Editorial

When to resect following neoadjuvant therapy for esophageal cancer—issues and limitations in addressing this decision

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Provenance: This is an invited Editorial commissioned by Section Editor Dr. Gang Shen, MMSC (The Second Affiliated Hospital Zhejiang University School of Medicine, Hangzhou, China).

Comment on: Ranney DN, Mulvihill MS, Yerokun BA, *et al.* Surgical resection after neoadjuvant chemoradiation for oesophageal adenocarcinoma: what is the optimal timing? Eur J Cardiothorac Surg 2017. [Epub ahead of print].

Submitted Jul 08, 2017. Accepted for publication Jul 11, 2017.
doi: 10.21037/jtd.2017.07.71
View this article at: http://dx.doi.org/10.21037/jtd.2017.07.71

In this issue of the *European Journal of Cardio-Thoracic Surgery*, Ranney *et al.* address the very pressing and often debated issue of the timing of esophagectomy following neoadjuvant chemoradiation (nCRT) for patients with esophageal adenocarcinoma (1). As the authors highlight, this question has persisted among those who treat esophageal cancer. Its importance lies in the balance of choosing the optimal time frame after nCRT. On the one hand, increasing the time to surgery can lead to superior pathologic responses (2,3). On the other, a prolonged period after nCRT can make surgical resection more technically challenging as the effects of radiation accumulate, and studies (including this one) have shown that overall survival (OS) may be more inferior the longer one waits to resect (4,5). Still other studies have reported no association between timing of resection and outcomes, further complicating this issue (6,7).

In this retrospective study using the National Cancer Data Base (NCDB), 2006–2012, the authors analyzed this issue using a novel approach. Utilizing the validated statistical technique of restricted cubic splines (RCS), albeit complex and unlikely to be familiar with the average physician, the authors identified an "inflection point" of 56 days, corresponding to the proposed optimal time for resection after nCRT. They concluded that patients who had surgery after this point (the "long-interval" group) had worse OS compared to those who underwent surgery prior to 56 days (the "short-interval" group). Specifically, the 5-year OS was 32.2% and 38.4% for the long- and short-interval groups, respectively (P<0.001). The authors also performed a propensity score matched analysis, yielding a similar result, albeit based on a fewer number of patients (31.4% *vs.* 41.3%, P<0.001).

Overall, the authors are to be commended for this study for completing a unique approach to a very pertinent clinical question, achieving a relatively large sample size from a national database, and producing results that were consistent with some previous studies. The endeavor to determine the optimal timing of resection, balancing OS with pathologic downstaging or pathologic complete response is noble, but the question remains: Is the NCDB an appropriate database to address this issue? While large databases like the NCDB are highly useful in generating hypotheses pertinent to contemporary topics, results derived from this and many other studies are limited in their general applicability to the prospective management of patients. This is due to the intrinsic limitations within the NCDB itself as discussed in other studies using the NCDB to study nCRT for esophageal cancer (8-10).

In the Discussion, the authors acknowledge many of the limitations of this study, though these are somewhat underscored. It is imperative to note that there are two main areas of limitation for this study using the NCDB: (I) determination of the inflection point, and (II) analysis of OS

between the short- and long-interval groups. With respect to the first item, it is highly questionable whether the NCDB can elucidate the reasons for when surgical resection was performed, which significantly impacts the calculation of the inflection point. First, the NCDB does not include information on treatment complications and tolerability from nCRT. These factors can both influence the decision of when to perform surgery. The authors excluded patients who had surgery <30 days after starting nCRT, but this is unlikely to be inclusive of all patients who completed nCRT. Timing of multimodal therapy also depends on certain personal and intangible factors that are not captured by the database, such as personal preference (scheduling conflicts around holidays or personal events) and disparities in health care treatment. Some socioeconomic factors were included in the study, namely insurance status, income, and education. However, other factors can influence treatment decisions, such as type of treatment facility, distance to treatment facility, geographic location (which are included in the NCDB), and expertise of the treating physicians, bias of the treating physicians, and perceptions/preferences of the patient (which are not captured by the NCDB). In other words, access to multimodal therapy also plays a role in treatment decision making. Thus, while a rigorous statistical calculation of the inflection point was possible, its relevance and applicability to patient care could prove challenging because of the uncertainty and bias underlying this calculation.

In assessing the limitations for OS, post-operative complications can significantly influence the study's results, but as the authors conceded, these are not captured by the NCDB. While post-operative length of stay and readmission rates can act as surrogates for post-operative complications, these are not always a direct measure of morbidity. Furthermore, while the NCDB does include the Charlson-Deyo score as a measure of comorbidity, this is a relatively crude measurement and does not discern among many specific comorbidities that are relevant to esophageal surgery, such as pulmonary function.

Other factors will influence OS, including the type of neoadjuvant chemotherapy received. As the authors note, the NCDB does not record the specific types of chemotherapy given, the dosages and/or potential dose reductions, or any treatment delays in therapy. As the time period of this study spanned 2006–2012, it is reasonable to assume that patients toward the latter years in the database received more modern regimens. As shown in Table 2, there were higher proportions of patients in the long-interval group diagnosed in the latter half of the study period compared to the short-interval group. It would be reasonable to hypothesize, therefore, that a greater number of patients in the long-interval group received modern chemotherapy regimens than the short-interval group, which in turn would result in superior OS. However, this was not the case observed by the authors. This may be explained by the different biases discussed. With regard to chemotherapy, more patients in the short-interval group received adjuvant treatment. This may not only have contributed to superior OS, but also implies that these patients may have been healthier to tolerate adjuvant therapy, thus introducing yet another OS bias. What is also questionable and not clearly delineated from this study is whether those patients who received "adjuvant therapy" truly received adjuvant therapy and what the indications were for this (positive margins, poor response to nCRT, metachronous metastatic disease) versus if adjuvant therapy actually represented peri-operative therapy, as would be indicated by the MAGIC trial for patients with distal esophageal or esophagogastric junction (EGJ) tumors (11).

Other important limitations exist in this study. As there were patients with missing data, exclusion of these patients potentially skewed the analysis. The number of excluded patients was not reported, but even within the cohorts analyzed, there was a significant amount of missing data that was not reconciled. Several of the variables listed in the study's tables do not equal the cohort totals, raising the question as to how many patients with complete data were incorporated in the analysis. Another important limitation is that the NCDB does not indicate by what methods the patients were clinically staged, i.e., endoscopic ultrasound, CT scan, PET scan, etc. As these modalities vary with their sensitivity and specificity for clinical T and N staging, clinical misstaging often occurs. Therefore, it is very difficult to discern between clinical misstaging and treatment effects from nCRT. Lastly, as the authors note, there is limited generalizability of these results as the cohort was comprised predominantly of white males.

Thus, while this study provided a unique approach to address an important issue, the question persists as to whether use of the NCDB is appropriate for this particular issue. Perhaps this was not the case due to the many relevant limitations acknowledged by the authors themselves and those raised in this commentary. While this study did serve to generate hypotheses for the optimal timing of esophagectomy following nCRT, its usefulness in the management of actual patient care may prove

challenging and should be addressed through prospective studies that more thoroughly control for bias and have a broader applicability to all patients with esophageal cancer.

Acknowledgements

None.

Footnote

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

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Cite this article as: Gabriel E, Hochwald SN. When to resect following neoadjuvant therapy for esophageal cancer—issues and limitations in addressing this decision. J Thorac Dis 2017;9(8):E727-E729. doi: 10.21037/jtd.2017.07.71

