Editorial

Neoadjuvant versus definitive chemoradiation for locally advanced esophageal squamous cell carcinoma

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A standard treatment option for patients with locally advanced thoracic esophageal squamous cell carcinoma (TESCC) is trimodality therapy, often consisting of neoadjuvant concurrent chemoradiotherapy (CCRT) followed by surgery (1-4). However, transhiatal esophagectomy poses significant risks, including tracheal and pulmonary injury, anastomotic leak, vagus nerve injury, infection, and death. Therefore, two randomized trials have addressed this concern by comparing definitive CCRT (dCCRT) alone versus neoadjuvant CCRT (nCCRT) plus surgery in esophageal cancer (5,6). Both trials found no difference in overall survival (OS), but fewer local recurrences were observed in the nCCRT plus surgery groups. Major limitations of these trials included salvage therapy potentially confounding OS, the usage of induction chemotherapy (which is a widely utilized treatment strategy), patient selection based on induction chemotherapy response (6), and diminished applicability to current practice utilizing more advanced radiation techniques like intensity-modulated radiation therapy (IMRT). Consequently, recent high volume data addressing the therapeutic benefits of dCCRT versus nCCRT followed by surgery are lacking, and such data are needed to help inform the optimal management approach for TESCC.

Recently, Yen *et al*. reported the results of a large (n=3,123) registry-based study that compared dCCRT (n=2,093) versus neoadjuvant radiation therapy (nRT) plus surgery (n=161) versus nCCRT plus surgery (n=869). The study included patients with stage I–III TESCC from the Taiwan Cancer Registry database from January 2006 to December 2014, thus specifically examining patients treated with the most current therapeutic methods, including IMRT). The primary endpoint of the study was mortality rate among treatment groups, with the dCCRT group serving as the control. Both experimental arms of the study (nCCRT plus surgery, and nRT plus surgery) were independent predictors of higher OS (as compared to dCCRT alone) at 1 and 2 years for stage ≥ IIA TESCC. The greatest benefit was observed in the nCCRT plus surgery group. Furthermore, while there was no survival benefit at 2 years observed for stage I TESCC, the benefit of nCCRT plus surgery over dCCRT alone was more pronounced with increasing stage of disease.

The strength of this study is centered on the large volume of patients utilized to address this question. Additionally, because the earliest patients were treated in January 2006, it is more likely that advances in surgical techniques and radiotherapy delivery were utilized in the cohort. With the utilization of newer surgical and radiation techniques, the statistical superiority observed in the surgical groups may be interpreted in a more "clean" manner, with potentially less risk of postoperative or operative morbidity and mortality negating a survival benefit from trimodality therapy (3,7-9).

The implications of the study by Yen *et al*. are vast.

Chiefly, the findings suggest that more advanced disease is best treated with trimodality therapy. There was no statistical difference in outcomes between the three groups for patients with stage I disease (although the number of patients among this group was quite low, n=59). Conversely, patients with higher stages (≥ IIA) had the best outcomes with nCCRT and surgery, with surgery likely driving a survival benefit, as even patients in the nRT plus surgery group had a statistically significant improvement (although to a lesser degree) in OS as compared to dCCRT alone. This result is not surprising, as the benefit to chemoradiation in disease control is inversely related to the bulk of treated disease; however, this result could be due to patient selection, with the healthiest patients receiving the most aggressive treatment. For instance, similar results have been reported with bulky (T4) laryngeal cancer, where the need for salvage surgery was markedly higher in those with T4 disease (10). This finding was further supported by Grover *et al*. in 2015, who showed that among patients with T4a laryngeal cancer, total laryngectomy was superior to larynx-preserving chemoradiation with regards to OS (11). This raises the question of which modality is superior in higher T-stage esophageal cancer. A small meta-analysis by Kranzfelder *et al*. in 2011 found that dCCRT is "not superior" (or inferior) to surgical approaches (12); however, further analysis mitigating confounders and comparing the two modalities directly would need to be completed to address this question.

Dose-escalation with IMRT comparing definitive versus neoadjuvant therapy in this setting would be an interesting area for supplementary analysis. Minsky *et al*. addressed this issue in the pre-IMRT era with RTOG 94-05, and they determined that dose-escalation with dCCRT in non-surgical candidates with esophageal cancer conferred no survival benefit (13). IMRT dose-escalation for esophageal cancer has been shown to increase delivery to the gross tumor volume (GTV), with no increased toxicity to adjacent structures (14). The benefit of dose-escalation with IMRT in esophageal cancer, however, has yet to be confirmed clinically. Furthermore, as is evident in non-small cell lung cancer (15), it is currently unknown if patients with esophageal cancer with more advanced disease burden would benefit more with neoadjuvant dose-escalation so as to increase rates of pathological nodal clearance. Additionally, what role does response-adapted surgery have in treating esophageal cancer? The accruing ESOSTRATE trial is addressing this question by comparing outcomes between systematic surgery versus rescue surgery in esophageal cancer patients with complete nCCRT response (16).

This article generates discussion in several other areas. First, there is limited applicability to adenocarcinoma of the lower esophagus/gastroesophageal junction, which is the most common and the most commonly increasing type of esophageal cancer in the United States (17). Higher incidence rates of adenocarcinoma compared to squamous cell cancer is also observed elsewhere, including parts of Asia and Northern Europe (18,19). Furthermore, research is needed to determine if the same increasing benefit in OS for more advanced stages with nCCRT plus surgery apply to EA. Additionally, the role that the addition of nRT has compared to neoadjuvant chemotherapy alone for EA needs to be defined. Future research on the efficacy of these treatment options for EA is needed, especially because of the increased metastatic potential in EA that occurs with higher stage disease.

The applicability of these results to the elderly and those with comorbid conditions must be questioned. Indeed, in the study by Yen *et al*., age ≥65 years was an independently poor prognostic factor for OS. Thus, some elderly patients or those with comorbid conditions may not survive long enough to benefit from trimodality therapy. This is an area of immense controversy. Lester *et al*. found that despite no difference in disease free survival, OS following trimodality therapy for esophageal cancer was notably less for elderly (≥65 years old) patients. This may, in part, be due to higher rates of cardiopulmonary toxicities and 90-day post-operative mortality, as has been reported in esophageal cancer (20-22) and more recently lung cancer (23). Additional studies addressing OS in the elderly versus young patients with esophageal cancer following esophagectomy have shown mixed results, although they all have been limited by small patient populations (24,25). Furthermore, the impact of histology on treatment response warrants additional study. Elderly patients with high stage disease (especially adenocarcinoma) may not benefit as greatly as younger patients with squamous cell carcinoma, as in this analysis (4). Results show elderly patients benefit from trimodality therapy; however, further subset analyses to identify which types of elderly patients benefit most is warranted (4,26). Adjusting for performance status in the elderly (and all age groups) is likely the best avenue for further analysis, as absolute age should be balanced with the functionality of each patient. The emerging role of advanced radiation technologies could be particularly noteworthy in elderly patients for these and other reasons (27,28).

The major limitation of this study is potential selection bias. As the authors acknowledged, dCCRT was overrepresented in the patients with large and unresectable disease (P<0.0001), worsening outcomes in the control arm of the study and inflating the benefit of the experimental groups. Additionally, any non-prospective study evaluating surgery versus non-surgical paradigms carries a bias insofar as the "medically healthier" patients may be most likely to receive surgery, whereas the nonsurgical arms likely consisted of "sicker" patients. It may be tempting to use this large cohort analysis to argue against dCCRT, however because of the biases stated above this would be a premature discreditation of an effective treatment modality. Subgroup analysis with more balanced cohorts would be the next step to determine modality superiority. This issue will likely remain unresolved unless a prospective randomized controlled trial with modern treatment modalities and techniques is performed. Nevertheless, the Yen *et al.* article adds a sizable voice to this controversial and ever-evolving field and should be considered by clinicians going forward.

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Footnote

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