients to an invasive surgical procedure. Whereas laparoscopy in more distal gastric cancers may have up to a 15% to 20% positive yield for occult peritoneal disease, in esophageal and gastroesophageal junction (GEJ) adenocarcinoma the yield for laparoscopy is much lower (a rate of 5% or less positivity).

The new American Joint Commission on Cancer (AJCC) staging system for both esophageal and gastric adenocarcinoma acknowledges the importance of a positive cytology even in the absence of visible peritoneal disease: positive cytology is now defined as part of stage IV disease, since all patients with this finding will unfortunately eventually die of their disease.

Combined Modality Therapy: Controversy and Consensus
Despite ongoing debate, there is an emerging consensus that adjuvant therapy, usually preoperative, should be combined with surgical management in the treatment of locally advanced T3 or node-positive esophageal and GEJ adenocarcinoma. Many neoadjuvant studies also include T2 disease, given the poor rates of 5-year survival even for T2,N0 disease (often less than 40%). Although Dr. Krasna declares combined chemotherapy and radiotherapy to be the “standard of care,” this choice of therapy is not universally accepted: in Europe there is more endorsement of preoperative chemotherapy followed by surgery, while in the United States the predominant approach is combined chemoradiotherapy followed by surgery.

Mixed results have been obtained with both preoperative chemotherapy and preoperative chemoradiotherapy. Many cite the recent MAGIC trial, conducted in the United Kingdom, which indicated a 13% improvement in 5-year overall survival (OS) for the pre- and postoperative use of ECF (epirubicin, cisplatin, and 5-fluorouracil [5-FU]) chemotherapy compared with surgery alone, unaccompanied by the use of radiotherapy.[2] One quarter of patients in this primarily gastric cancer
trial had esophageal or GEJ adenocarcinoma, and these patients also experienced a survival benefit with preoperative therapy. Another recent study from France (FFCD 9703), published in abstract form, involved patients with GEJ or gastric cancer and indicated a similar improvement in survival with the use of pre- and postoperative 5-FU and cisplatin, compared with surgery alone.[3] Neither study achieved any significant rate of pathologic complete response with preoperative chemotherapy alone.

On the other hand, older trials of preoperative chemotherapy focused more exclusively on esophageal cancer have been updated with long-term follow up, with either negative or disappointing results. The American Intergroup Trial 113 compared the administration of three pre-operative cycles and two postoperative cycles of 5-FU and cisplatin to surgery alone in nearly 450 patients with esophageal squamous cell carcinoma or adenocarcinoma. This trial failed to show improvement in median survival or OS, or improved rates of curative resection.[4] The updated trial report reinforced the prognostic importance of a negative-margin surgical resection to the achievement of long-term survival. An update of the UK OEO-2 trial, which compared the administration of two cycles of preoperative 5-FU and cisplatin to surgery alone in 800 patients with esophageal squamous cell carcinoma or adenocarcinoma, reported a disappointing 6% improvement in 5-year OS.[5] The authors attributed any improvement in OS with chemotherapy to the improved rate of curative resection seen with chemotherapy; however, this observation has not been confirmed in other preoperative chemotherapy trials.

Of the modern published trials of combined chemoradiotherapy in esophageal cancer, only two have indicated a survival benefit for preoperative therapy. The Walsh trial from Ireland indicated a survival benefit in esophageal adenocarcinoma for 5-FU, cisplatin, and radiation therapy (32%) compared with surgery alone (6%). However, the exceedingly poor performance of the surgical control arm in this study renders the study difficult to interpret at best. Although the Cancer and Leukemia Group B (CALGB) trial 9781 indicated a significant improvement in 5-year OS with preoperative 5-FU and cisplatin–based chemoradiotherapy, compared with surgery alone, the trial was severely underpowered and treated a mixed population of squamous cell carcinoma and adenocarcinoma. Only 30 patients were included in the preoperative therapy arm, compared with 26 patients who underwent surgery alone, and data on pathologic response were reported “missing” in 5 patients who received combined modality therapy; thus, the analysis was limited to only 25 patients receiving chemoradiotherapy.

Not cited by Dr. Krasna is the recent CROSS trial conducted in the Netherlands and reported at the 2010 ASCO meeting.[6] This multicenter, randomized phase III trial involved more than 360 patients with esophageal squamous cell or adenocarcinoma. Patients were all staged by endoscopic ultrasound and were randomly assigned to undergo immediate surgery or to receive 41.4 Gy plus 5 weeks of weekly carboplatin and paclitaxel followed by surgery. The trial was strongly positive for a benefit for preoperative therapy, with a nearly 2-year improvement in median survival (P=.011) and an 11% improvement in 3-year survival. Therapy was active, achieving a pathologic complete response rate of 30% and an improved rate of R0 resection (67% versus 92%, P<.002). Toxicity was modest and tolerable. Neither surgical morbidity nor mortality (3.4% to 3.8%) was worsened with preoperative therapy. Three quarters of patients had T3 or node-positive disease, and the majority had esophageal or GEJ adenocarcinoma. Once published, this trial may provide a new standard of care for chemoradiotherapy in esophageal cancer.

**Targeted Agents and Future Trials**

Dr. Krasna provides a limited discussion of targeted-agent trials in esophageal cancer. Completed and published phase II trials indicating the feasibility of adding targeted agents to chemoradiotherapy in esophageal cancer have combined the epidermal growth factor receptor (EGFR)-targeted agent cetuximab (Erbitux) with carboplatin/paclitaxel and radiation therapy,[7] and the human epidermal growth factor receptor 2 (HER2)-targeted agent trastuzumab with cisplatin/paclitaxel and radiation therapy.[8] Radiation Therapy Oncology Group (RTOG) trial 0436 is now ongoing in the United States, treating patients with esophageal cancer who are not operative candidates with paclitaxel/cisplatin and radiation therapy with or without the addition of cetuximab; over 200 of 400 planned patients have already been accrued. The SCOPE trial in the United Kingdom is also evaluating cetuximab in the nonoperative setting, treating patients with 5-FU, cisplatin, and radiation with or without cetuximab. RTOG is about to open trial 1010, treating HER2-positive esophageal and GEJ cancers with preoperative carboplatin, paclitaxel, and radiation therapy with or without trastuzumab. Studies have also evaluated the addition of the vascular endothelial growth factor (VEGF)-targeted agent bevacizumab to preoperative chemoradiotherapy in esophageal cancer; these have demonstrated the safety and tolerability of this therapy.[9,10] However, a
recently completed phase II trial combining the agents bevacizumab and erlotinib and chemoradiotherapy as preoperative treatment reported a disappointing median survival of only 18 months.[10]

Another area of active research is the use of PET scanning to assess response to induction chemotherapy in esophageal cancer. Recent studies from Germany have indicated that the response observed on PET scans during induction chemotherapy has significant predictive and prognostic benefit.[11,12] Based on these results, CALGB is developing trial 80803. Patients will receive induction chemotherapy with either mFOLFOX-6 (infusional 5-FU, folinic acid, and exaliplatin), or weekly carboplatin and paclitaxel. Patients whose PET scan indicates a response to induction therapy will then continue the same chemotherapy regimen during subsequent combined chemoradiotherapy, followed by surgery. Patients whose PET scan indicates nonresponse will cross over to the other regimen during radiotherapy, with the hope that the response in PET nonresponders will be optimized by changing chemotherapy during radiation.

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