

# Oncological outcomes of the TIME trial in esophageal cancer: is it the era of minimally invasive esophagectomy?

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Esophageal cancer is one of the most common digestive tract cancers worldwide. Although multimodality therapy has been used in the treatment of esophageal cancer, there is still a poor prognosis (1). For decades, esophageal resection remains the mainstream of multimodality treatment for esophageal cancer, but traditional open esophagectomy (OE) is associated with high perioperative morbidity and mortality. The unstopping advances in surgical devices and techniques have contributed to the transition from OE approach to minimally invasive esophagectomy (MIE) approach, which has demonstrated advantages in reducing postoperative pulmonary complications and improving short-term quality-of-life (QoL) verified by some prospective trials (2,3). However, debate is ongoing as to whether MIE is equivalent to open resection regarding long-term oncologic outcomes. Although many retrospective studies reported equivalent or even superior long-term outcomes of MIE over OE (4-6), we could not ignore the fact that conclusion was underpowered due to the biases, such as selection of cases, surgeon's experience and non-uniform surgical procedure. With the intent to solve the predicament, the long-term results of multiple prospective randomized clinical trials, including MIRO (7), TIME (2) and ROMIO (8) have been waiting all the time.

Recently, the TIME-trial reported the long-term survival outcomes (9). In this article, Dr. Straatman and colleagues demonstrated there were no differences in disease-free (37.3% *vs.* 42.9%,  $P=0.602$ ) and overall (41.2% *vs.* 42.9%,  $P=0.633$ ) 3-year survival between OE and MIE approach and postoperative local recurrence and metastases were also similar between these two arms ( $P=0.258$ ). When

analysis was stratified by TNM stage, it also revealed no significant differences for survival. Multivariable regression analysis indicated surgery approach was not an affecting factor for survival. There is no doubt that the TIME-trial excludes all the potential impacts, such as selection bias, surgical approach diversity and so on. It gives us a definite conclusion. Previously, it is considered that neoadjuvant chemoradiotherapy was a contraindication for MIE because of radiation fibrosis, especially for tumors in upper or middle third of esophagus closely to the bronchus. Notably, eligible patients in the trial included those with locally advanced resectable esophageal cancer (cT3) receiving neoadjuvant therapy, and it showed no differences in resection rate between these two approaches. Therefore, this trial stated that MIE may be performed safely and feasibly after neoadjuvant therapy, which was consistent with our experiences and some recent studies (10-12). With the maturity of technique, MIE could also be a component for multimodality treatment

Though the design of the trial is rigorous and the evidence rank is high, it is also far from satisfactory. Just as the authors referred, the number of patients included in both groups are relatively small (59 *vs.* 56 cases, respectively), this probably underpowered for a robust analysis of long-term oncological outcome, especially carrying out subgroup analysis of stages or pathological types. Therefore, high-volume randomized trials are still of great significance. Secondly, in the trial the median follow-up time is 22 months in the open group versus 27 months in the MIE group. The follow-up time is still not enough. Outcomes with a longer follow-up time are expected,

5-year survival is more valuable. Thirdly, the follow-up interval is every 6 months and a little longer, so it is less accurate for assessing disease-free survival. In addition, “a minimum of 10 MIE performed” is the criterion of participating surgeons; it is questionable of whether the surgeons had overcome the learning curve for MIE. If not, the overall effectiveness of the minimally invasive procedure is compromised (13,14), and the conclusions are not convincing.

MIE is demonstrated to reduce pulmonary complications and improve QoL without compromising long-term survival according to present trails. However, other large, multicenter, randomized clinical trials are still needed to validate its conclusion and guide therapy.

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## Footnote

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

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