Drs. Ilson and Kelsen present an excellent review of the current investigations and treatment recommendations for patients with esophageal cancer. In a comprehensive and concise fashion, they detail controversies in surgical and nonsurgical management, neoadjuvant therapies, and regimens for treating metastatic disease. Their review provides an opportunity to further highlight several research questions.

Anatomic Considerations and Natural History

When esophageal cancer is initially treated for cure with one local treatment modality (surgery or radiotherapy), treatment failure is due to both local and distant disease and both contribute to mortality. This is important to keep in mind when designing trials to improve survival. Early distant spread is explained by the dense network of lymphatics in the mucosa and submucosa that interconnect with lymphatic vessels in the muscular layers of the esophagus. These lymphatic channels drain primarily longitudinally to regional and distant nodal beds. Local recurrence is also to be expected because circumferential "margins" of resection are nearly always positive for microscopic tumor, whereas proximal and distal margins of resection, provided in the surgical pathology report, are usually negative. Thus, it does make sense that utilizing all three modalities--radiation therapy and surgery for local control and chemotherapy for distant spread--would offer the best chance for cure in a patient presenting with localized disease. Surgery is the most effective means for debulking the primary tumor or eradicating residual disease in the esophagus after preoperative therapy. It makes sense to add radiotherapy to surgery to improve local control, particularly for patients with T3 and T4 disease, in whom residual microscopic disease in the tumor bed is likely. Chemotherapy certainly has a role in enhancing the effects of radiation and as a systemic therapy for occult distant spread. The critical question is how to optimally sequence these three therapies to cure or significantly increase survival time in the highest percentage of patients who present with potentially curable localized disease.

Surgery Combined With Radiotherapy

Controlled trials of surgery combined with preoperative or postoperative radiotherapy do not demonstrate an improvement in survival and are conflicting with regard to the effects of this combination on locoregional control. One trial of preoperative radiotherapy showed a decrease in locoregional failure (46% vs 67%), but others showed no effect.[1-4] Postoperative radiotherapy has a high rate of toxicity to normal tissues because of the potentially large volumes irradiated. Only two controlled trials of surgery combined with postoperative radiotherapy are available.[5,6] One trial showed a reduction in locoregional failure in a subset analysis of pathologically staged N0 patients, and the other, which involved patients who had all gross tumor removed and negative resection margins, showed no effect.

Surgery Combined With Chemotherapy

Because distant metastasis is a major cause of death and early failure in patients with esophageal cancer, the addition of preoperative (neoadjuvant) systemic therapy to surgery makes intuitive sense. The limitation of this two-modality approach is that only 50% of tumors are sensitive to current cisplatin (Platinol)-based chemotherapy regimens and pathologic complete response is infrequent. This situation is in contrast to squamous cell cancer of the head and neck (after which these esophageal trials were modeled), in which 80% to 90% of patients respond and 30% to 50% may achieve a pathologic complete response. This is a major weakness in this treatment strategy and diminishes the possibility that adjunctive chemotherapy will have sufficient impact on
locoregional failure and distant metastasis rates to significantly improve survival over surgery alone. The GI Intergroup Trial, which enrolled over 400 patients and is now undergoing analysis, will provide a definitive answer to the question of whether the combination of preoperative chemotherapy and surgery affords a survival benefit. In addition, this trial was open to patients with adenocarcinoma of the esophagus, as well as squamous cell carcinoma, so that for the first time comparisons can be made between the two histologic types with statistical confidence. This information and that gleaned from various subset analyses should yield important insights for future trial design. Until the data analysis of this critically important trial is mature, surgery remains the standard of care for patients with localized disease.

Currently, the role of postoperative adjuvant chemotherapy or chemoradiation is undefined. There are no data to suggest that administering postoperative adjuvant chemotherapy prolongs either the disease-free interval or survival, particularly in patients who have undergone a curative resection and have negative nodes. Patients who have positive margins of resection, however, should be considered for postoperative radiation.

**Concurrent Chemotherapy and Radiotherapy Without Surgery**

Survival benefit has clearly been established for concurrent chemoradiotherapy and radiotherapy, compared to radiotherapy alone, in patients with squamous cell cancer, but this has not been adequately addressed in patients with adenocarcinoma. This conclusion is supported by the intergroup trial results published by Herskovic, Al-Sarraf, and colleagues.[7,8] Despite improved survival (median survival, 14 months; 3-year survival rate, 30%) in patients treated with chemoradiation, the rate of persistent or recurrent disease in the esophagus at 1 year was unacceptably high.

Results from nonsurgical trials indicate that local failure occurs in at least 45% to 50% of patients.[7,9,10] This is of particular concern when treating patients with localized, potentially curable disease. For most patients, chemoradiation (cisplatin, fluorouracil [5-FU], or mitomycin [Mutamycin] with 50 to 60 Gy of radiation) alone will not eradicate bulk disease in the esophagus. Thus, oncologists should not be satisfied with this therapy as "recommended treatment" except for patients with disease extending outside of the esophagus into adjacent structures (T4) or those with medical risks that preclude resection.

No doubt, there is a subset of patients with squamous cell cancer who can be cured without surgery. Identifying these patients poses a challenge since we know that the results of endoscopic biopsy greatly overestimate the pathologic complete response rate when compared to resection specimens.[11,12] Esophageal endoscopic ultrasound is being studied for its accuracy in predicting complete response but is unlikely to be able to accurately discriminate tumor given the degree of acute tissue injury and subsequent fibrosis that occur after chemotherapy and radiotherapy. The best way to address the question is with very careful staging that includes endoscopic ultrasound, radiologic imaging, and laparoscopy for distal lesions before patients enter a controlled trial. It may then be feasible to identify patient subgroups who are likely to be cured without surgery.

**Concurrent Chemotherapy and Radiotherapy Followed by Surgery**

Drs. Ilson and Kelsen discuss several published trials of concurrent chemoradiation followed by surgery that were conducted in the 1980s. Pilot trials from Wayne State University, the Southwest Oncology Group (SWOG), and the Radiation Therapy Oncology Group (RTOG), which entailed the administration of two courses of cisplatin, with or without 5-FU, combined with 30 Gy of radiation, reported pathologic complete response rates in 25% to 30% of patients and suggested a survival advantage for pathologic complete responders. Most patients died from distant disease without local recurrence. This finding lends support to the importance of removing the esophagus, which, in 50% to 70% of patients, harbors residual disease. The preponderence of distant disease indicates a need for improved systemic therapy. The data published from the University of Michigan,[13] Johns Hopkins,[14,15] and, most recently, the University of North Carolina[11] support this alternative interpretation of the results of those early trials cited by Dr. Ilson and Dr. Kelsen in their review. Using protracted low-dose infusional 5-FU and continuous-infusion cisplatin with concurrent radiotherapy, comparable results from two sequential pilot trials (total of 93 patients) have been published by Forastiere and colleagues: median survivals of 29 and 31 months, respectively; 2-year survival rates of 57% and 58%, respectively; and long-term survival in approximately 30% of patients with residual tumor in the resected esophagus and in 60% of pathologic complete responders.[13-15] Bates, Tepper, and colleagues reported a median survival of 26 months, 2-year survival rate of 53%, and survival beyond 3 years in 25% of patients with tumor in the resected esophageal specimen and in 61% of pathologic complete responders.[11]
These and other recently published trials not included in Table 2 of this review support the need for further evaluation of the three-modality approach in large randomized trials. [16-19] Local control was observed in 75% to 90% of patients in these trials and appears to be optimized. The challenge is to find alternative, more effective systemic therapies to decrease distant metastases. Controlled trials that accrue large numbers of patients are needed so that clinically meaningful survival differences can be demonstrated with statistical confidence. This has yet to be done. A comparison of preoperative chemoradiation followed by surgery to surgery alone and a comparison of a surgical to a nonsurgical multimodality approach are two randomized trials that need to be conducted. Until these trials have been carried out, these multimodality approaches must be considered experimental. Patients will be afforded the best outcome if treated at centers that have a dedicated multidisciplinary team and a formal esophageal cancer research program.

References:


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