Editorial

Testing the waters of adjuvant chemotherapy after esophagectomy

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Esophageal cancer continues to be associated with a high mortality rate despite significant advances in the therapeutic treatment over the past 15 years; in patients with resectable tumors, a 15–25% rate of 5-year overall survival (OS) has been reported (1). Multimodality therapy has been demonstrated to be beneficial in improving survival for patients with locally advanced disease. Options include chemotherapy and radiation, either alone or in combination, administered before or after esophagectomy. When considering the utility of adjuvant chemotherapy (aCT) in esophageal cancer, it is important to understand current areas of debate pertaining to multimodality therapy.

Neoadjuvant therapy is currently accepted as the most effective multimodality approach to improving survival in patients with esophageal cancer. In a recent meta-analysis of 33 randomized controlled trials (RCTs), neoadjuvant treatment prior to surgery was superior to surgery alone (HR=0.83, 95% CI: 0.76–0.90) while adjuvant therapy demonstrated no advantage (HR=0.87, 95% CI: 0.67–1.14) (1). The optimal approach to neoadjuvant therapy has yet to be defined. On the basis of the MRC OEO2 trial, it is common practice in the United Kingdom to administer neoadjuvant chemotherapy (nCT) alone prior to surgery (2). In contrast, the RTOG 8911 failed to identify a survival advantage; as such, this has led to a lack of international consensus as to the best neoadjuvant approach (3,4). The addition of radiation prior to surgical resection may be beneficial in achieving an R0 resection and reducing local recurrence; however, there is concern as to the negative sequelae of performing surgery following neoadjuvant chemoradiation (nCRT) as it has been demonstrated to have a higher incidence of postoperative cardiopulmonary complications (5). The CROSS trial, which demonstrated improved survival with concurrent nCRT, established the current standard of practice in the United States (6). There remains no definitive answer as to which approach is better as both therapies have been demonstrated to significantly reduce the risk of death.

In contrast to neoadjuvant therapy, the role of adjuvant therapy has not been as clearly defined. There is a suggestion that aCT or adjuvant radiotherapy (aRT) may have a benefit in select patient groups, such as those with positive nodal disease; however, no survival benefit has been demonstrated with aCT, aRT or adjuvant chemoradiotherapy (aCRT) in RCT (1,7). In a recent large study utilizing a national cancer database, the addition of aRT after definitive esophagectomy was associated with improved OS in patients with node-positive disease and positive margins (8). Administration of adjuvant treatment is limited by concerns regarding patient fitness after esophagectomy, which is a highly morbid procedure often complicated by a prolonged recovery time. The addition of aCT is a high-risk intervention in this often debilitated patient population (1,9,10).

In this setting of uncertain benefits of adjuvant therapy, a subsequent question that arises is whether it may have a role in the management of patients who previously undergo neoadjuvant therapy. Pathological response has been demonstrated to be the most important determinant of disease free and OS after neoadjuvant therapy; however, less than one-third of patients achieve this outcome (6,11). As

such, there may be a beneficial role for adjuvant therapy in patients with residual disease. The impetus for this question is secondary to two RCT, MAGIC and FNCLCC/FFCD, which evaluated the use of perioperative chemotherapy in patients with gastric, esophagogastric junction (EGJ) and esophageal cancers. Both studies demonstrated improved OS; however, this must be interpreted cautiously as less than 50% of patients completed the planned course of postoperative chemotherapy (12,13). As such, the decision to provide aCT is currently controversial.

Limited data exists to support the use of adjuvant treatment in patients who have previously had neoadjuvant treatment. Currently available studies include patients with both gastric and esophageal cancer and suggest that aCT has a role in treatment of patients with residual disease (14-17). In a series of 101 patients with esophageal cancer alone, Brescia *et al.* found that aCT significantly improved OS in patients with residual nodal disease; of these, 92% also received neoadjuvant radiation (10). In contrast, another paper examining patients with esophageal cancer who underwent neoadjuvant treatment with chemotherapy alone failed to demonstrate similar results; however, it is possible these patients did not receive adequate treatment as patients typically only received a single cycle of chemotherapy (18). It has been previously suggested that at least 2 cycles of chemotherapy is associated with improved survival (14,16). While Sisic *et al.* failed to demonstrate improved survival with aCT, the authors noted that additional chemotherapy appeared to delay relapse in patients with residual tumor at time of surgery (19).

In the 2017 article by Burt *et al.*, the authors utilize a hospital-based cancer database to consider the role of aCT for patients with esophageal cancer who received nCRT and esophagectomy (20). This retrospective study utilizing the National Cancer Data Base (NCDB) (21) is the largest series to date to evaluate the impact of aCT on patient survival after nCRT. Amongst the patients evaluated, 335/3,592 (9.3%) received aCT. No survival benefit was found with aCT in patients with no residual disease or residual non-nodal disease on postoperative pathology; however, patients with positive lymph nodes had a 30% lower risk of death if they received aCT (HR=0.70, 95% CI: 0.57–0.85) (20).

The authors acknowledge several limitations to their study, including the retrospective nature of the NCDB. Additionally, the NCDB does not provide information on postoperative complications after esophagectomy or on intent to treat. It does not contain data on patient functional and nutritional status, factors that would help sway the determination for whether a patient will be able to tolerate treatment. Therefore, patients who were intended to receive aCT but were unable to, are not accounted for; this could introduce a potential for selection bias. To address this, the authors performed a subgroup analysis including patients who had a short length of stay (≤10 days) and no unplanned 30-day readmissions. The results were similar; aCT was associated with approximately 40% lower risk of death in patients with residual nodal disease (HR=0.63, CI: 0.48–0.84), thus upholding their overall findings. Furthermore, the NCDB does not collect data regarding availability of a medical oncologist at the institution, or the chemotherapy regimen/dose administered. As discussed above, this may have an impact on observed improved survival following adjuvant treatment. Finally, the authors note that, similarly to the CROSS trial, the majority of the tumors in the cohort are adenocarcinomas (6). They accounted for this by performing a separate analysis of patients with adenocarcinoma which demonstrated similar results to the analysis of the overall cohort (20).

The optimal approach to patients with residual disease after neoadjuvant therapy and surgical resection has yet to be defined. This large series by Burt *et al.* suggests that aCT is associated with improved survival in patients with residual nodal disease following neoadjuvant chemoradiation and esophagectomy (20), and raises several important questions that will be important to answer in future investigations. Given that esophageal cancer has a high recurrence rate, identification of the optimal patient population to receive adjuvant therapy after neoadjuvant treatment may help improve survival. While several studies above find that patients with both residual nodal disease and poor pathologic response have improved survival, Burt *et al.* only found improved OS for patients with residual nodal disease (14-17,20). Furthermore, the majority of the studies above included patients with EGJ and gastric cancers (14-17). These tumors have a distinct treatment algorithm, and as such, these results may not be generalizable to esophageal cancer alone. As a result of the Intergroup Trial 0116, the currently accepted treatment for patients with node positive EGJ tumors is nCT with subsequent postoperative aCRT (21). Other characteristics that may influence response to adjuvant therapy should be elucidated. Current guidelines from the National Comprehensive Cancer Network Guidelines (NCCN) have different recommendations based on histology type. For patients who have had preoperative chemotherapy or chemoradiation and

subsequent esophagectomy, current recommendations include consideration of adjuvant therapy for all patients with adenocarcinoma, regardless of pathologic response; in contrast, surveillance alone is considered adequate for patients with squamous cell carcinoma (SCC) undergoing chemoradiation and esophagectomy regardless of residual disease (22). Burt *et al.* note the importance of this distinction, as the CROSS trial demonstrated that 49% of patients with SCC versus 23% of patients with adenocarcinoma achieved a pathologic complete response (6,20). The data used by Burt *et al.* is from the US where the standard approach is to administer nCRT, and as such, only aCT is considered in the paper. Further study might consider whether the combination of nCT and aCRT may have better outcomes. Additionally, the optimal chemotherapy regimen and dosage will have to be established. Currently, there are several ongoing RCT that may help clarify some of the answers to these questions and evaluate the role of new systemic treatment options (23,24). Additionally, the ongoing Neo-AEGIS trial comparing the regimen of the CROSS trial to perioperative chemotherapy, as in the MAGIC trial, will hopefully provide further insight as to the optimal therapeutic approach (1,4,25).

Although the data do not currently provide a clear answer to guide management of patients with previous neoadjuvant treatment after esophagectomy, this preliminary work by Burt *et al.* suggests that a select group of patients may benefit from aCT. Given the persistent poor long-term prognosis associated with esophageal carcinoma, this may prove to be exciting information.

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