Editorial

Deciding on the neoadjuvant approach for esophageal adenocarcinomas

Cai Xu[1], Steven Hsesheng Lin[2]

[1]Department of Radiation Oncology, Cancer Hospital, Tianjin Medical University, Tianjin 300070, China; [2]Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas 77030, USA

Correspondence to: Steven Hsesheng Lin, MD, PhD. Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas 77030, USA. Email: SHLin@mdanderson.org.

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Surgery alone has long been the single most effective treatment modality for the management of esophageal cancer. However, despite modern advances in surgical techniques, the 5-year survival with surgery alone is only in the range of 16–33% (1,2). The addition of neoadjuvant therapy, whether it is neoadjuvant chemoradiotherapy (NCRT) or neoadjuvant chemotherapy (NCT), can significantly improve clinical outcomes compared with surgery alone. In studies using NCRT, a higher complete resection rate can be achieved compared to surgery (80–92% *vs*. 59–69%) (2,3), as well as the pathologic complete response (pCR) rate, ranging from 16% to 33% (1-4), which can be an independent favorable prognostic factor (5,6). The benefit of NCRT seems larger for squamous cell carcinomas (SCCA) compared to adenocarcinomas (ADC), with higher pCR rates (49% *vs*. 23%) and relatively better overall survival as seen in the CROSS trial (2,7). As a result of these studies, NCRT is the accepted standard of care for the treatment of localized esophageal cancer in western countries, especially in USA. Because of the predilection of SCCA in the Asian countries, this is also being tested prospectively in Japan and China.

The second approach has used NCT, which is mostly adopted in the UK and parts of Europe, particularly in patients with lower esophageal and esophagogastric junction (EGJ) cancers (8-10). The survival benefit of NCT in patients with operable esophageal cancer has been observed in several randomized trials (9-11). The long-term results of a randomized trial comparing NCT and surgery showed an improved 5-year OS for NCT (22.6% *vs*. 17.6%, P=0.03) (9). Another randomized trial demonstrated a significant advantage of NCT of 14% in 5-year OS (P=0.02), and a 5-year DFS benefit of 15% (P=0.003) (10). A meta-analysis on NCT trials in esophageal cancers, including nine randomized comparisons of NCT *vs*. surgery alone (n=1,981), convincingly demonstrated a survival benefit of NCT over surgery alone in patients with esophageal ADC, with a hazard ratio (HR) of 0.83 [95% confidence interval (CI), 0.71–0.95; P=0.01] (6). Although limited compared to NCRT, NCT could also downstage the tumor and increase the complete resection rate, which may result in improved survival and loco-regional control (9-12). Patients downstaged by chemotherapy, compared with patients with no response, experienced lower rates of local recurrence (6% *vs*. 13%, respectively; P=0.030) and systemic recurrence (19% *vs*. 29%, respectively; P=0.027) (12). Perioperative chemotherapy also significantly improved the curative resection rate (84% *vs*. 73%; P=0.04) (10). The postoperative complications and mortality were not increased after NCT than surgery alone (10,13).

So, which of the two, NCRT or NCT, is the preferred approach? The paper by Markar *et al*. was an attempt to examine this from a large retrospective, multi-institutional study by which outcomes of NCRT and NCT were

compared for the treatment of esophageal and EGJ ADC (Siewert type I and II) (14). This study included 608 patients with stage II/III esophageal or EGJ ADC (301 NCRT *vs.* 307 NCT) from prospectively collected databases at 10 institutions across Europe and included data from the CROSS trial. To adjust for potential confounders, propensity score matching (PSM) was used. As expected, NCRS resulted in significantly better pathological response with far better pCR rates (26.7% *vs.* 5%; P<0.001), more ypN0 (63.3% *vs.* 32.1%; P<0.001), and reduced R1/2 resection margins (7.7% *vs.* 21.8%; P<0.001). NCRT however yielded less lymph nodes in the pathologic specimen, with the median harvest of 14 (range, 0–52) for NCRT *vs.* 27 (range, 0–129) (P<0.001) nodes for NCT. Despite the far greater pCR rate and completeness of resection, NCRT did not appear to confer a significant benefit in overall survival or recurrence free survival over NCT. There are several potential reasons. Firstly, part of the reason could be due to a non-significant increase in postoperative mortality in the NCRT group compared to NCT, with the 30-day and 90-day mortality of 4.1% *vs.* 1.4% and 5.9% *vs.* 2.3%, respectively. There was also a non-significantly higher pulmonary complications and reoperation rate, and a significantly higher anastomotic leak rate in the NCRT group (23.1% *vs.* 6.8%; P<0.001). This could have been attributed by the differences in the surgical techniques employed for these two approaches, and since this was not adjusted for by the PSM, the difference may have confounded the results. Fourthly, the retrospective nature of the study, despite the effort of using PSM to reduce the potential heterogeneity of techniques and patient characteristics across the various institutions, reduced the reliability of the results. However, the authors are to be commended for publishing a high quality analysis that represented a largest series of patients that directly compared NCT *vs.* NCRT in esophageal ADC. Their data does seem to be supported by an updated meta-analysis that included two small underpowered randomized studies that directly compared NCRT *vs.* NCT and pooled data that indirectly compared the relative benefit of NCRT and NCT (N=2,220). That study also failed to show a significant advantage of NCRT over NCT in esophageal ADC (6). However, the heterogeneity in tumor staging, treatment techniques and dosing, were major confounders that couldn't be accounted for in the meta-analysis. So while there is the theoretical benefit of NCRT as compared to NCT, the addition of concurrent radiation to NCT does not seem to improve treatment outcomes, with the potential of added toxicities. However, the lack of benefit of NCRT in the Markar *et al.* study shouldn't be extrapolated to SCCA, as both the CROSS trial and meta-analysis of clinical trials have shown NCRT to offer a greater benefit compared to NCT.

One of the two randomized trials that directly compared NCRT *vs.* NCT and included in the meta-analysis was a German randomized trial called the Preoperative Chemotherapy or Radio-chemotherapy in Esophagogastric Adenocarcinoma Trial (POET) (15). It was an ambitious attempt to directly compare NCRT and NCT in mostly locally advanced ADC of the EGJ (T3–4Nx). Patients were randomized to NCRT to 30 Gy in 15 fractions or NCT. Unfortunately, due to poor accrual, the study closed early after enrolling 126 patients out of the anticipated 354 patients. Despite the small numbers in the randomized cohorts, NCRT non-significantly improved 3-year survival rate from 27.7% to 47.4% (log-rank P=0.07; HR, 0.67; 95% CI, 0.41–1.07). NCRT did significantly increased pCR rate and the rate of tumor-free lymph nodes (15.6% *vs.* 2.0% and 64.4% *vs.* 37.7%, respectively). Postoperative mortality was numerically higher in the NCRT group (10.2% *vs.* 3.8%, P=0.26), which may have compromised the survival benefit of NCRT, but conclusions cannot be drawn due to the limited number of events seen (in-hospital mortality of 5 *vs.* 2 for NCRT *vs.* NCT, respectively). In contrast, a second smaller and underpowered randomized trial that targeted mostly earlier stage disease (>80% stage II) also demonstrated significantly improved pathologic response and completeness of resection but no differences were seen in survival outcomes comparing NCRT *vs.* NCT (5-year OS 45% *vs.* 36%, P=0.60, respectively) (16). Unfortunately, at this point there is still a lack of high quality evidence to demonstrate the benefits of NCRT over NCT for esophageal ADC. Large randomized trials are still needed to resolve the question of whether NCRT is beneficial, a benefit likely best reserved for locally advanced esophageal/EGJ ADC.

We believe NCRT's undisputed ability to improve the completeness of resection and to enhance pCR, especially with more conventional radiation dosing between 41.4 to 50 Gy, are specific advantages of NCRT over NCT, particularly in patients who ultimately are not considered great surgical candidates. Observation without surgery after completing CRT in clinical responders is a feasible approach, which can improve the quality of life for patients by sparing responders the potential morbidity and mortality of surgery. A selective approach using salvage surgery can

be reserved for patients who have local-only recurrence without compromising disease control compared to upfront elective surgery (17). We also believe the benefits of NCRT should translate to survival benefit especially in the modern era where advances in surgical techniques and radiation delivery approaches could further reduce postoperative complications and mortality (18,19). This unresolved question continues to be investigated as we anticipate the results of the ongoing NeoAEGIS trial, which is a randomized comparison in 366 patients of the MAGIC regimen (NCT) and the CROSS regimen (NCRT) in cT2–3N0–1 adenocarcinoma of the esophagus and EGJ (ClinicalTrials.gov NCT01726452).

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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