

ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

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The Role of Chemotherapy in the Treatment of Esophageal Cancer

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H&O What is the current role of chemotherapy in the treatment of esophageal cancer?

AF Over the last 20 years, the role of chemotherapy has evolved from solely a palliative treatment to being integrated into the initial curative treatment of patients with newly diagnosed esophageal cancer. Currently, there are surgical and nonsurgical approaches to definitive treatment of nonmetastatic esophageal cancer. Both treatments administer chemotherapy concurrent with radiotherapy either as the definitive treatment or followed by surgery. For patients whose disease can be resected and there are no medical contraindications to surgery, preoperative chemoradiation has become an accepted standard within the community. The standard of care is surgery alone. For patients with locoregional disease that cannot be completely resected or have comorbidities that preclude surgery, concurrent chemoradiation is the standard of care.

H&O Could you describe some of the work that has led to the identification of this role?

AF In the United States, the majority of patients with esophageal cancer have stage IIB or III disease at diagnosis (involvement of regional nodes and a primary at least invading the muscularis propria). For these patients, the 5-year survival rate is about 20% after treatment with surgery alone. However, phase II studies evaluating preoperative chemoradiation show that two thirds of patients have their cancer downstaged and approximately 30% have no residual cancer in the resection specimen or very minimally invasive disease remaining. The 5-year survival rate of this latter group is 60–70%. Including all patients, the 5-year survival rate is 40%, approximately double that expected with surgery alone from historic controls. The survival prognosis correlates with post-treatment surgical

stage demonstrating an impact of the addition of preoperative chemoradiation. Investigators at many centers have reported these outcomes. The feasibility of obtaining pathologic complete response in patients with locally advanced disease and subsequent high cure rates is compelling and is the reason why preoperative chemoradiation is commonly utilized. The results of randomized trials, however, are conflicting. One randomized trial in patients with esophageal adenocarcinoma reported by Walsh and colleagues showed a significant survival improvement when preoperative cisplatin/5-fluorouracil (5-FU) and radiation was compared to immediate surgery alone. In contrast, 3 other trials in squamous cell cancer or including both histologies have not shown significant survival gain. Unfortunately, a well-designed trial mounted by the US Intergroup that could have answered this important question was terminated early because of poor enrollment.

The recommendation is clear, however, when non-surgical management is indicated. In a randomized trial in which 88% of patients had squamous cell esophageal cancer, radiotherapy alone was compared to radiotherapy plus 4 courses of cisplatin/5-FU. After 3 and 5 years, 30% and 26%, respectively, of patients who had received the combined treatment were alive while all patients in the radiotherapy alone treatment group had died by 3 years. Attempts to improve upon these results through intensification of chemotherapy or radiotherapy have not been successful.

H&O What characterizes the subgroup of patients whose disease does not respond to chemoradiation and who have residual tumor in the surgical specimen?

AF There are 2 subgroups of patients: those who have been downstaged, for example from stage III to IIA, and those with no change in stage or progression. A proportion of the former group will still achieve long-term survival through removal of the remaining cancer at surgery. The latter group will generally experience metastasis quickly. There is no specific clinical or histological characteristic that predicts for poor outcome other than advanced stage. The identification of molecular genetic predictive markers of pathologic complete response and survival is of great interest. Tissue correlative studies suggest that increased

epidermal growth factor receptor (EGFR) expression is associated with poor survival. Promotor hypermethylation of multiple genes has been shown to predict for poor survival and early tumor recurrence. Approximately half of patients in this subgroup will be cured through surgery. The other half will experience recurrent disease fairly quickly, and will die from their disease.

H&O What are the major challenges facing esophageal cancer therapy right now?

AF A major challenge is to increase the number of patients achieving pathological complete response to chemoradiation, which confers a favorable prognosis, without augmenting toxicity. Accomplishing this goal requires greater knowledge of the biology of these cancers and identification of tissue markers that predict sensitivity or resistance to therapies, or which may be targeted by a particular agent. Newer drugs and combinations are being evaluated, in particular, irinotecan and taxane combinations. Some regimens appear to cause less toxicity than cisplatin/5-FU but without major gain in survival. Another challenge is finding effective adjuvant therapies for patients who have had a complete resection as most of our patients die from distant metastases.

H&O Has adjuvant therapy been explored in the past?

AF Yes, adjuvant chemotherapy following chemoradiation and surgery has been tried and been largely unsuccessful simply because less than half of patients are able to tolerate this additional therapy. Chemotherapy given after resection only has had limited evaluation. Data from Japanese investigators suggest a benefit for cisplatin/5-FU adjuvant chemotherapy in node-positive patients and not in node-negative disease. This data led the Eastern Cooperative Oncology Group to conduct a phase II trial of adjuvant paclitaxel and cisplatin chemotherapy in patients who had complete resection of adenocarcinoma of the distal esophagus, G-E junction or cardia and positive regional nodes. The results were encouraging, with a 60% 2-year survival rate reported for this poor-risk group suggesting that further study is warranted. An Intergroup randomized trial for patients with resected gastric cancer compared observation with adjuvant radiation, 5-FU and leucovorin. A significant survival advantage was observed for the adjuvant therapy group. Because 20% of patients enrolled in this trial had G-E junction primaries, these results have been extrapolated to esophageal adenocarcinoma/G-E junction cancers. The trial was not powered to look at the outcome in this subset that has a different failure pattern (distant metastasis as the site of first failure in 80%), while gastric cancers fail locoregionally. However, with this caveat, the results do provide a therapeutic option.

H&O What strategies for adjuvant therapy are being explored?

AF The difficulty in delivering adjuvant chemotherapy after patients have received preoperative systemic therapy and surgery has led some investigators to administer several cycles of chemotherapy up-front, followed by chemoradiation and then surgery. Some preliminary data are encouraging, but we do not yet know whether this approach will improve survival. Advances in staging procedures, specifically positron emission tomography (PET) scanning, and potential stage migration confound comparisons to historical controls.

H&O Is it possible to avoid surgery for patients who have no residual disease after preoperative chemoradiation?

AF This is another challenging area of esophageal cancer research. Identifying patients who do not require surgery would be a tremendous step toward improved quality of life and of course avoiding the potential morbidity and mortality of esophageal surgery. Currently, there is no technology that can reliably identify residual microscopic disease after chemoradiation. The Radiation Therapy Oncology Group is conducting a study in which patients are treated with chemoradiation and are then evaluated for the presence of residual disease using the best currently available technologies (PET, endoscopic ultrasound and repeat biopsy). Patients for whom a histologic diagnosis of residual disease can be made proceed to surgery. If residual disease cannot be identified, the patient is followed and monitored. If cancer is subsequently detected in the esophagus and is confined to this location, then salvage surgery will be attempted. However, no trial randomizes patients to chemoradiation with or without surgery.

H&O Would such a trial ever be conducted?

AF It is highly unlikely that this trial could be accomplished in the United States. One reason for this is physician bias: some believe that esophagectomy should be performed whenever feasible to remove residual cancer that cannot be otherwise detected; while others believe that surgery does not add appreciably to survival rates achievable with chemoradiation. This presents problems for patient informed consent and enrollment.

H&O What initially led to the hypothesis that not all patients who had received chemoradiation required surgery?

AF In the 1980s, a landmark study was performed in which patients with disease confined to the chest were randomized to receive radiation alone, the standard treat-

ment at that time for inoperable patients, or radiation with cisplatin/5-FU (Hershkovic et al, *N Engl J Med*, 1991). Patients who received chemoradiation experienced a clear survival benefit. At 3 years, all patients who received radiation alone had died, while 30% of those receiving chemoradiation were alive. The study was stopped early because of the highly significant results.

The staging requirements were quite unlike those of today; a chest radiograph, computed tomography scan of the abdomen, bone scan and panendoscopy with biopsy were performed with the goal of ruling out distant metastases. Most had squamous cell cancers (88%), and the true stage of these cancers and operability status is unclear. Unresectability was not an eligibility requirement. Nonetheless, patients receiving the combined therapy had a lower rate of distant metastases and local recurrence than those receiving radiation alone. The findings indicated that chemoradiation alone could cure a proportion of patients. However, almost half of the chemoradiation patients had local recurrence or persistent disease in the esophagus approximately 1 year after therapy, which was considered unacceptable.

To address this, a subsequent study compared chemoradiation with a higher dose of radiation, 6,480 cGy versus the chemoradiation regimen in the prior study. This trial was stopped at the first interim analysis because of an inferior projected survival outcome for the high-dose radiation regimen and a low statistical probability that continuing to full enrollment would yield a positive trial result. Thus, the standard of care for patients not undergoing surgery is the chemoradiation regimen developed in the 1980s: radiation 5,040 cGy plus 4 cycles of cisplatin 75 mg/m² and infusional 5-FU 1,000mg/m² over 24 hours for 96 hours, 2 cycles concurrent with radiotherapy and 2 cycles following.

Essentially, there are 2 ways of treating esophageal cancer: surgical and nonsurgical. Squamous cell carcinoma may be more appropriate for nonsurgical management than adenocarcinoma for 2 reasons. The pathologic complete response rate for squamous cell cancers treated with preoperative cisplatin-based chemoradiation is generally higher than for adenocarcinoma. Secondly, because most squamous cell carcinomas are located in the middle or upper thoracic esophagus, with surgical management, circumferential margins are almost always positive. This is in contrast to resection of distal and G-E junction adenocarcinomas. For patients with adenocarcinoma,

the most common histology today, surgery may be more important for achieving complete removal of residual cancer and potential cure. Right now, because we do not have an accurate way of determining whether or not a patient has residual cancer after chemoradiation, all patients with adenocarcinoma should undergo surgery.

H&O What recent associations have been made between tumor markers and prognosis?

AF A recent study found that patients with overexpression of the EGFR experienced worse survival rates. This study prompted the thought that blocking the EGFR may improve outcomes, and formed the rationale for a study to be conducted by the Eastern Cooperative Oncology Group in which the anti-EGFR monoclonal antibody cetuximab (Erbix, ImClone/Bristol-Myers Squibb) will be added to chemotherapy and radiation to see if this combination improves pathologic complete response rate and, ultimately, increases the proportion of long-term survivors.

Studies of EGFR in esophageal cancer have generated a great deal of interest particularly because of the results of EGFR inhibitors in other G-I adenocarcinomas, such as colorectal cancer. The principles developed for EGFR-targeted therapy in lower gastrointestinal cancers are the same as those being incorporated into the studies in esophageal cancer.

Suggested Reading

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