rate for trimodality therapy vs CRT alone overall and in SCC patients only. This benefit was not maintained at 5 years according to Wang and colleagues,[53] although this outcome had significant heterogeneity.[51,52]

The more recent matched and registry studies also find less recurrence with trimodality therapy. However, patients with more advanced disease (stage III) continued to have an increased risk of recurrence regardless of the addition of surgery in a recent retrospective study published by Jung and colleagues.[54]

Complications

Very little data exist on complications related to surgery. In the trials by Stahl and Bedenne and their colleagues,[48,49] postoperative complications contributed to higher short-term mortality in patients treated with surgery, although Vellayappan and colleagues[51] rated this as a low-quality of evidence. The meta-analysis by Voeten and colleagues[52] found an 80% reduction in 90-day mortality in the no-surgery arm.

Quality of Life

Only the Bedenne and colleagues[49] study reported quality of life data. The quality of life scores in the dCRT patients were superior to patients in the trimodality therapy arm at 6 months but were equivalent between the treatment arms at later time points.

For patients considered to be at low operative risk, the benefits of trimodality therapy likely outweigh the risks, even in the setting of cCR. Finally, for patients with SCC at higher operative risk where cCR is achieved after CRT, deferral of surgery is reasonable. Close surveillance is recommended to potentially provide the opportunity for salvage surgery if local recurrence is detected in the absence of metastatic disease. Close surveillance in the Surgery as Needed for Oesophageal Cancer (SANO) trial consisted of endoscopic evaluation every 3 months for the first year, every 4 months in the second year, every 6 months in the third year, and annually until the fifth year.[55]

Limitations

The recommendations on the value of surgery after chemotherapy and radiotherapy are based on the ability to accurately identify patients with a pCR. The current recommendations by the National Comprehensive Cancer Network are fluorodeoxyglucose-PET/computed tomography, chest/abdominal computed tomographic scan with contrast, and endoscopy with biopsy. These modalities all have limitations, making close follow-up and a critical discussion with the patient paramount.

The consequences of inaccurately defining a pCR is that if disease is found at a time further out from completion of CT and radiotherapy, then the patient will require a delayed or salvage esophagectomy, if feasible. Salvage esophagectomy historically has been associated with an increased risk of morbidity and mortality. Data from recent literature are mixed, with some suggesting similar outcomes and others still reporting higher rates of morbidity and mortality.[56,57] These factors make a thoughtful discussion with the patient important before following nonoperative recommendations for patients with a cCR. Further data on the ability to safely avoid surgery will be available once the SANO trial concludes.[55]

Timing of Esophagectomy After Neoadjuvant CRT

- **In patients who have recovered sufficiently and are ready for surgery, timing of surgery before 7 to 8 weeks after nCRT may result in a slight OS advantage, with a lower risk of perioperative morbidity and mortality and is reasonable when possible. (Class IIA, Level B-NR)**
- **For patients undergoing surgery after nCRT, surgery should not be scheduled before 4 weeks after completion of nCRT (Class III: Harm, Level C-LD).**

The ideal timing of surgery after completion of nCRT is not well settled, and studies have used varying definitions of short vs long duration as well as analyzing multiple time ranges in the same data set. As such, several meta-analyses addressed this by defining any surgery at <7 to 8 weeks as a short interval.[58-60] The lowest cutoff for any single individual study was 30 days, and few patients overall were operated on before then.

The 7- to 8-week cutoff was used to assess an association with increased perioperative mortality and pneumonia. Dichotomizing into generic "shorter" and "longer" groups revealed a potential increased risk of anastomotic leak with a longer duration to surgery.

Two of the available meta-analyses showed an increased rate of R0 resection with a shorter duration to operation,[59,61] and 1 study reported that pCR is superior with a longer duration,[60] but overall, the signal for these outcomes was neither strong nor consistent, and it is not clear that an improved pCR would translate to improved outcomes for the patient.

These results provide no strong evidence of worse OS with a longer delay to surgery. Inclusion of the NCDB data suggests modest but statistically significant benefits might be possible at 2 and 5 years with a longer duration to surgery, and this advantage may be more robust in patients with AC. However, not all analyses confirm this.