Is it possible that radiotherapy for local control does not matter in patients with esophageal adenocarcinoma? More studies are needed

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Central Message

Adding preoperative radiation to chemotherapy before resection may not improve survival but conveys other benefits and should be considered for most patients with locally advanced esophageal cancer.

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Neoadjuvant therapy before resection is the current standard of care for patients with esophageal adenocarcinoma staged higher than stage IIB, and the National Comprehensive Cancer Network recommends preoperative chemoradiation therapy as the preferred treatment.¹ This recommendation is based on multiple randomized studies that have shown survival advantages for preoperative chemoradiation compared with surgery alone, the most influential of which was the Chemoradiotherapy for Oesophageal Cancer followed by Surgery Study (CROSS) published in 2012.² Randomized studies that compared preoperative chemoradiation with preoperative chemotherapy have not shown a clear survival advantage of chemoradiation relative to chemotherapy, but they have demonstrated a higher rate of complete resection (R0) and a higher rate of downstaging with preoperative chemoradiation.³⁻⁵

In the current issue of the *Journal*, Liou and colleagues⁶ report a large study in which they used the National Cancer Database (NCDB) to compare patients who received preoperative chemotherapy with those who received preoperative chemoradiation therapy. Except for tumor size, there were no significant differences in the baseline characteristics of the 2 groups. The vast majority of patients (91%) received preoperative chemoradiation. Interestingly, the study revealed strong institutional preferences: 609 facilities (77%) treated at least 90% of their patients with chemoradiation, whereas 11 facilities (4%) treated more than 90% of their patients with chemotherapy alone. Patients who underwent preoperative chemoradiation had higher incidences of tumor and nodal downstaging, pathologic complete response, and complete resection. Survival, however, did not differ between the 2 treatments. Liou and colleagues⁶ concluded that radiation therapy before resection may not be uniformly necessary for all patients with esophageal adenocarcinoma.

Studies that use the NCDB are important in gathering population-based information. Even when NCDB studies

confirm the findings of a randomized trial, however, caution is warranted. Liou and colleagues⁶ did not demonstrate a survival advantage to preoperative chemoradiation, but all parameters for local control (downstaging, pathologic complete response, and complete resection) were improved by adding radiation. Furthermore, the interpretation of several of the randomized studies that compared preoperative chemotherapy with preoperative chemoradiation is far from conclusive. For example, the study of Stahl and colleagues,³ which randomized 126 patients to receive either preoperative chemotherapy or preoperative chemotherapy followed by preoperative chemoradiotherapy, closed early because of accrual problems and had a radiation dose (30 Gy) significantly below that used in the CROSS study; however, the investigators still observed a strong trend toward improved survival of patients receiving chemoradiation ($P = .07$). Burmeister and colleagues⁴ randomized fewer than 40 patients per treatment arm, and patients in the preoperative chemoradiation arm received a relatively low dose of radiation (35 Gy). There were no differences in survival, but patients who received radiation did have a higher rate of complete resection and a higher rate of tumor response. Finally, Klevebro and colleagues⁵ randomized patients to receive chemotherapy or 40G y of radiation plus chemotherapy preoperatively. Again, there were no

differences in survival, but patients who received radiation had a higher rate of complete resection and also more pathologic complete responses.

Completeness of resection, downstaging, and pathologic complete response are all important factors affecting survival in patients with esophageal cancer. It is hard to explain how a treatment modality that favorably affects these factors does not affect overall survival. One possibility is that studies have been underpowered to detect differences; another possibility is that the dose of radiation administered was too low. A well-executed randomized trial is urgently needed to determine the value of neoadjuvant radiation in patients with locally advanced esophageal adenocarcinoma. Until then, the clinician will serve his or her patients well by improving local control with preoperative chemoradiation and reserving chemotherapy without radiation for a selected few patients.

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