Editorial

Adjuvant chemotherapy for poor pathologic response after pre-operative chemoradiation in esophageal cancer: infeasible and illogical

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While recent decades have seen incremental improvements in the treatment of esophageal carcinoma, outcomes remain modest. The five-year overall survival (OS) rate for locally advanced esophageal cancer with surgery alone is 23–33% in contemporary studies (1-3). In locally advanced esophageal cancer, the risk of incomplete (R1) resection, local recurrence and systemic dissemination is significant. Numerous studies have demonstrated that the addition of chemotherapy and/or radiation to surgery improve outcomes, leading to multimodal treatment becoming standard-of-care. In particular, pre-operative chemoradiation has emerged as a standard-of-care in the US and Western Europe (4).

In esophageal cancer, multiple data sets suggest that patients who achieve a pathologic complete response (pCR) to chemoradiation have improved outcomes compared to those who do not (5). Patients with residual disease at surgery can be further stratified into those with node-positive disease who have worse outcomes compared to those with node-negative disease, based on an analysis from our group at Memorial Sloan Kettering Cancer Center (6). A similar observation was made by Smyth and colleagues in her analysis of the results of the UK MAGIC study of peri-operative chemotherapy in patients with gastric/gastroesophageal junction (GEJ) cancer (7).

Despite the poor outcomes in these patients, there are no prospective data to support changing or augmenting chemotherapy in esophageal cancer patients with node-positive disease after pre-operative chemoradiation and surgery. Virtually every contemporary study of chemoradiation in esophageal cancer (e.g., the Dutch CROSS study) has administered all treatments in the pre-operative setting, with no additional treatment following surgery. This is largely because of the difficulty of administering adjuvant cytotoxic chemotherapy following trimodality therapy in such patients, whose recovery may take 3–6 months following esophagectomy.

Even studies of peri-operative chemotherapy for gastric cancer that have also enrolled patients with GEJ tumors have not attempted to modify treatment in the adjuvant setting. The current standard-of-care was established by the German FLOT4 study, in which the experimental arm consisted of peri-operative FLOT chemotherapy (5-fluorouracil or 5-FU/ leucovorin (LV)/oxaliplatin/docetaxel) (8). As such, National Comprehensive Cancer Network (NCCN) guidelines currently recommend, in patients with node-positive disease post-surgery, completion of chemotherapy in patients treated with a peri-operative approach and observation in patients who were treated with preoperative chemoradiation or chemotherapy (9).

In the *Journal of Thoracic Disease* in June 2019, Drake and colleagues report results of a population-based study evaluating the role of adjuvant chemotherapy in patients with persistent node positive lower third esophageal adenocarcinoma following pre-operative chemoradiation and surgery (10). Patients treated between 2006 and 2012 who received pre-operative chemoradiation, underwent complete resection (R0) and had node-positive disease

on surgical pathology, were identified from the National Cancer Database (NCDB). OS was compared between patients who received adjuvant chemotherapy and those who underwent observation alone. Survival was also compared between these two cohorts using a propensity-score matching analysis. Of note, patients who died within 90 days of surgery (n=186) were excluded to decrease selection bias. Patients with upper and middle esophageal tumors were also excluded.

The initial analysis compared 295 patients who received adjuvant chemotherapy to 1,751 who did not. Patients treated with adjuvant chemotherapy were younger (57.9 *vs.* 61 years), more likely to have private insurance, had more lymph nodes examined and more positive lymph nodes (3.4 *vs.* 2.8) than patients in the observation group. At a median follow-up of approximately 2 years, median OS was 2.6 years in patients who had adjuvant chemotherapy *vs.* 2.1 years in patients who underwent observation alone (P=0.0185), corresponding to a 27.9% *vs.* 21.5% 5-year survival in the adjuvant chemotherapy and observation groups respectively. In multivariable analysis adjuvant chemotherapy continued to be associated with improved survival [hazard ratio (HR) 0.839, P=0.03]. A similar survival benefit for adjuvant chemotherapy was observed in the propensity matched analysis; 2.6 years in the adjuvant chemotherapy group *vs.* 2.0 years in the observation group with 5-year survival of 27.9% and 20.2% in the chemotherapy and observation groups respectively.

To support a role for adjuvant treatment, the authors cite three studies (the E8296 phase II trial, CLASSIC and Intergroup 0116) which evaluated adjuvant chemotherapy (CLASSIC and E8296) or chemoradiation (INT 0116) in patients with resected adenocarcinoma of the distal esophagus, GE junction and stomach who were not treated with pre-operative therapy (11-13). The majority of patients enrolled in Intergroup 0116 and CLASSIC had gastric tumors. However, we see no relevance of these studies since none of them involved administering pre-operative therapy.

The authors also cite data from a retrospective study in the United Kingdom, which suggested that patients who received pre-operative chemotherapy followed by surgery and the same adjuvant chemotherapy had improved outcomes *vs.* patients treated with pre-operative chemotherapy alone (14). However, the benefit for adjuvant chemotherapy was restricted to patients whose tumors exhibited pathologic response to pre-operative chemotherapy indicating that doubling down on more of the same chemotherapy when it has had little or no effect on the primary tumor does not seem to be an effective strategy as advocated by the authors in this study.

Similar to the study discussed herein, Burt *et al.* also performed a retrospective cohort study evaluating the benefit of adjuvant chemotherapy in patients with esophageal cancer treated with pre-operative chemoradiation and esophagectomy in the NCDB during the same time period (15). They also found that adjuvant chemotherapy was associated with improved survival in patients with node positive disease at surgery. In contrast to the current study, this analysis included patients with squamous cell histology, those who had undergone incomplete resection and those with node negative disease at surgery.

Both of these studies have several significant limitations inherent to the retrospective observational nature of the analyses. Of particular importance is the absence of key data points in the NCDB database including performance and nutritional status, pre-operative treatment toxicity, response to neo-adjuvant treatment, post-operative complications, type and cumulative dose of chemotherapy administered and whether patients completed the planned course of treatment. In the absence of these clinical variables, the available data lack sufficient granularity to allow any conclusions to be drawn.

For example, it is very likely that patients with better performance status received adjuvant therapy, which acts as a major confounder to the positive results. In addition, patients who received adjuvant chemotherapy had more nodes examined which may indicate that patients who underwent observation were understaged pathologically. In the context of these limitations, these studies should not be used to justify the use of adjuvant chemotherapy in such patients. For reasons that we will discuss, these retrospective studies should also certainly not form the basis of a prospective study design.

Firstly, the ability to deliver meaningful doses of chemotherapy following chemoradiation and surgery is extremely doubtful. While there are no randomized data to answer this question in esophageal cancer, the peri-operative MAGIC and FLOT4 studies in gastric cancer reported that only 50–60% of patients were able to initiate or complete adjuvant chemotherapy following pre-operative chemotherapy and gastrectomy. Given the increased morbidity of pre-operative chemoradiation and esophagectomy, these numbers are almost certainly likely to be even smaller in esophageal cancer patients.

Secondly and more importantly, completed phase III

studies in esophagogastric cancer patients have essentially shown no benefit to augmenting chemotherapy in an unselected population. The likelihood that such a benefit is possible in a pre-determined population with chemorefractory disease is even more improbable.

The Cancer and Leukemia Group B (CALGB) 80101 trial evaluated the role of more intensive adjuvant therapy [*vs.* bolus 5-FU/LV] in 546 patients with gastric cancer, 30% of whom had GE junction and proximal stomach tumors (16). Patients who had undergone surgical resection were randomized to bolus 5-FU/LV preceding and following chemoradiation with infusional 5-FU or ECF (epirubicin/cisplatin/5-FU) preceding and following chemoradiation with infusional 5-FU/LV. There was no improvement in 5-year disease-free survival (DFS; 44% *vs.* 44%, P=0.69) or OS (39% *vs.* 37%, P=0.94) with the addition of an anthracycline and platinum to 5-FU.

The Japanese SAMIT study randomized patients with T4 gastric cancer, who had undergone D2 gastrectomy, to sequential paclitaxel followed by tegafur/uracil (UFT) or S-1 or to monotherapy with UFT or S-1 alone (17). The addition of sequential paclitaxel to S-1 or UFT did not improve DFS and S-1 monotherapy remained a standard of care for locally advanced gastric cancer at that time. Finally, the Italian ITACA study also evaluated a strategy of intensifying adjuvant treatment (18). Patients with gastric and GE junction (approximately 15%) adenocarcinoma who underwent D1 or D2 gastrectomy were randomized to adjuvant FOLFIRI (irinotecan/5-FU/LV) followed by docetaxel plus cisplatin or to 5-FU/LV alone. There was no difference in DFS or OS between the study arms.

Of note, the recently published JACCRO GC-07 phase III study demonstrated a benefit for concurrent treatment with adjuvant S-1 plus docetaxel in patients with stage III gastric cancer who undergone D2 resection; approximately 25% of patients had upper gastric tumors (19). Furthermore, the FLOT4 study showed benefit for a more intensive 3 drug approach in the peri-operative setting (*vs.* epirubicin/cisplatin/capecitabine) (8). However, both of these studies evaluated intensified concurrent treatment rather than sequential treatment. In any event, taxane-based combination chemotherapy in the adjuvant setting is not a relevant consideration since many patients already receive pre-operative radiation in combination with carboplatin/paclitaxel. As noted above, doubling down on ineffective chemotherapy is a flawed strategy.

Results from the UK MRC OEO5 study also call into question the optimal duration of chemotherapy. This study randomized patients with esophageal and GE junction adenocarcinoma to 6 weeks of pre-operative chemotherapy with 5-FU/cisplatin or 12 weeks of ECX (epirubicin/cisplatin/capecitabine) (20). While an improved pCR rate was observed in patients who received ECX, this regimen was not associated with an improvement in DFS or OS. These results are supported by the CROSS study, which reported a 14% improvement (similar to the 10–15% benefit seen in other positive phase III studies) in OS with only 5 weeks of systemic therapy with carboplatin/paclitaxel (3). Furthermore, only 40–50% of patients in the MAGIC and FLOT4 studies received or completed all planned adjuvant therapy suggesting that patients may benefit from relatively short exposure to chemotherapy (1,8). Cumulatively, the data discussed regarding intensification of systemic therapy and the optimal duration of chemotherapy lead us to question the merits of additional adjuvant chemotherapy following pre-operative therapy.

Rather than focusing on more chemotherapy, experimental strategies with novel therapies or biomarker-driven approaches are urgently needed. Immune checkpoint inhibitors have shown a modest benefit in the metastatic setting, especially in patients who are programmed cell death ligand-1 (PD-L1) positive, MMR deficient or EBV positive (21,22) and are now being evaluated in the adjuvant setting. The phase III Checkmate-577 study (NCT02743494) is a global trial evaluating adjuvant nivolumab or placebo in patients with stage II/III esophageal/GE junction adenocarcinoma who have residual pathologic disease following pre-operative chemoradiation and surgery (with R0 resection).

Over the last decade, PET-directed treatment strategies have also emerged as a tool which may optimize outcomes in esophageal adenocarcinoma. Most recently the CALGB 80803 study evaluated if changing chemotherapy during chemoradiation based on PET response [≥35% reduction in standard uptake value (SUV) between baseline and repeat PET] to induction chemotherapy impacts on the pCR rate (23). Preliminary data showed that patients who were PET non-responders and changed chemotherapy regimens had a pCR rate of 17–19%, meeting the primary endpoint of improving the pCR rate from a historical control rate of 3%. Median OS was 47.3 months in PET responders *vs.* 28.9 months in PET non-responders (P=0.09). The highest median OS of 50.3 months was reported in the patients who received induction FOLFOX chemotherapy, were PET responders and continued with FOLFOX/radiation prior to surgery (24). When considered in the context

of historical controls, the strategy of leveraging PET non-response to optimize the chemotherapy regimen during radiation may improve outcomes. Our group is evaluating a PET directed approach along with the immune checkpoint inhibitor durvalumab, a monoclonal antibody directed against PD-L1 (NCT01196390). Patients are treated with 2 cycles of induction FOLFOX followed by a repeat PET. Patients who are PET-responders then continue to receive fluoropyrimidine/oxaliplatin during radiation, while patients who are PET non-responders switch to carboplatin/paclitaxel during radiation. Patients receive durvalumab 2 weeks prior to commencing chemoradiation and a second dose during chemoradiation. Patients who undergo surgery with an R0 resection then continue adjuvant durvalumab for 6 cycles.

Two studies have also evaluated the combination of nivolumab (NCT03044613) and avelumab (NCT03490292) with pre-operative chemoradiation with carboplatin/paclitaxel and have reported that this strategy appears feasible with no new safety concerns (25,26). The study evaluating nivolumab in combination with chemoradiation (NCT03044613) is now enrolling patients to a second arm evaluating nivolumab plus relatlimab, an anti-lymphocyte activation gene-3 (LAG-3) antibody.

In terms of targeted approaches, the RTOG 1010 study (NCT01196390) evaluated the addition of Her2-directed therapy with trastuzumab to preoperative chemoradiation, and for 9 months following surgery, in the approximately 20% of patients with Her2 positive esophageal/GEJ adenocarcinoma. The results of this trial are awaited.

Finally, the evaluation of biomarkers of response/resistance to chemotherapy are urgently needed to guide the development of new strategies. For example, recent retrospective analyses in gastric cancer of the MAGIC study of peri-operative chemotherapy (7) and the CLASSIC study of adjuvant chemotherapy (27) strongly suggest that patients with microsatellite unstable (MSI) tumors have a significantly better prognosis than those with microsatellite stable (MSS) tumors. In addition, patients with MSI tumors either derive no benefit from adjuvant treatment or may even be harmed by peri-operative chemotherapy. At this time, no data exist regarding the role of MSI status in esophageal and GEJ cancers and their responsiveness to chemotherapy and radiation. However, biomarker analyses such as this need to be urgently performed both in completed and ongoing studies of chemoradiation.

In summary, ongoing focus on the incorporation of new strategies into the preoperative and adjuvant treatment of patients with locally advanced esophageal adenocarcinoma who are at high risk of systemic recurrence is imperative. Correlative studies from accrued and ongoing studies may allow us to better predict patients at highest risk of relapse and those most likely to respond to emerging therapies. Older strategies focusing on combinations of "tried and tested" (and toxic) chemotherapy agents are unlikely to significantly impact on improving outcomes in these patients. They should be avoided in standard clinical care and should not form the basis for prospective trial design.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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