possible that patients who had a long delay from the time of neoadjuvant therapy to surgery were different than those who had a shorter delay. None of the studies statistically matched the groups, although multivariable analysis was consistently used to address some of the potential confounding variables. Overall, the studies rate moderately well to high quality on the Newcastle-Ottawa scale, generally getting scores of 6 to 8.

The available meta-analyses used different inclusion criteria and frequently reported contrasting results. Although large registry data, such as that from the NCDB, has its limitations, there does not seem to be a strong rationale to specifically exclude it from pooled analysis of retrospective studies. The meta-analyses by Qin and colleagues[60] (when there is little to no heterogeneity) and Shang and colleagues[58] (for survival) appear to have the most reliable data, although the questionable use of fixed-effect models by Qin and colleagues[60] makes that study's conclusion on pCR difficult to parse.

Patients who had a longer delay to surgery may have had significant complications during nCRT, failure to thrive, or other comorbidities that delayed their ability to undergo surgery. These factors may have impacted perioperative morbidity and mortality and long-term survival. Those who had perioperative morbidity may have had lower long-term survival due to the impacts of the in-hospital complications and not from the impact of delay to surgery.

There were very few complications found to be associated with timing from nCRT to surgery. This may have been in part because most studies do not report an effect in rates of pulmonary complications, reintubation, reoperation, or recurrent laryngeal nerve paralysis. This may be a result of lack of statistical power, because trends are generally suggestive that a longer duration could lead to more complications in larger studies.

Transhiatal Esophagectomy vs Transthoracic Esophagectomy

- **In the setting of nCRT, both transhiatal esophagectomy (THE) and transthoracic esophagectomy (TTE) are reasonable approaches. (Class IIA, Level B-NR)**

Numerous techniques have been described for resection of the esophagus and regional lymph nodes. TTE offers the advantage of a more extensive mediastinal lymphadenectomy compared with approaches where a chest incision is avoided, such as THE. TTE does, however, have an increased risk of pain, longer operative times, the need for single-lung ventilation, and the potential for more perioperative respiratory complications compared with THE. A randomized trial comparing THE vs TTE, without the use of neoadjuvant therapy, did not support one approach over the other.[67] THE was associated with lower morbidity than TTE with extended en bloc lymphadenectomy; however, a trend toward improved long-term survival at 5 years was noted with TTE. In the setting of nCRT, the critical question is whether the more extensive lymphadenectomy afforded by TTE is beneficial, because the tumor spread to regional lymph nodes may be eradicated by preoperative treatment.

Lymph Node Yield vs Perioperative Morbidity and Mortality

The most extensive data regarding surgical approach in the setting of nCRT come from a retrospective cohort study of a Dutch national registry that included >4000 patients, most with esophageal AC (>85%).[68] After propensity score matching, 1532 patients were included in the analysis. Although TTE was associated with a more thorough oncologic resection, with a higher number of lymph nodes harvested (transthoracic median 19 vs transhiatal median 14, $P < .001$), no differences were noted between approaches in the number of positive lymph nodes. The use of a thoracotomy, however, came at the cost of an increased rate of respiratory complications (35.5% vs 26.1%, $P < .001$), longer lengths of stay in the hospital (median 14 days vs 11 days, $P < .001$) and intensive care unit (median 3 days vs 1 day, $P < .001$), more reoperations (14.8% vs 9.3%, $P = .002$), and higher mortality in-hospital or within 30 days of surgery (4.0% vs 1.7%, $P = .009$) compared with THE. Two smaller studies did not find differences in complication rates between the surgical approaches, although they were underpowered.[69,70]

Overall Survival

Six studies have compared TTE and THE after nCRT with regards to OS.[70-75] Of these, only 1 small study of 58 patients found a survival difference between approaches, favoring TTE.[71] This survival advantage, however, was likely explained by a selection bias, with older patients having significant pulmonary or cardiac comorbidities undergoing THE. In a Dutch study of 2698 patients, improved OS was associated with ≥15 lymph nodes resected (HR, 0.77; 95% CI, 0.68-0.86), but not with use of THE vs TTE (HR, 0.89; 95% CI, 0.79-1.1) on multivariate analysis.[75]

Limitations

A significant limitation in the reported studies is that they did not assess the impact of performing a TTE with a cervical anastomosis, because patients with either a cervical or thoracic anastomosis were grouped together within the TTE category. It is possible that patients with TTE