Editorial

Adjuvant chemotherapy following trimodality therapy for esophageal carcinoma—Is the evidence sufficient?

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The preferred management of localized esophageal carcinoma consists of multi-modality therapy (chemotherapy, radiation, and surgery). The ideal timing, treatment sequence, and dose of therapy remain active areas of investigation and controversy. Following publication of favorable outcomes for neoadjuvant chemoradiation prior to definitive resection, tri-modality therapy has become the standard approach in the United States for patients with local/regionally advanced disease (1-5). As the experience with trimodality therapy has grown, adjuvant treatment following completion of all planned therapy has become an area of interest. For those 15–30% of patients with a pathologic complete response (pathCR), the decision to reserve further therapy until the time of recurrence appears straightforward, with no clear evidence of significant clinical benefit for either adjuvant chemotherapy or radiation. However, even for patients with pathCR, recurrence rates remain high with approximately >33% of patients developing distant metastases. In patients with residual disease burden following trimodality therapy, the question of adjuvant chemotherapy becomes more relevant (6-8). This group of patients (pT+ and/or N+) remains at high-risk for both local and/or distant failure. The addition of adjuvant systemic therapy is hoped to provide superior outcomes compared to observation alone (9). Taken together, the evidence would suggest a potential role for adjuvant systemic therapy regardless of pathologic response; the challenge becomes identifying those patients in whom further systemic therapy, with its inherent risks, will offer a relevant clinical benefit.

Recently, Burt and colleagues evaluated a large national series examining the role of adjuvant chemotherapy following completion of traditional trimodality therapy, (neoadjuvant chemoradiation + esophagectomy) (10). Utilizing the National Cancer Database (NCDB) and a relatively strict selection algorithm, patients with adenocarcinoma (AC) and squamous cell carcinoma (SCC) treated with neoadjuvant chemoradiation followed by esophagectomy were identified. Despite a large initial cohort (>3,500 patients), adjuvant chemotherapy was administered to less than 10% (AC =300/SCC =35) of eligible patients. Comparing those patients who received adjuvant therapy to overall cohort, no overall survival (OS) benefit was identified. When patients with without residual disease (pathCR) were excluded, OS favored adjuvant chemotherapy. This benefit was most evident in patients with AC histology and residual nodal disease. Multivariable Cox Regression modeling performed on a further restricted cohort (length of stay <10 days and no 30-day readmission), demonstrated a reduction in the risk of death with administration of adjuvant chemotherapy. Similar to the full cohort, this effect was seen in those patients with persistent nodal involvement. The authors concluded that adjuvant chemotherapy is associated with in improvement in OS

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following completion of planned trimodality therapy, when persistent nodal disease is present.

To date, there have been no randomized studies evaluating the use of adjuvant chemotherapy following neoadjuvant CXRT + esophagectomy (11). The use of adjuvant chemotherapy for esophageal carcinoma is driven primarily by studies of perioperative chemotherapy without radiation, consisting ideally of both pre- and post-operative administration. Two well-designed randomized studies demonstrated a 12–13% improvement in 5-year OS with administration of perioperative chemotherapy as compared to surgery alone (12,13). Some caution should be taken when looking to apply these results more broadly. Although GEJ tumors were included, the primary tumor site was gastric in 75% (372/503) and 25% (55/224) of enrolled patients respectively. Putting topography aside, teasing out the survival effect of adjuvant chemotherapy, in the setting of neoadjuvant chemotherapy, remains a challenge. Nearly half of patients in both randomized studies received no post-operative chemotherapy, leading to the question of whether administration alone, regardless of timing is the contributing factor.

One of the few randomized studies to evaluate the efficacy of adjuvant *vs.* neoadjuvant chemotherapy was the Japan Clinical Oncology Group (JCOG) trial 9907, which randomized 330 patients with locally advanced esophageal carcinoma to two cycles of neoadjuvant or adjuvant chemotherapy in addition to complete resection (14). The trial was closed early after an interim analysis demonstrated superior outcomes in the neoadjuvant arm. There are two major caveats to interpretation of these results: (I) only SCC was included; and (II) patients who were pN0 were not administered adjuvant chemotherapy based on results from JCOG 9204 (15). Interestingly, consistent with the study by Burt, only pN+ patients derived benefit from adjuvant administration of chemotherapy. Several smaller series attempting to identify the effect of adjuvant chemotherapy, in the setting of neoadjuvant administration, have shown disparate results. A retrospective review of nearly 300 patients with esophagogastric AC who underwent complete resection following neoadjuvant chemotherapy demonstrated no change in either overall or recurrence free survival with the administration of adjuvant chemotherapy (16). Conversely, two retrospective studies of patients with gastric or esophagogastric carcinoma identified administration of adjuvant chemotherapy (following neoadjuvant chemotherapy + esophagectomy) as being associated with an improvement in both overall and recurrence free survival (17,18). Similar to previous studies, the greatest benefit was realized by those patients with persistent nodal disease following neoadjuvant therapy.

We congratulate the authors for completing this large retrospective review as they have attempted to address a difficult question of appropriate patient selection for adjuvant chemotherapy following induction chemoradiation and surgery. Although their data point towards a possible survival advantage with adjuvant chemotherapy in patients with residual nodal disease, selection bias for adjuvant therapy is difficult to overcome.

At baseline, patients receiving adjuvant therapy were younger, had a higher level of education, and were more likely to be insured. Moreover, the NCDB PUF dataset does not provide a variable field with information regarding the number of cycles or the type of chemotherapy delivered, which could potentially impact the decision to offer additional treatment.

Of the patients selected for adjuvant chemotherapy, recovery following esophagectomy was presumably without significant morbidity, such that they were deemed fit to receive additional therapy. In an attempt to address this source of bias, a subgroup analysis of patients with length of stay (LOS) <10 days and no readmissions was performed separately. The limitation to this is that neither of these surrogate markers for perioperative morbidity was significantly different when comparing the initial, unselected groups (median LOS 10/10, P=0.13; re-admission rates 5.5%/4.8%, P=0.69). As such, these variables may not represent a reliable metric for estimating the fitness of patients to undergo systemic chemotherapy following esophagectomy. In an effort to limit survivor treatment bias, a 90-day landmark cohort was analyzed as well; the results were essentially unchanged as compared to the unselected cohort.

Attempting to reconcile these somewhat contrasting results leads to two contrasting observations: (I) the presence of residual node involvement would suggest an ineffective initial regimen such that further administration would be of marginal benefit; (II) a substantial percentage of patients manifesting a pathCR will recur, with 75% of recurrences being distant (7). We are left to ask, is the simple binary metric of pathCR appropriate to accurately differentiate the biologic potential of a malignancy on an individual patient basis, and therefore guide therapy? If not, how then are we to identify this at-risk cohort of patients, while avoiding futile therapy to non-responders? It appears that persistent nodal disease represents an independent marker of aggressive disease biology, and at the same time may identify patients who will respond well to further

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chemotherapy. Interestingly, those patients with residual primary disease alone (ypT + N0) did not appear to derive benefit from adjuvant chemotherapy.

Although clinicopathologic response to neoadjuvant chemoradiotherapy is a well validated predictor of outcomes for esophageal carcinoma, it remains a rather blunt descriptor (19). As demonstrated by Burt *et al.*, the specific presence of persistent nodal disease, as opposed to primary tumor, may provide some additional clarity to predictions of recurrence and survival. Shifting towards a focus on the underlying molecular and/or genetic mechanisms contributing to both response to therapy and long-term outcomes may add granularity to guide therapeutic decision making. Recent work has suggested genetic bottlenecking or intratumoral heterogeneity as potential markers for response to platinum-based therapy (20,21). In a study of 149 esophageal ACs potentially actionable gene alterations were identified in nearly half, while only one [*ERBB2* (HER2)], is being routinely targeted (21). Though intriguing, these molecular and genetic signatures have yet to be well validated clinically, and are not currently applicable to guide treatment. At present we are left utilizing broader, less elegant, though well validated descriptors of disease when determining the appropriate overall therapeutic strategy for a patient.

Current evidence for adjuvant chemotherapy after completion of traditional trimodality therapy for locally advanced esophageal carcinoma remains unclear. Prospective clinical trials to establish if a true benefit exists are needed. As shown, the presence of persistent nodal disease represents a marker for the presence of otherwise undetectable systemic disease where adjuvant therapy may provide a significant outcome benefit. An ongoing clinical trial with adjuvant immunotherapy versus placebo in resected esophageal and GEJ AC after chemoradiation (NCT02743494) will establish if the addition of immunotherapy provides survival benefit in these group of patients. Further perioperative trials should focus on tumor biology that could allow us to develop personalized therapy.

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Footnote

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

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