To radiate or not to radiate: that is the question?—a commentary on "*Neoadjuvant chemoradiotherapy versus neoadjuvant chemotherapy followed by minimally invasive esophagectomy for locally advanced esophageal squamous cell carcinoma: a prospective multicenter randomized clinical trial*"

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Multi-modal therapy has become the standard of care for locally advanced esophageal carcinoma. However, the optimal regimen remains elusive. Neoadjuvant chemoradiation (nCRT) has become the standard of care after publication of the CROSS trial (1). The biologic principle behind nCRT lies in the dual effect of both locoregional disease control (radiation) and ablation of micrometastatic disease (chemotherapy), putatively enhancing the efficacy of surgical resection in removing all possible tumor burden (2). At the same time, both therapies may also work synergistically at the tumor site itself with chemotherapy providing both direct cytotoxicity and promoting radiosensitization of tumor cells (2). In esophageal cancer, tumors that are T2 and beyond are at high risk for nodal metastasis or micrometastatic disease, as these lesions have either invaded through submucosa (which contains a rich network of lymphatics) or involve the muscularis propria to regional lymph nodes or surrounding structures (3). For these patients, while nCRT provides excellent local control, it is associated with significant perioperative concerns including the inherent risks of operating in an irradiated field, while balancing the systemic efficacy of the chemotherapy component with increased toxicity. In esophageal squamous cell carcinoma (ESCC), several studies have revealed equivalent survival in patients treated with chemoradiation and those with chemoradiation and surgery (4,5). However, a recent meta-analysis recommends surgery after nCRT given that it may delay locoregional relapse, provided that morbidity and mortality are low (6). Despite these conflicting findings, the National Comprehensive Cancer Network (NCCN) guidelines suggest definitive or neoadjuvant chemoradiation for locally advanced ESCC [T2N0 (+LVI, ≥3 cm, poorly differentiated), T1b-T2N+, or T3-T4a] (7). Therefore, this randomized controlled trial published by Tang *et al.* is particularly timely, as it aims to address this knowledge gap in the optimal strategy for neoadjuvant therapy for ESCC.

Tang *et al.* present a prospective multicenter randomized controlled investigating neoadjuvant chemoradiation (nCRT) *vs.* chemotherapy alone (nCT) followed by minimally invasive esophagectomy (MIE) for locally advanced ESCC (8). In this study, 264 adult patients with

cT3-4N0-1M0 (locally advanced) ESCC of adequate performance status were randomized 1:1 to receive either nCRT (cisplatin + paclitaxel + 40 Gy radiation) or nCT (cisplatin + paclitaxel alone) followed by minimally invasive esophagectomy with either a 2-field or 3-field lymphadenectomy. The authors demonstrated no significant differences in R0 resection rates, 3-year overall survival (OS) (64.1% *vs.* 54.9%), progression-free survival (PFS) (46.5 *vs.* 34.1 months), and resection-free survival after R0 resection (48.2 *vs.* 50.2 months) between the two arms. Median OS was not reached in the nCRT group and was 43.2 months in the nCT group. However, patients who received nCRT achieved significantly greater rates of pathologic complete response (pCR) (27.7% *vs.* 2.9%, P<0.001), superior primary tumor regression grade (0% *vs.* 3.8% residual tumor, P<0.001), fewer metastatic lymph nodes (ypN0 rate 66.1% *vs.* 46.2%, P=0.03), and reduced lymphovascular and perineural invasion (10.7% *vs.* 26%, P=0.004). Furthermore, final treated ypTNM stage was significantly lower in the nCRT arm (51.8% *vs.* 20.2%, P<0.001). Overall, the authors conclude that there were no differences in 3-year survival or morbidity between both arms for bulky locally advanced ESCC and suggest that continued investigation into the necessity of neoadjuvant radiation for locally advanced ESCC is warranted.

This is a well-designed study with several strengths. First, it is reasonably high-powered with appropriate randomization of patients with an intention-to-treat approach into both the nCRT and nCT arms. The authors standardized the operative approach (MIE) for both arms, which strengthens their comparisons of postoperative complications. In their investigation of nCRT *vs.* nCT, the authors directly address the key knowledge gap in the optimal strategy for the management of locally advanced ESCC. However, there are several limitations to this study. The chemotherapy regimen used in this trial was based on cisplatin, while most chemotherapy alone regimens in the Western hemisphere use fluorouracil (5-FU), leucovorin, oxaliplatin and docetaxel (FLOT) which has an acceptable toxicity profile (9). To this end, retrospective investigation has suggested that cisplatin-based regimen may be associated with higher incidence of grade 3 or higher febrile neutropenia in locally advanced ESCC (10). The major contribution of this study's findings is that it raises fundamental, yet unanswered questions about the utility of pCR for prognostication and the utility of dual-local therapy (surgery and radiation) for the management of ESCC.

Instinctively, a pCR would portend a better prognosis, and therefore, if nCRT is associated with more pCR, then it should be associated with a better OS. The NEOCRTEC5010 trial, published by Yang *et al.*, demonstrated that nCRT (vinorelbine + cisplatin + 40 Gy) followed by MIE or open esophagectomy for locally advanced ESCC resulted improved overall and 5-year survival compared to surgery alone (11). Subgroup analyses of patients in NEOCRTEC5010 who achieved pCR had longer OS (12). A retrospective study from MD Anderson Cancer Center demonstrated a pCR of 32% after nCRT + surgery in ESCC; for both adenocarcinoma and ESCC, pCR was significantly associated with improved OS and recurrence-free survival (RFS) (13). Additionally, a recent singe-center study which consisted primarily of ESCC patients (75%) demonstrated that obtaining pCR was associated with significantly superior 5-year OS and disease-free survival compared to non-PCR (14). Furthermore, Miyata *et al.* reported that post nCT nodal status predicts outcomes in ESCC (15). These results are concordant with the above hypothesis but do not agree with the results of Tang *et al.*'s findings.

However, the prognostic impact of ypTNM staging on postoperative outcomes is mixed. Indeed, a recent investigation by Han *et al.* suggested that while higher ypT stage is associated with worse OS, differences in ypN stage or overall Stage II and IIIA were not associated with survival (16).

As noted in the current report, the NeoRes trial, which compared nCT to nCRT in both adenocarcinoma and squamous cell carcinoma, reported no difference in 3-year OS (48% *vs.* 43%) respectively which is concordant with the results of the current study (17). Similar to most Western trials, such as CROSS, the NeoRes trial had a predominance of adenocarcinoma (23% ESCC in CROSS and 27% ESCC in NeoRes) (1,17).

How do we interpret these two disparate results? We can rely on the standard power argument; the 3-year OS in the two groups differed by over 9% (64.1% *vs.* 54.9%). Perhaps if the study population was larger, this difference would have been statistically significant. The cancer-specific survival, presented in Tang *et al.*' supplementary figure, also showed a trend towards improved outcomes with nCRT [HR 0.71 (95% CI: 0.47–1.07, P=0.099)]. An alternative answer may lie in the treatment effect of radiation. Radiation primarily exerts local disease control, as does surgery. Current minimally invasive techniques including robotic approaches, provide a more detailed view of the mediastinum and the

tumor bed, which facilitates more extensive resection. This may potentially obviate the need for secondary local therapy with radiation. This theory has been raised by Tang *et al.* and previously in a discussion of the NeoRes trial (18). The excellent rate of R0 resection in this study (over 96%) further support this theory. As an intention-to-treat study, the patients who did not undergo resection may cloud the picture, since there was a trend toward improved survival in the nCRT non-surgical group compared to the nCT non-surgical group. This strategy may have artificially narrowed the differences between the groups. Patients who received nCT but did not undergo resection may be offered additional therapy including radiation.

Overall, the trial suggests major implications for the management of ESCC. While it clearly demonstrates that survival was not significantly different between cohorts, nCRT conferred superior local biologic control compared to nCT including pCR, across several metrics. The authors suggest that this biologic benefit did not correspond to a survival benefit because radiation may not increase local control in the setting of radical resection as evidenced by a lack of difference in the rate of local/regional recurrence and rate of R0 resection (97.3% and 96.2%).

The trend in nCRT is for higher doses of radiation up to 50.4 Gy, while this study utilized 40 Gy. It is not clear that an increased radiation dose would have any effect on local or overall outcomes (7). Despite the lower radiation dose, in those cases in which nCRT or nCT was not followed by surgical resection, nCRT patients had superior survival which is concordant with earlier studies supporting chemoradiation alone in ESCC and may strengthen the theory that effective local control requires only radical surgery or radiation, but not necessarily both. While there were no differences in the rates of postoperative complications between both arms, nCRT patients were significantly more likely to have more severe postoperative complications. Additionally, the authors report a trend toward improved cancer-specific survival in the nCRT group, which is counterbalanced by increased treatment-related deaths.

The importance of pCR and other pathologic downstaging should be considered in the calculus of whether to incorporate neoadjuvant radiation. Can the lack of pCR and other local effects be mitigated by radical resection? This study and NeoRes both suggest that pCR is not as important factor in OS while other reports contradict this argument (12-14,17). As suggested in the manuscript, one strategy would be to use radiation selectively for patients with bulky tumors or lymphadenopathy where the likelihood of R0 resection is less, or in those who may not have the physiologic reserve to undergo surgery after induction therapy. It is important to consider that the overall treatment paradigm itself for perioperative adjuncts for esophageal cancer may be in flux. Indeed, the ongoing ESOPEC trial is investigating CROSS-style nCRT against perioperative chemotherapy (FLOT: 5-FU, leucovorin, oxaliplatin, docetaxel) for CT1N+M0 or CT2-4AN0/1M0 disease (19). This study, which is estimated to be completed in 2024, is eagerly awaited; a recent propensity-matched comparison between these protocols for locally advanced esophageal adenocarcinoma demonstrated non-inferior 3-year survival (63% and 60% for FLOT and CROSS, respectively) despite superior pCR in the CROSS arm (44% *vs.* 27%) (20). In addition to further raising questions about the long-term clinical utility of pCR, these investigations further corroborate Tang *et al.*'s findings that chemotherapy alone with complete surgical resection may be clinically defensible. Furthermore, in Donlon *et al.*'s propensity-matched comparison, rates of postoperative respiratory failure and atrial fibrillation were higher in the nCRT group compared to the perioperative chemotherapy group; this further highlights a putative advantage of a non-radiation strategy in select patients (20).

Overall, we commend the authors for conducting this rigorously performed, randomized prospective trial investigating the differences in postoperative survival outcomes between nCRT and nCT for locally advanced ESCC. While no differences in 3-year survival were observed, the authors identify significantly better biologic disease control with nCRT. An ongoing three-armed trial comparing platinum doublet, platinum triplet, and nCRT in ESCC may provide more insight (21). A search of Clinicaltrials.gov reveals multiple ongoing studies that include immunotherapy with chemotherapy or chemoradiation (22). The results of this trial by Tang *et al.* may foreshadow the next generation of ongoing studies that use different chemotherapy regimens, and especially for those that combine nCT or nCRT with immunotherapy.

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