

Contemporary issues in endoscopic resection for esophageal squamous cell cancer

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Provenance: This is a Guest Commentary commissioned by Section Editor Jianfei Shen, MD (Department of Thoracic Surgery, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China).

Comment on: Jin XF, Gai W, Chai TH, *et al.* Comparison of Endoscopic Resection and Minimally Invasive Esophagectomy in Patients With Early Esophageal Cancer. *J Clin Gastroenterol* 2016. [Epub ahead of print].

Submitted Nov 19, 2016. Accepted for publication Nov 24, 2016.

doi: 10.21037/atm.2016.12.66

View this article at: <http://dx.doi.org/10.21037/atm.2016.12.66>

Jin *et al.* (1) reported their experience with endoscopic resection (ER) versus minimally invasive esophagectomy (MIE) for 99 consecutively treated patients with early, clinically staged esophageal cancer (T0–T1b). In this retrospective analysis, 59 patients underwent ER and 40 had MIE. The majority of patients (85.9%) had squamous cell carcinoma (SCC). There were no statistically significant differences in the R0 resection rate (their primary endpoint) or in local recurrence rate (their secondary endpoint). Regarding adverse events (their tertiary endpoint), patients who underwent ER had a lower rate of minor complications compared to those who underwent MIE (11.8% *vs.* 32.5%, respectively, $P < 0.05$), although there was no significant difference in major complications. Patients who underwent ER also had shorter inpatient length of stay (LOS) compared to those who had MIE (average LOS of 6 *vs.* 19 days, respectively, $P < 0.001$). Thus, the authors concluded that for early stage esophageal cancer, mainly of SCC histology, ER offers several post-operative advantages while providing similar oncologic benefits to MIE.

The conclusions set forth by Jin *et al.* contribute to a growing body of evidence that ER is the preferred option for patients with early stage esophageal cancer, as endorsed by Western guidelines including the National Comprehensive Cancer Network (NCCN) (2). While much of the Western literature endorses ER techniques for esophageal adenocarcinoma, there is also evidence that supports ER for SCC, which has mainly been derived from Eastern groups. Shimizu *et al.* reported their experience in 2002 of 26 patients

with SCC limited to the mucosa or submucosa, showing no significant difference in 5-year overall survival (77.4% and 84.5% for ER and radical resection, respectively) (3). In addition, Katada *et al.* performed a multicenter retrospective cohort study consisting of 86 patients with SCC confined to the mucosa treated with ER alone who had a 5-year survival of 79.5% (4). Similarly, Yoshii *et al.* found a similar overall survival of 75.6% in their series of 44 patients with T1a/T1b SCC (5). Interestingly, in the study by Jin *et al.* which has the largest series, the observed 4-year overall survival for patients who underwent ER was 91.5%. This increase in long-term survival compared to previous studies may reflect optimization of ER techniques over time, resulting in improved outcomes.

However, there are some pertinent questions regarding the management of early stage esophageal cancer that are raised and highlighted by the results of this study. The first of these issues pertains to the risk of nodal disease related to depth of invasion. The authors report that among patients who underwent MIE, the number of patients with N1 disease was two. There were two patients with N0 and no patients with N2–3 disease. However, it is unclear as to the extent of invasion (M/SM level) that correlated with the pathologic nodal disease reported in this study. In fact, the nodal staging for the majority of the 40 patients who had MIE was not reported. It has been shown that patients with intraepithelial SCC (M1/M2) have almost no risk of nodal disease (6), whereas those with M3 and SM invasion (SM1–3) have rates of nodal disease ranging

from 0–10% and 50–55%, respectively (7,8). Thus, the rate of nodal disease in this study appears to be significantly lower than those reported in the literature. Further, the average number of lymph nodes (LN) examined from MIE procedures was not reported. While the optimal number of LN retrieval is controversial, it is recommended by the NCCN that a minimum of 15 LN should be examined. The surgical approach may influence nodal retrieval, although the authors do not include the number of Ivor-Lewis, McKeown or transhiatal MIE procedures. Therefore, complete pathologic staging including number of LN examined should be reported. In addition, the numbers and types of MIE procedures performed should be stated. These are limitations of the study, which highlight ongoing challenges in esophageal cancer treatment.

A second challenging issue that this study raises pertains to the accuracy of clinical T staging of early esophageal cancers. As the authors describe in the methods, patients underwent routine endoscopic ultrasound (EUS) prior to treatment. The accuracy of EUS in determining T stage has been reported to be 70–75% (9,10). While the pretreatment clinical T stage was reported, the pathologic stage was not. Therefore, the correlation between clinical and pathologic stages in this study is unknown. Complete T stage from ER specimens as well as surgical resection specimens is important as stage migration has been shown to influence long-term oncologic outcomes and therefore may play a role in local recurrence rates and survival (11). This could have important implications on the authors' conclusions in the current setting of limited clinical staging methods. Furthermore, while the authors excluded patients with lymphovascular invasion (LVI) or perineural invasion (PNI) (12), other high risk features including more aggressive grade (undifferentiated or poorly differentiated) and the presence of multifocality, have been associated with increased risk for nodal disease (13). It would be of interest to have investigated these other factors because these have also shown relevance to the choice of resection, i.e., ER or a radical procedure.

Lastly, the authors conclude that ER provided superior short-term benefits with respect to operative time, hospital LOS and complications. This has been reported by others and together with the similar oncologic outcomes to radical resection, supports the NCCN recommendation for ER in early stage esophageal cancers. It is interesting to note, however, that while the authors' experience is consistent with other studies showing improved short-term outcomes, the magnitude of these differences between ER and MIE

with respect to LOS is larger. The average LOS for MIE was reported to be 19 days (standard deviation =8 days). In contrast, others including our group have reported a median LOS of 7–8 days (14,15). The authors reported that the rates of major and minor complications were 6.7% and 32.5%, respectively, which is consistent with our own experience (14). Other factors may be contributing to the longer hospital LOS for MIE patients, including pre- and post-operative pathways (such as ERAS or Enhanced Recovery After Surgery) and differences with center case volume.

In conclusion, Jin *et al.* provide further evidence that ER provide equivalent oncologic outcomes and superior short-term outcomes to MIE for patients with early stage esophageal cancer. The limitations of this study highlight the persistent challenges in the management of esophageal cancer, including suboptimal staging for T and N disease. Although an increased understanding of tumor biology and newer techniques in endoscopic and minimally invasive surgery have improved short-term outcomes, there is still clinically significant morbidity associated with these procedures. Further refinement and peri-operative approaches to minimize morbidity for patients with esophageal cancer are warranted and continue to be the subject of active investigation.

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. Contemporary issues in endoscopic resection for esophageal squamous cell cancer. *Ann Transl Med* 2017;5(1):20. doi: 10.21037/atm.2016.12.66