



Improving Oncologic Outcomes for Esophageal Cancer After Open and Minimally Invasive Esophagectomy

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As more and more complex surgical resections for cancer are being performed minimally invasively, there is a continued emphasis on comparing outcomes between minimally invasive surgery and its open surgical counterpart. Whereas, originally, minimally invasive proponents have tried to prove noninferiority in oncologic outcomes of their approach, there is a growing recognition of potential improved short- and long-term outcomes, let alone equivalent outcomes, compared with the traditional operative methods. Esophagectomy, for the treatment of esophageal or gastroesophageal junction (GEJ) cancer, has been known to cause high morbidity and mortality, with the development of the transhiatal approach in response to complications due to the thoracotomies seen with the traditional transthoracic (Ivor Lewis) method.¹ However, the minimally invasive esophagectomy (MIE) has reduced the invasiveness of the surgery to laparoscopic and/or thoracoscopic access. Multiple studies have demonstrated improved short-term postoperative outcomes and reduced length of stay with MIE versus open esophagectomy (OE), favoring a shift toward increased minimally invasive esophageal resections since MIE's introduction.² However, the literature surrounding the impact on overall survival for those who undergo MIE compared with OE has been limited, with existing meta-analyses demonstrating mixed

results.^{3,4} In their study, Hayami et al. executed a population-based cohort study using registry data to compare the overall survival between those who underwent MIE and OE for esophageal or GEJ cancer.⁵ On the basis of their analysis, they suggest that MIE results in improved overall survival compared with OE after controlling for multiple confounding variables, such as age, ASA score, and neoadjuvant treatment.⁵ However, despite controlling for these important factors, there are significant limitations in their analysis that should be considered when assessing the validity of their conclusion.

Hospital volume is a key variable that must be accounted for in both outcomes and survival analysis, and is especially relevant considering the complexity and morbidity of an esophagectomy. Increased esophagectomy hospital volume has been shown to improve postoperative outcomes and in-hospital mortality, driving a minimal annual caseload of 20 esophagectomies per year to meet high-volume threshold standards.⁶ Recent studies have revealed improved overall survival for those who undergo esophagectomy at high-volume institutions, proving not only volume's role in mitigating operative morbidity but also improving longitudinal survival well after surgery.⁷ In Hayami et al.'s study, the vast majority of the MIEs were performed at high-volume institutions. Additionally, after further stratifying MIEs into those that underwent totally minimally invasive esophagectomy (TMIE) and hybrid minimally invasive esophagectomy (HMIE), the overall survival benefit persisted in the TMIE cohort but not in the HMIE. Indeed, none of the TMIEs was performed at low-volume centers and 72.8% were completed at high-volume hospitals, while over half of the HMIEs were done at low- and middle-volume institutions.⁵ Consequently, hospital volume likely played a larger role in the overall survival benefit seen in the MIE cohort, especially since the benefit

ceased to exist within the patients undergoing HMIE. While the authors state that they adjust for hospital volume, this is a clear confounder that we think is the most limiting factor in our ability to accept their conclusions.

Related to volume is the centralization of the procedure to a few regional, high-volume centers with high-volume surgeons. A recent meta-analysis demonstrated superior long-term survival in those who had an esophagectomy performed by a high-volume surgeon (more than seven esophagectomies per year), with surgeon volume being an even stronger predictor of improved overall survival than institutional volume, supporting the benefit of esophagectomy centralization.⁸ Given the immense learning curve associated with mastering laparoscopic and thoracoscopic esophageal resection, the emphasis on centralization is even more pronounced as the push for esophagectomy referrals to large, high-volume centers has resulted in relatively few surgeons having the MIE caseload and infrastructure to frequently train and gain proficiency in the MIE.⁸ Thus, the majority of those who reach expert status in the MIE are disproportionately composed of providers within high-volume surgeon groups at fewer larger hospital systems.⁹ Further, centralization also results in better perioperative care due to the treatment team's familiarity addressing postoperative complications, allowing for standardized treatment pathways with predictable efficacy.¹⁰ In Hayami et al.'s study, centralization was not included in the adjusted overall survival analysis, but likely contributed to the survival benefit in those who underwent MIE versus OE. As stated above, most of the MIEs were performed at high-volume centers, which likely consisted of more high-volume surgeons and higher-quality postoperative care compared with low-volume hospitals where OEs were more commonly performed.⁵ Furthermore, with the survival benefit being most pronounced in the TMIE cohort, one can infer that high-volume surgeons who have reached expert proficiency in MIE were the ones more likely to perform these cases given that both the abdominal and thoracic components of the procedure were done laparoscopically, necessitating even greater MIE case volume—a surrogate for centralization—to gain the skills to do both parts under laparoscopic guidance. The proportion of MIEs completed increased over the study period since its introduction in 2012, with this same trend also existing for esophagectomy centralization.¹¹ Although it was not analyzed, it appears that an increasing number of the MIEs were performed at higher-volume centers. While the authors did control for the year of the procedure, they did not control for surgeon volume. Further analysis assessing the number of institutions performing MIE and esophagectomies overall since its implementation would better account for any role centralization played in the improved overall survival found in the MIE group.

Finally, the implementation of the Enhanced Recovery After Surgery (ERAS) pathway guidelines has resulted in markedly improved perioperative outcomes for many major surgeries, and also should be considered in overall survival analysis that was not explicitly accounted for in Hayami et al.'s study. The application of ERAS for esophagectomies in particular has been associated with reduced length of stay and pulmonary complications.¹² Although there is limited evidence ascertaining an overall survival benefit after ERAS implementation for esophagectomies, ERAS has been shown to reduce the risk of severe complications such as anastomotic leak, which is an independent predictor of overall survival.^{13,14} Thus, it is reasonable to extrapolate ERAS's beneficial effect on overall survival in esophageal resection. With more institutions recently adopting the ERAS guidelines and this likely occurring in the higher-volume centers first, the influence this had on overall survival in the OE versus MIE cohort in Hayami et al.'s study cannot be overlooked. Perhaps, the most plausible reason this played a role in improved outcomes in the MIE cohort is the fact that the proportion of MIEs compared with OEs performed increased exponentially after 2012, likely coinciding with an increase in the number of institutions implementing the ERAS guidelines into their routine perioperative practice.⁵ While they controlled for the year of the procedure, this is not specific enough to assert that this controlled for ERAS implementation. Further information on the proportion of patients who underwent ERAS-guided perioperative care between the MIE versus OE cohorts would better account for this possible confounder.

In conclusion, while Hayami et al.'s population-based cohort study comes with the benefit of more accurately emulating the population of those undergoing esophageal resection for esophageal and GEJ cancers without the eligibility constraints of randomized trials, there are limitations to the study that should make one more heavily scrutinize their claim that MIE confers an overall survival benefit compared with OE. And, although we (R.M.R.) have performed MIEs for 10 years and would favor the conclusions stated by Hayami et al., we do not feel that the current analysis justifies the conclusions as stated. Randomized control trials and large population-based studies accounting for hospital volume, centralization of care, and ERAS implementation are needed to truly ascertain an overall survival benefit of the MIE compared with the conventional OE.

DISCLOSURES Rishindra M. Reddy: Medtronic—Advisory Board Member; Atricure—Advisory Board Member; Genentech—Advisory Board Member; On Target Labs—Grant Funding; Intuitive Surgical—Consultant (Robotic Surgery Platform); Auris Health—Consultant (Robotic Surgery Platform).

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