This study clearly shows that the timing of esophagectomy did not influence overall survival, even though it was associated with increased 90-day mortality. The study suggests that waiting until documented recurrence occurs is not a bad option for patients with a clinical complete response on imaging and endoscopy who are reluctant to undergo surgery. Furthermore, surgeons should be less pressed to operate on patients who appear frail from a nutritional or a medical standpoint after chemoradiation. Waiting will not change these patients' overall likelihood of survival, and optimizing their clinical status may improve outcomes.

Another intriguing finding of the study is the observation that a higher rate of complete pathological response, as assessed after esophagectomy, was seen when esophagectomy was delayed. This raises some important questions: are we operating too early on some of these patients, and would waiting a few extra weeks improve their response to neoadjuvant therapy? Regardless, until better trials are available to address the timing of esophageal resection, we believe that the higher 90-day mortality observed in patients with delayed esophagectomy in this study supports operating

within 90 days of completion of chemoradiation therapy whenever possible.

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Commentary: Delayed resection for esophageal adenocarcinoma

Wayne Hofstetter, MD

There have now been multiple retrospective studies examining the potential effect of a delayed operation for esophageal adenocarcinoma after chemoradiation therapy. Uniformly, these studies have shown overall survival results comparable to those of immediate, planned resection, but with some differences in short-term outcomes.^{1,2} Results from these single- and multi-institutional studies are now recapitulated in the study by Levinsky and colleagues³

Wayne Hofstetter, MD

CENTRAL MESSAGE

Patients with persistent or recurrent esophageal adenocarcinoma may undergo delayed esophagectomy beyond 90 days after neoadjuvant or definitive chemoradiation with similar prognosis compared with timely, planned esophagectomy.

From the Department of Thoracic and Cardiovascular Surgery, The University of Texas MD Anderson Cancer Center, Houston, Tex.

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Address for reprints: Wayne Hofstetter, MD, 1400 Pressler Ave, Unit 1489, Houston, TX 77030 (E-mail: Whofstetter@mdanderson.org).

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derived from the National Cancer Database (NCDB) reported in this issue of the *Journal*.

What conclusions can be drawn from these data? There are clearly selection biases that affect the decision to operate in a timely versus delayed fashion. None are more apparent than the need/desire to avoid an upfront operation on a sicker patient or one who initially seemed able to tolerate trimodality therapy only to present to the surgeon's office after therapy looking far from an optimal surgical candidate. In those cases, a period of observation and rehabilitation will often lead to an improvement in performance status and/or recognition of persistent disease that would "force" a delayed operation outside the initial 90-day post-chemoradiation (CXRT) period. On the other hand, patients with good performance status who clearly have residual disease after CXRT typically would be offered resection within 90 days. Adding to the heterogeneity, this population differs from those patients who initially had a complete response to therapy and avoided surgery out of choice, risk, or recommendation. These patients would have been under observation but were sent back to a surgeon when the tumor recurred to weigh the risks/benefits of esophagectomy. These are the "true" salvage patients.

Levinsky and colleagues provide evidence that the more remote the surgical date from completion of CXRT, the higher the rate of pathological complete response (pCR). There are several ways to interpret these data, but the most important implication is that these were not all salvage patients. If they were, we would expect a very low rate of pCR in the final pathology, reflecting the need to undergo esophagectomy only in the situation where tumor was confirmed or highly suspected based on a nondilatable stricture. Critical to making a case for selection bias, these data imply that a reasonable proportion of the delay in surgery within the NCDB data was a result of waiting for patients to recover from CXRT. It would then be a reasonable expectation that patients who had a more delayed course through CXRT and surgery were potentially more susceptible to perioperative events. Kim and colleagues⁴ reported similar findings in a retrospective single-institution analysis of nonsalvage patients who were delayed going to surgery. It is unfortunate that the NCDB data do not offer data on patients' functional decline after CXRT or other surrogates that would allow an imputation of the subgroups. Levinsky and colleagues were left with only the time to surgery as differentiation.

Though there are perioperative event differences, not all of the short-term outcomes described by Levinsky and colleagues are clinically very relevant. Length of stay (LOS) was significantly increased, but the median difference of 1 hospital day with a heavy overlap of the interquartile range does not translate to a clinically relevant endpoint. Nonetheless, as described by the authors, it may be a surrogate

endpoint for relatively minor perioperative events that are not otherwise reflected in the data. More importantly, this study reports a significant increase in perioperative mortality, whereas other studies did not.^{1,2} Admitting conjecture, I believe that this is due to heterogeneity in the patient population and not a result of increasing mortality due simply to a time delay from CXRT. The inference of disparity and social differences reported by Levinsky and colleagues seem to be kinetic and attributable variables. Multiple other disease sites (eg, head/neck, rectal) have reported comparable outcomes for early versus late operation after neoadjuvant or definitive CXRT. Yet the concept of radiation "setting in" and increasing the risk of surgery is of concern nonetheless. In fact, the studies of Marks and colleagues¹ and Markar and colleagues² both call into question the issue of higher mortality surrounding higher radiation doses.^{1,2} These data are not available in the NCDB and are only hypothesis-generating in the other reports. I am interested to see the results of the SANO study,⁵ in which the radiation dose is lower (41.4 Gy), based on the CROSS study.⁶

Finally, the data in the current study are limited to a select number of patients who actually made it to surgery. There is no denominator of total treated, including unresected patients. Because of this, these studies cannot serve as endorsements for selective surgery. Overall, the only conclusion that we should appropriately draw from this study and others like it is that when faced with a situation in which delayed surgery is needed in a patient with esophageal adenocarcinoma, this operation can be done with some confidence and a reasonable prognosis. As to the questions around selective surgery, prospective randomized trials are needed to explore the potential for observation in patients with esophageal adenocarcinomas who are clinical responders.

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