Editorial

Neoadjuvant chemotherapy versus chemoradiotherapy for esophageal cancer: a tradeoff between dysphagia and pathologic response

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Sunde *et al.* reported their findings on the relief of dysphagia after neoadjuvant chemoradiotherapy versus chemotherapy in patients with esophageal cancer (1). Dysphagia was a secondary endpoint in a multicenter, randomized clinical trial, NEOadjuvant therapy in RESectable esophageal cancer (NeoRes) (2,3). They found that patients who underwent neoadjuvant chemoradiotherapy had higher rates of dysphagia, but a better pathologic response, compared to patients who underwent neoadjuvant chemotherapy. However, there was no association between dysphagia and pathologic response for individual patients. The question of whether neoadjuvant chemoradiotherapy or chemotherapy is superior for locally advanced esophageal cancer is unresolved, and dysphagia is an important endpoint to be considered. Dysphagia affects nutritional status, which is important for recovery after esophagectomy, and greatly affects quality of life. The authors, as well as others, have previously shown that both neoadjuvant chemotherapy and chemoradiotherapy improve dysphagia (4,5). This study is unique in its randomized design and ability to compare dysphagia with pathologic response.

In NeoRes, patients with T1N1M0 to T4aN3M0 esophageal or gastroesophageal junction cancer who were eligible for surgery were randomized to neoadjuvant chemoradiotherapy or chemotherapy. The chemotherapy regimen in both groups was three cycles of cisplatin and 5-fluorouracil, and the radiation dose in the chemoradiotherapy arm was 40 Gy administered in 20 fractions over 4 weeks. Patients were scheduled for esophagectomy 4–6 weeks after completion of neoadjuvant treatment.

One of the secondary endpoints in NeoRes was dysphagia, which was assessed before and after neoadjuvant treatment. The European Organization of Research and Treatment of Cancer (EORTC) core questionnaire (QLQ-C30) and the disease-specific modules for esophageal cancer (QLQ-OES24) and gastroesophageal junction or gastric cancer (QLQ-OG25) were used to obtain patient-reported outcomes. The questionnaires ask patients to rate their ability in three categories: to eat solid food, to eat semisolid food, and to drink. The scale ranged from 1 'not at all,' to 2 'a little,' to 3 'quite a bit,' to 4 'very much.' The scores on those three questions were then linearly transformed to a score from 0 to 100, with a higher score reflecting worse symptoms.

From 2006 to 2013, 181 patients were randomized, 90 to neoadjuvant chemoradiotherapy and 91 to neoadjuvant chemotherapy. Twenty patients were excluded from the analysis of dysphagia because they underwent esophageal stenting. There were 47 patients in the neoadjuvant chemoradiotherapy group and 51 patients in the neoadjuvant chemotherapy group who completed dysphagia questionnaires both before and after neoadjuvant treatment and were not excluded for other reasons. Among patients with dysphagia at baseline, dysphagia scores improved significantly after both neoadjuvant chemoradiotherapy (41 to 28, P=0.039) and neoadjuvant chemotherapy (42 to 25, P=0.012). There was no difference in the improvement in dysphagia between the two groups (P=0.686). However, among patients with no dysphagia at baseline, dysphagia scores were similar after neoadjuvant chemotherapy (0 to 3, P=0.216), but increased significantly

after neoadjuvant chemoradiotherapy (0 to 17, P=0.014). The difference in mean scores was significantly higher in the patients who underwent chemoradiotherapy compared to those who underwent chemotherapy (P=0.014).

The primary outcome of NeoRes was pathologic complete response of the primary tumor. The tumor regression grade (TRG) was scored with the Chirieac classification. TRG1 was complete response; while TRG2, TRG3, and TRG4 were 1–10%, 11–50%, and >50% remaining tumor cells, respectively. Additional secondary endpoints were lymph node metastases and extent of resection. Among the 156 patients who underwent esophagectomy, patients who underwent neoadjuvant chemoradiotherapy were more likely than those who underwent neoadjuvant chemotherapy to have a complete pathologic response (28% *vs.* 9%, P=0.002), not have any lymph node metastases (62% *vs.* 35%, P=0.001), and have an R0 resection (87% *vs.* 74%, P=0.04) (2). Despite the differences in pathologic response and extent of resection, there was no difference in the secondary endpoints of five-year overall (42% *vs.* 40%, P=0.60) or progression-free (39% *vs.* 33%, P=0.82) survival between the neoadjuvant chemoradiotherapy versus chemotherapy groups (3).

The primary endpoint of pathologic response was compared to dysphagia scores, with the hypothesis that tumors with a better pathologic response would be associated with improved dysphagia. However, there was no association between dysphagia and pathologic response, overall or within either of the treatment groups, for individual patients. Sunde *et al.* described potential explanations for these findings at a pathologic level. Radiotherapy is known to cause esophagitis, and this effect may be counteracting the treatment effect of the tumor (6). Or tumors overall may respond well to radiotherapy, but not decrease in size or in fact become more fibrotic, leading to dysphagia. In any case, the tradeoff between dysphagia and pathologic response was apparent for the group of patients who underwent neoadjuvant chemoradiotherapy compared to chemotherapy, but did not hold at the individual patient level.

There were a couple unanswered questions from the study. The timing of the development and resolution of dysphagia symptoms during neoadjuvant therapy was not assessed. Many patients did not fill out both questionnaires, and the timing of the questionnaire after neoadjuvant treatment was variable, at a median of 26 days and range 0–77 days after completion of neoadjuvant treatment. Surgery was performed a median of 92 and 97 days after neoadjuvant chemotherapy and chemoradiotherapy, respectively. Patients in the neoadjuvant chemoradiotherapy group were more likely to undergo percutaneous endoscopic gastrostomy for tube feeding (P=0.005), but the indications were not described. Despite this uncertainty, however, the difference in dysphagia did correlate with weight loss. Patients who underwent neoadjuvant chemotherapy had no significant weight loss, while those who underwent neoadjuvant chemoradiotherapy lost a mean of 3 kg from baseline to the day before surgery (P<0.0001).

It would also be important to assess whether there was a difference in dysphagia between patients with adenocarcinoma versus squamous cell carcinoma. In NeoRes, while there was no difference in overall survival between the neoadjuvant chemotherapy versus chemoradiotherapy groups, there was a trend towards improved overall survival after neoadjuvant chemoradiotherapy in patients with squamous cell carcinoma. NeoRes is also the only randomized clinical trial to compare neoadjuvant chemoradiotherapy versus chemotherapy in both adenocarcinoma and squamous cell carcinoma.

Several other studies showed similar findings to NeoRes, including two other randomized clinical trials studying patients with esophageal adenocarcinoma. Burmeister *et al.* showed a higher complete pathologic response (13% *vs.* 0%, P=0.02) but no difference in overall survival (5-year survival, 45% *vs.* 36%, P=0.60) after neoadjuvant chemoradiotherapy versus chemotherapy (7). Stahl *et al.* also showed a higher complete pathologic response (14.3% *vs.* 1.9%, P=0.03) and a trend towards improved overall survival (5-year survival, 40% *vs.* 24%, P=0.055) after neoadjuvant chemoradiotherapy versus chemotherapy (8). In addition, an analysis of 4,763 patients with esophageal adenocarcinoma in the National Cancer Database showed higher rates of complete pathologic response (13% *vs.* 6%, P<0.001) but no difference in overall survival (5-year survival, 36% *vs.* 37%, P=0.33) after neoadjuvant chemoradiotherapy versus chemotherapy (9).

In conclusion, the question of whether neoadjuvant chemoradiotherapy or chemotherapy is superior for locally advanced esophageal cancer is unresolved. Several studies have shown a better pathologic response to chemoradiotherapy, but no significant difference in overall survival. In this study, Sunde *et al.* showed that neoadjuvant chemoradiotherapy may actually cause harm in the form of worsening dysphagia, especially in patients who did not have dysphagia at baseline. These results warrant consideration of neoadjuvant chemotherapy instead of chemoradiotherapy for patients with locally advanced esophageal cancer.

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Footnote

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Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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