The first randomised controlled trial on minimally invasive esophagectomy (MIE) and the ongoing quest for greater evidence

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J Thorac Dis 2012;4(5):459-461. DOI: 10.3978/j.issn.2072-1439.2012.08.10

Esophagectomy remains a key component in the multi modality treatment of cancer of the esophagus. The incidence of esophageal adenocarcinoma has increased worldwide (1,2) and so the impetus for researching more efficacious methods for treating this disease has been growing especially in the area of minimally invasive techniques. An international survey report in 2009 covering 41 countries found that 52% of responders preferred open transthoracic approach over transhiatal esophagectomy (THE) or minimally invasive esophagectomy (MIE). Transhiatal esophagectomy was preferred by 26% of responders and MIE, by 14% (3). Certainly, MIE is far from being adopted as common practice. The cost of MIE in terms of material and training is significant and therefore a clear benefit to patients must be established prior to its adoption.

Despite the length of time (>20 years) that has passed since the first MIE was performed by Cushieri *et al.* (4), the debate continues as to the safety, efficacy and oncologic benefit of MIE techniques (5-8). There have been a number of systematic reviews and meta-analyses (9-11) comparing open versus MIE with regards to short term post operative outcomes. These studies conclude that MIE is a safe alternative with some stating improved operative benefits such as fewer pulmonary complications, reduced blood loss and reduced hospital stay (12-18). All these studies however, concede that due to a lack of feasible evidence by way of prospective randomized controlled trials (RCT), no definitive statement of MIE 'superiority' over standard open techniques can be made.

The first RCT on MIE versus open techniques by Biere and colleagues (19) is a welcome addition for greater levels of evidence for MIE. The authors report reduced pulmonary infection rates (RR: 0.35, 95% CI: 0.16-0.78; P=0.005), reduced blood loss (P<0.001) and some improved short term quality of life factors. This study provides a significant contribution in the expanse of data that exists on MIE which until recently have only included case series, and retrospective case-control studies. In terms of the validity of the study, the protocols for the RCT appear sound with randomization, intention to treat, PICO (population, intervention, comparison and outcome) and bias elimination (exclusion and detection). The issue of open labeling (no blinding) of the intervention arms in the study may have a reduction in the quality of the findings. Understandably the ability to double blind these types of studies is not feasible. Furthermore, the outline of peri-operative procedures have not been thoroughly detailed such as: (I) anaesthetic protocol - pharmacological, ventilatory and transfusion; (II) post operative care - thromboprophylaxis, IV fluid therapy, pulmonary physiotherapy, non-invasive ventilation, speech pathology review and standardized post-operative medications such as prokinetics and proton pump inhibitors; and (III) pathologic analysis - tumor clearance, staging and tumor regression (neoadjuvant therapy).

The study in focus places great emphasis on pulmonary infection and whilst an important and frequent complication of esophagetomy, other studies have focused on other outcomes such as 30 day mortality, total morbidity and anastomotic leak. Other secondary outcomes should have included; 30 day morbidity, anastomotic stricture, delayed gastric emptying, recurrent laryngeal nerve injury and the global economic impact of each surgical procedure. Perhaps the focus on pulmonary complications could have been further detailed by describing not only infection rates but other pulmonary complications such as respiratory insufficiency, presence of acute respiratory distress syndrome (ARDS), incidence of effusions, incidence of chyle leaks and the need for bronchoscopy peri-operatively.

In terms of the author's primary outcome, previous meta-analytic data has been published with mixed results. Biere and colleagues in their meta-analysis have published data that suggests no difference with pulmonary outcomes (OR: 1.05, 95% CI: 042-2.66; P=0.91) (9). Other studies have shown

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Submitted Jul 24, 2012. Accepted for publication Aug 14, 2012.
Available at www.jthoracdis.com

ISSN: 2072-1439

similar outcomes (OR: 1.31, 95% CI: 0.52-3.31; P=0.73) (10) with only one meta-analysis showing statistically significant improved pulmonary outcomes (OR: 0.58, 95% CI: 0.35-0.98; P=0.04) (11). More recent retrospective comparative studies report favorable rates of pulmonary complications for MIE (10.64%) and open (34.61%) (20). Indeed, such variation in the data being published especially on short term outcomes reinforces the need for better levels of evidence. Another point of note is the method of statistical analysis that was used in the study and the basis for the nominated sample size (n=50) in each arm to ensure sufficient statistical power. Although the alpha value of 0.05 was used and is appropriate, this is applied to a margin of error for pulmonary infection only and not on pulmonary complications. The sample size for sufficient statistical power for major morbidity, survival, total morbidity and other similarly important outcomes may actually be larger.

In the selection of patients recruited in the study, it is worthwhile noting that the exclusion criteria was not as comprehensive as similar clinical studies and that only those patients with cervical and other malignancy were excluded. If the author's primary outcome was focused on pulmonary infection, perhaps other patient associated inclusion/exclusion criteria may have been of value. These would include patients with: poor pulmonary function parameters - PaO_2, $PaCO_2$, and FEV_1, patients with major organ disease - cirrhosis, congestive heart failure or evolving coronary arterial disease, and recent history of prior malignancy. Other disease associated inclusion/exclusion criteria could include patients with distal metastases including peritoneal carcinomatosis and other lymph nodes, and tumor invasion of adjacent structures.

It is encouraging that the authors included data on quality of life assessments with the use of the European Organization for Research and Treatment of Cancer (EORTC) questionnaires C30 and OES18 module measured 6 weeks post surgery. It would be of benefit when compared to existing data of a background population for each of the operative arms. For EORTC 30 Global quality of life, Derogar and colleagues published mean scores of 68 (SD: 22) at the 6 month mark for patients post esophagectomy and compared this with a score of 76 (SD: 23) for the background population (21). In comparison, Biere and colleagues report a Global health score of 51 (SD: 21) and 61 (SD: 18) for open and MIE, respectively. It would be of interest and value to compare the other quality of life factors over a longer term follow-up of 5 years and compare these to those acquired at the 6 week mark and whether these factors were stable, improved or deteriorated for each of the surgical arms. Data from long term studies of patients post esophagectomy conclude that health related quality of life (HRQL) recovers to a level comparable to that in the background population (20). There is value in investigating whether each operative arm in the study by Biere follows this trend.

The difficulty of conducting a prospective RCT is the necessity for access to high volume centers conducting both open and MIE techniques as well as the time frame required to accrue an adequate sample size. Moreover, previous studies were not able to be matched for all patient groups within the right TNM stage, type of cancer (squamous cell carcinoma *vs.* adenocarcinoma), location of the cancer, use of neoadjuvant therapy, operative technique, extent of lymphadenectomy, and intention to treat or palliate, all factors that clearly affect both short term mortality and long-term survival. This study has a high proportion of patients treated with neoadjuvant therapy and to date there is still no definite evidence on the effect of such therapies on patient morbidity and mortality. It would be of great value if comparisons can be made for tumor stage, type and location especially in focus to long-term oncological outcomes and HRQL. Data in a recent meta-analysis comparing oncological outcomes show no statistically significant difference in long-term survival and recurrence between MIE and open techniques (22).

While this study presents valid and valuable data for the future adoption of MIE, further analysis of the existing data within the study in focus and long term follow-up is what is required. It would be of great utility to provide evidence on the long term HRQL and oncological outcomes (survival, disease free survival, recurrence and morbidity) of these patients enrolled in the study with follow-up in 2, 3 and 5 year intervals.

If the evidence on MIE improves to the point of being adopted as first line, then the effect on the cost and length of surgical training will be significant. Due to the required numbers of procedures to be conducted per trainee to attain proficiency, an additional one to two years of extra training in MIE may be required.

Acknowledgements

Disclosure: The authors declare no conflict of interest.

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Cite this article as: Dantoc MM, Cox MR, Eslick GD. The first randomised controlled trial on minimally invasive esophagectomy (MIE) and the ongoing quest for greater evidence. J Thorac Dis 2012;4(5):459-461. DOI: 10.3978/j.issn.2072-1439.2012.08.10