Esophageal resection after neoadjuvant therapy: understanding the limitations of large database analyses

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

Response to: 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:E727-9.

Determining the optimal timing of surgical resection for esophageal adenocarcinoma following neoadjuvant therapy has proven to be a challenging task, and the clinical implications for patients undergoing surgery at various time intervals remain elusive. In an effort to fill a gap in the current retrospective literature pertaining to this clinical question, we utilized the method of restricted cubic splines (RCS) to investigate the balance in this timing from a unique statistical perspective. Using the National Cancer Database (NCDB), we determined an inflection point of 56 days wherein an increased incidence of pathologic complete response was balanced with a decreased rate of overall survival (1).

As with any study, the source and context of the data must be scrutinized to understand the applicability of the results and clinical relevance of the conclusions. We appreciate the additional insights by Gabriel and Hochwald into the limitations of using the NCDB for this and other studies. As they describe, the NCDB is limited in capturing specific patient level data, which may contribute to biases in patient selection and management (2). Regarding the present study, we concede that certain variables such as results of pulmonary function testing and more granular classifications of comorbidity may influence the analysis. While there are certain surrogates to these variables, such as Charleston Deyo comorbidity scores, a more granular dataset may provide increased precision, which must be understood by the reader to effectively interpret our results. The authors, however, also alluded to variables such as

scheduling conflicts around holidays and vacations, and patient preferences toward treatment. While these may certainly impact patient selection, these details are difficult to quantify or capture, and are thus inherent flaws of virtually any study and are not specific to our study by any means. These conflicts will also arise in a prospective study design, from accrual to follow up, as well as the real-world setting to which these results are applied. Furthermore, our independent variable was time, and although the aforementioned factors may influence the real-world time interval, they do not contribute to the outcomes we modeled as a function of time.

Although many of the limitations cited by Gabriel and Hochwald are not confined to our article of mention, it is worth restating the importance of considering these limitations in any large database study. In fact, this very concept has been studied. In their article from 2014, Yoshihara and Yoneoka provide several additional cautions regarding large database analyses. For example, coding of procedures and clinical events is at the discretion of the provider or hospital billing department. These may be influenced by reimbursement priorities over time as well as internal shifts in clinical practice (3). Procedures and conditions may also be coded incorrectly or differently among facilities, further reducing the accuracy of results (4). Furthermore, complications are often limited to in-hospital events due to systematic constraints, thus the rates of various complications may be underestimated (5). This is in addition to the fact that some complications per se, or at

least contributing factors, may be present prior to surgery, which would further bias results. Lastly, many variables have the potential to not be captured in large data sets leading to a high degree of missingness. While these deficits may sometimes be managed statistically, they certainly contribute to imperfections that may influence results (6).

While it is true that the NCDB, as with any large database, has inherent limitations, prospective analysis will likely provide a more controlled setting for answering the clinical question of how long to wait after neoadjuvant therapy before performing surgical resection of esophageal adenocarcinoma. That said, attempts to "correct" these limitations will likely prove difficult even in the most carefully designed prospective studies. Our choice to use RCS as a statistical tool is based on the need to provide a novel strategy for analyzing a large dataset retrospectively, though as we mentioned in our index article, this likely exhausts the capabilities of a large retrospective analysis. Further study is certainly warranted to better understand the biology and mechanism of esophageal cancer, the patient level factors that influence outcomes, and the tumor response to modern neoadjuvant therapy, any of which may help determine the true optimal timing of surgery for a specific patient.

Acknowledgements

None.

Footnote

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

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