The Society of Thoracic Surgeons Practice Guidelines on the Role of Multimodality Treatment for Cancer of the Esophagus and Gastroesophageal Junction

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Executive Summary

1. **Class I Recommendation:** Patients with potentially curable, locally advanced esophageal cancer should be cared for in a multidisciplinary setting. (Level of Evidence B)
2. **Class I Recommendation:** Restaging studies after neoadjuvant therapy are recommended before resection to rule out interval development of distant metastatic disease. (Level of Evidence B)
3. **Class IIA Recommendation:** Endoscopic ultrasound restaging for residual local (mural) disease is inaccurate and can be omitted. (Level of Evidence B)
4. **Class IIA Recommendation:** A positron emission tomography scan is recommended for restaging after neoadjuvant therapy to detect interval development of distant metastatic disease. (Level of Evidence B)
5. **Class III Recommendation:** Radiotherapy as monotherapy before resection is not recommended. (Level of Evidence A)
6. **Class IIA recommendation:** Neoadjuvant platinum-based doublet chemotherapy alone is beneficial before resection for patients with locally advanced esophageal adenocarcinoma. (Level of Evidence A)
7. **Class IIA Recommendation:** Neoadjuvant chemoradiation therapy should be used for locally advanced squamous cell cancer and either neoadjuvant chemotherapy or chemoradiation therapy for locally advanced adenocarcinoma; multimodality therapy has advantages over surgical resection alone. (Level of Evidence A)
8. **Class I Recommendation:** After neoadjuvant therapy, patients without metastatic disease, in whom surgical resection can be safely performed, should receive esophageal resection. (Level of Evidence A)
9. **Class IIA Recommendation:** Patients with adenocarcinoma who have not received neoadjuvant therapy should be considered for adjuvant chemoradiotherapy if the pathologic specimen reveals regional lymph node disease. (Level of Evidence B)

This is one of a series of guidelines from the Task Force of the General Thoracic Workforce of The Society of Thoracic Surgeons (STS) focusing on the management of esophageal cancer. This article addresses the role of multimodality therapy in the treatment of this disease. Evidence-based guidelines are recommendations, not absolutes, and are intended to assist health care providers in clinical decision making by reviewing a range of acceptable approaches for the management of specific conditions. The ultimate judgment regarding care of a particular patient under specific circumstances must be made by the provider, and there are certainly circumstances in which management that falls outside of these guidelines is appropriate.

Methods

Our Task Force was tasked with addressing the factors affecting the treatment of locoregional esophageal cancers. This clearly includes patients with stage III disease because they have involved regional lymph nodes. It may also be reasonable to consider multimodality therapy for clinical stage II patients that are at high risk for systemic disease such as cT3 N0 patients [1, 2]. For this systematic review of multimodality therapy, specific search terms

Report from The Society of Thoracic Surgeons Workforces on Evidence Based Surgery and General Thoracic Surgery.

The Society of Thoracic Surgeons Clinical Practice Guidelines are intended to assist physicians and other health care providers in clinical decision making by describing a range of generally acceptable approaches for the diagnosis, management, or prevention of specific diseases or conditions. These guidelines should not be considered inclusive of all proper methods of care or exclusive of other methods of care reasonably directed at obtaining the same results. Moreover, these guidelines are subject to change over time, without notice. The ultimate judgment regarding the care of a particular patient must be made by the physician in light of the individual circumstances presented by the patient.

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were identified, and targeted searches were run in PubMed/MEDLINE, EMBASE, and the Cochrane databases in June 2012 and reinforced in April 2014. The results were limited to publications since 1990 and to human subjects.

We augmented our computerized literature search by manually reviewing the reference lists of identified studies and relevant reviews. In addition, the writing group identified articles from personal files. The following three Medical Subject Heading (MeSH) terms were used: "Esophageal Neoplasms," "Early Detection of Cancer," and 'Neoplasm Staging." Additional search strategies incorporated the MeSH subheadings of "Analysis," "Histology," "Methods," "Pathology," "Standards," "Trends chemotherapy, radiation therapy, trimodality therapy, surgery," and "Trends."

Abstracts were reviewed by at least 2 authors and excluded if data were duplicative, did not specify esophageal cancer, were purely descriptive, or were incomplete. The resulting articles served as the source for the review. Guideline recommendations were taken from the American College of Cardiology/American Heart Association methodology manual for writing guidelines and were formulated and reviewed by all members of the writing group before approval by the Workforce on Evidence Based Surgery and the STS Executive Committee.

Multimodality Care

1. **Class I Recommendation:** Patients with potentially curable, locally advanced esophageal cancer should be cared for in a multidisciplinary setting. (Level of Evidence B)

Advances in surgical techniques, postoperative management, and staging modalities, combined with multidisciplinary team approaches, have resulted in a dramatic improvement in outcome results in the surgical treatment of cancer of the esophagus and gastroesophageal junction during the last 3 decades, with 5-year survival now in the range of 35% and as much as 25% in stage III patients treated in high-volume centers [3]. Most patients however, still die of systemic or locoregional metastasis, or both. This has resulted in an interest in combined modality approaches to address patients with advanced locoregional disease but with no evidence of systemic spread by clinical staging. Potential options are radiotherapy (RT) only, chemotherapy (CT) only, or CT and RT (CRT) before (neoadjuvant) or after (adjuvant) surgical resection.

Restaging

2. **Class I Recommendation:** Restaging studies after neoadjuvant therapy are recommended before resection to rule out interval development of distant metastatic disease. (Level of Evidence B)
3. **Class IIA Recommendation:** Endoscopic ultrasound restaging for residual local (mural) disease is inaccurate and can be omitted. (Level of Evidence B)
4. **Class IIA Recommendation:** A positron emission tomography scan is recommended for restaging after neoadjuvant therapy to detect interval development of distant metastatic disease. (Level of Evidence B)

After completion of any neoadjuvant therapy protocol, restaging results in a patient being categorized as having a complete response (CR), a partial response, progressive disease, or no response. Patients can also simply be assigned a new clinical stage identification based on the restaging results. This postinduction therapy stage is identified by the "y" prefix before the new clinical stage designation; for example, yc Tx Nx Mx. The extent of restaging that is necessary after completion of the neoadjuvant course of therapy is not definitely established. Computed tomography scans assess the response extent with sensitivity for persistent disease of only between 27% and 55% and a specificity of 50% to 91% [4]. The uncertainty in interpretation of computed tomography scans in this setting is the difficulty or even impossibility of differentiating between residual cancer and reactive inflammation [4].

Interpreting endoscopic ultrasound (EUS) findings after neoadjuvant therapy is similarly challenging, and this procedure frequently overstages patients. Inflammatory changes associated with response are indistinguishable from persistent disease; specifically, the alternating sonographic bright and dark layers are obliterated by viable tumor and scar related to a therapeutic response [5]. Yen and colleagues [6] investigated the efficacy of EUS for restaging esophageal cancer after neoadjuvant therapy and found the sensitivity was only 5% and the specificity was 38%. Eloubeidi and colleagues [7] assessed the true negative rate of EUS–fine-needle aspiration in 107 patients and found a specificity of 88% and a negative predictive value of 78%.

Yen and colleagues [6] also showed that positron emission tomography (PET) scans with computed tomography scans were superior, with a sensitivity of 32% and specificity of 90%. In contrast, Erasmus and colleagues [8] found that CRT-induced ulceration caused false-positive results with PET; in their report of 42 patients, the sensitivity of PET was 43% and the specificity was 50%. PET scans can spare some patients futile operations by finding new, interval distant metastases [8]. They may also help identify patients who have the best chance of a good outcome from completion of the full multimodality program.

Several studies found that patients whose PET scan standardized uptake value decreased by more than 50% after CRT had a longer overall survival and lower risk of death after the operation [9]. This observation was confirmed in the reports from the Metabolic Response Evaluation for Individualisation of Neoadjuvant Chemotherapy in Esophageal and Esophagogastric Adenocarcinoma (MUNICON) trials [10]. In MUNICON II, 33 "metabolic responders" (who had a decrease in their standardized uptake value of more than 35% after induction CT) were compared with 23 nonresponders. The 1-year progression-free rate was 74% in responders and

57% in nonresponders ($p = 0.035$) [11]. However, a Swiss multicenter study by Klaeser and colleagues [12] found a limited predictive value of PET scans for response assessment in the preoperative treatment of esophageal cancer. After completion of CT, the PET sensitivity was 68% and specificity was 52%, with a positive predictive value of 58% and a negative predictive value of 63% [12].

Neoadjuvant RT

5. **Class III Recommendation:** Radiotherapy as monotherapy before resection is not recommended. (Level of Evidence A)

None of the five randomized trials comparing preoperative RT plus operation with operation alone or meta-analyses have found an improvement in resectability or outcome for esophageal cancer [13–15]. As a consequence, preoperative RT alone is not considered to be efficacious as the neoadjuvant component of a multimodality program for esophageal cancer.

Neoadjuvant CT

6. **Class IIA Recommendation:** Neoadjuvant platinum-based doublet chemotherapy alone is beneficial before resection for patients with locally advanced esophageal adenocarcinoma. (Level of Evidence A)

Ten randomized trials comparing CT plus operation vs a primary operation have been reported. The two largest of these reported conflicting results. The United States trial did not show any difference in the variables that were analyzed [16]. In contrast, the United Kingdom–based trial did find a small but statistically significant 5-year survival benefit favoring the combined arm, and these findings were confirmed in a recent update [16, 17].

Several meta-analyses were published between 1992 and 2011. These included randomized clinical trials (RCTs) of neoadjuvant CT vs operation alone. In the meta-analysis by Sjoquist and colleagues [18], the absolute survival benefit at 2 years was 5.1%. The hazard ratio (HR) for squamous-cell carcinoma only was 0.92 (95% confidence interval [CI], 0.81 to 1.04; $p = 0.18$) and for adenocarcinomas only was 0.83 (95% confidence interval, 0.71 to 0.95; $p = 0.01$).

Kranzfelder and colleagues [19] published a meta-analysis with additional outcomes. The likelihood of R0 resection was significantly higher after neoadjuvant CT (HR, 1.16; 95% CI, 1.05 to 1.30; $p = 0.006$). Morbidity (HR, 1.03; 95% CI, 0.90 to 1.19; $p = 0.638$) and 30-day mortality (HR, 1.04; 95% CI, 0.76 to 1.43; $p = 0.810$) rates after neoadjuvant CT and operation did not differ from those after operation alone. Finally, a French multicenter trial showed that for resectable adenocarcinoma of the esophagus or gastroesophageal junction, perioperative CT with fluorouracil plus cisplatin compared with operation alone increased the curative resection rate, 5-year disease-free survival (34% vs 19%, $p = .003$), and overall survival (38% vs. 24%, $p = .02$) [20].

Altogether, data from the literature are somewhat supportive of CT alone for neoadjuvant therapy; however, the benefit of CT alone is less than the results obtained from the CRT combination.

Neoadjuvant CRT

7. **Class IIA Recommendation:** Neoadjuvant chemoradiotherapy should be used for locally advanced squamous cell cancer and either neoadjuvant chemotherapy or chemoradiotherapy for locally advanced adenocarcinoma; multimodality therapy has advantages over operation alone. (Level of Evidence A)

Three of 11 published RCTs have been able to show a significant difference in overall survival in favor of the multimodality arm. The trial in Ireland by Walsh and colleagues [21] was criticized because of the very poor outcome in the operation-alone arm, with 6% survival after 3 years, most likely due to selection bias. The Cancer and Leukemia Group B trial by Tepper and colleagues [22] was criticized because of the small numbers of patients. The very recent Dutch Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study (CROSS) trial [23] enrolled 368 patients who presented with mostly adenocarcinomas of the distal esophagus and gastroesophageal junction (75%). Survival in the induction group was significantly better, with median survival of 49.4 months vs 24 months in the operation-alone group ($p = 0.003$). A subgroup analysis showed induction therapy affected survival more in patients with squamous cell carcinoma than in those with adenocarcinomas.

Several meta-analyses were published between 1992 and 2011. Of the earlier meta-analyses, the study by Fiorica and colleagues [24] favors operation alone because of the effect on postoperative mortality in the multimodality arm. The meta-analysis by Jin and colleagues [25] found that patients with squamous cell carcinoma did not receive any survival benefit, which was in sharp contrast with the Burmeister and colleagues trial [26] showing the opposite.

The most recent studies, from Sjoquist and colleagues [18] and Kranzfelder and colleagues [19], included 10 RCTs. In the meta-analysis by Sjoquist and colleagues [18], the absolute survival benefit at 2 years was 8.7% with an HR for squamous cell carcinoma only of 0.80 (95% CI, 0.68 to 0.93; $p = 0.004$) and for adenocarcinoma only of 0.75 (95% CI, 0.59 to 0.95; $p = 0.02$).

The meta-analysis by Kranzfelder and colleagues [19] compared only patients with squamous cell carcinoma. They reported a significantly higher likelihood of R0 resection after neoadjuvant CRT (HR, 1.15; 95% CI, 1.00 to 1.32; $p = 0.043$). Morbidity rates were not increased after neoadjuvant CRT (HR, 0.94; 95% CI, 0.82 to 1.07; $p = 0.363$), and 30-day mortality was nonsignificantly higher with combined treatment (HR, 1.46; 95% CI, 0.91 to 2.33). For overall survival, the estimates of effect significantly favored neoadjuvant CRT (HR, 0.81; 95% CI, 0.70 to 0.95; $p = 0.008$). When preoperative CT is compared with CRT for adenocarcinoma, there seems to be a beneficial

effect of CRT with more pN0 and pCR results but no difference in survival, as suggested by Stahl and colleagues [23].

A weakness of these RCTs and meta-analyses is that their surgical results are suboptimal, with 3-year overall survival figures varying between 6% and 36%. Also of note is that different aspects of the trials vary considerably, such as location of the tumor, histologic types, clinical stage, the CT drugs, and RT schedules, all of which may cause differences in outcomes. Most of trials also have insufficient power to indicate significant differences. As a consequence, the results may suffer from varying definitions, methodology, and treatment protocols.

Further support of CRT as neoadjuvant therapy may be found in several single-institution reports [1, 27, 28]. These experiences show that 25% to 32% of patients have a pCR, with no cancer detected in the surgical specimen. As always, long-term survival varies by the cancer stage, but overall survival in these series is reported between 25% and 34% and up to 55% in pCR patients. An estimated 50% of patients have a partial or no response to this induction treatment. Although the major responders benefit from induction therapy, the nonresponders do less well. Ancona and colleagues [29] showed that nonresponders had a relatively poor 5-year survival of 12% after surgical resection.

The recently reported CROSS trial showed definitive improvement in locoregional control as well as in survival in patients receiving CRT, followed by surgical resection, vs surgical resection alone [30]. This Dutch group enrolled 363 patients with T2 3N0 1M0 tumors who were randomized to CRT, followed by surgical resection, or to resection alone. The complete resection (R0) rate was 92.3% in the CRT arm vs 64.9% in the resection-alone group. Perioperative mortality rates were similar, 3.7% in the resection-alone group and 3.8% in the CRT arm. Median survival was 49 months in the CRT arm but only 26 months in the resection-alone arm. Overall survival was significantly better in the CRT group (HR, 0.67; 95% CI, 0.50 to 0.92; $p = 0.011$).

In summary, the selection of candidates for primary surgical resection vs combined modality treatment should be individualized based on the pros and cons at the institution where the patient will receive treatment. Physicians involved in the selection process should take into account today's standard of a primary operation; that is, an overall 5-year survival of more than 35%, and 25% for locally advanced stage III cancer in high-volume centers [3].

Value of Surgical Resection After Neoadjuvant Therapy

8. **Class I Recommendation:** After neoadjuvant therapy, patients without metastatic disease, in whom surgical resection can be safely performed, should receive esophageal resection. (Level of Evidence A)

Surgical resection after neoadjuvant therapy in patients with a CR or PR should take place as long as all known disease, primary tumor, and regional lymph nodes are completely resectable (ie, a R0 resection is expected). Of course, this excludes patients with new metastases or local disease progression that cannot be encompassed surgically and assumes that the patient is judged to have sufficient physiologic reserve to undergo a major surgical procedure. Reported series of patients treated with this multimodality approach demonstrate improved long-term survival in patients selected for resection based on these criteria compared with previous outcomes in similarly staged patients treated with resection alone [14, 27]. When complete resection is not reasonably possible or the patient is not sufficiently fit, the care of the patient should turn to palliative measures, such as endoluminal stent placement, to facilitate swallowing.

The need for surgical resection in clinical CR patients has been challenged by some recent publications that report a 5-year survival of 32% with definitive CRT [27, 28]. However, these reports are primarily in patients with squamous cell carcinoma, and most American and Western European patients have adenocarcinoma [28]. Restaging after concomitant CRT, even with an endoscopic biopsy specimen, is known to be insensitive. The final pathologic specimen in most patients who appear to be clinical CRs will ultimately reveal carcinoma in the esophageal wall, regional lymph nodes, or both [31, 32]. Without resection, this remaining disease could eventually progress, and if resection is delayed until time of recurrence, the resection may be compromised and perhaps impossible because of tumor advancement.

Esophagectomy is currently being performed with diminished mortality and morbidity and the expectation of a good to excellent quality of life. The best long-term survivals reported are in patients who exhibit not only a clinical CR but also have a complete pathologic response with no residual cancer found after thorough histologic review of resected tissue [30–32]. A recent report showed that after resection, identifying a solitary micrometastasis, even as little disease as one residual cancer cell in one lymph node, significantly reduces survival, emphasizing the oncologic importance of an appropriately performed esophagectomy in all patients who are judged able to tolerate the operative procedure [3].

These observations do not mean that every patient must have an operation. The patient's ability to withstand the operative risks and the postoperative recovery sufficiently to enjoy a reasonable quality of life must be considered by the surgeon and the patient. Because there is currently no way to prove with complete accuracy that all microscopic cancer has been eradicated, resection should be recommended in all patients who are good risk. The overall message is that surgical resection combined with successful neoadjuvant therapy is the most effective oncologic strategy.

Adjuvant Therapy

9. **Class IIA Recommendation:** Patients with adenocarcinoma who have not received neoadjuvant therapy should be considered for adjuvant chemoradiotherapy

if the pathologic specimen reveals regional lymph node disease. (Level of Evidence B)

Conflicting results obtained from different trials of induction therapy and the difficulties in distinguishing the patients who will benefit (responders) from those who will not (nonresponders) have suggested assessing the value of adjuvant therapy.

Postoperative RT, in contrast to preoperative RT, may be useful. A recent population-based review by Schreiber and colleagues [33] suggested an overall survival benefit for adenocarcinoma and squamous cell carcinoma when administering RT after esophagectomy for stage III (pT3 N1 M0 and pT4 N0-1 M0) cancer; however, these results were derived from the Surveillance, Epidemiology and End Results database, and some patients may also have received CT.

Two RCTs of the use of adjuvant CT did not detect any benefit [34, 35]. However Liu and colleagues [36] found a significant survival advantage compared with adjuvant RT, with 3-year survival of 70% vs 30%. Bédard and colleagues [37] found a significant benefit for adenocarcinoma in favor of adjuvant CRT in overall survival and locoregional recurrence. The MacDonald and colleagues' [38] trial dealing with adenocarcinoma of the esophagus and gastroesophageal junction indicated a survival benefit in lymph node-positive patients in the adjuvant CRT arm for disease-free survival and overall survival. However, a flaw of these last two studies was the absence of lymphadenectomy as part of the surgical treatment.

Patients with adenocarcinoma who do not receive neoadjuvant induction therapy and are found to have regional lymph node involvement on final pathologic staging have an undefined benefit from adjuvant therapy. Similarly, whether repeat resection or adjuvant therapy provides better outcomes in the case of a R1 resection is not known.

In conclusion, despite the widespread enthusiasm for multimodality therapy for esophageal cancer, currently available data are not truly definitive. However, given the widespread use in clinical practice of multimodality approaches, large-scale prospective RCTs would be useful in clarifying and identifying the ideal treatment algorithm. Such trials should standardize all treatment arms, including the surgical procedure. This will allow comparable results to be obtained and valid comparisons to be made.

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