Randomised trial, Minimally Invasive Oesophagectomy versus open oesophagectomy for patients with resectable oesophageal cancer

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J Thorac Dis 2012;4(5):462-464. DOI: 10.3978/j.issn.2072-1439.2012.08.12

In 1991, Dallemagne introduced the right thoracoscopic approach for oesophageal cancer with total lung block, thereby mimicking the conventional approach (1). Initial reports showed a high conversion rate to thoracotomy of 10% to 17% and a high respiratory morbidity of 17% to 42% (2,3). Searching for reduction of the conversion rate and the respiratory infection rate, Cuschieri *et al*. designed the thoracoscopic approach in prone decubitus position so that a total collapse of the lung was no longer necessary for dissecting the oesophagus and thereby possibly reducing the rate of respiratory infections (4).

After a feasibility period, the Minimally Invasive Oesophagectomy (MIO) approach in prone or lateral position is widely implemented and increasingly performed all over the world for patients with resectable oesophageal cancer (5,6).

Analysing the outcome of these patients, three meta-analyses comparing MIO and Open Oesophagectomy (OO) served as starting points in the quest for evidence based surgery.

We would like to comment the study performed in our Department by Biere *et al*. (7), identified 10 studies after a comprehensive search. Three comparative groups were created for analysis: (I) total MIO versus open transthoracic oesophagectomy (TTE); (II) thoracoscopy and laparotomy versus open thoracotomy and laparotomy; and (III) thoracotomy and laparoscopy versus open transhiatal esophagectomy (THE). Our conclusion was that with MIO a faster post-operative recovery and therefore a reduction in morbidity could be achieved. Furthermore, we expect a lower mortality rate following the implementation of MIO. It was accentuated that MIO had been only investigated in case control studies and hence bias may have been introduced simply by the pertaining study design.

The other two meta-analysis of Nagpal *et al*. (8), and of Sgourakis *et al*. (9) support the concept that MIO may benefit from shorter hospital stay, lower respiratory complications and total morbidity as compared to OO.

These three meta-analysis generated the initiative for further prospective comparative or randomized-controlled trials focusing on the short term and oncological impact of MIO. Following this quest, we went on to assess the reduction of pulmonary infections and improved quality of life associated with MIO. Therefore, we decided to start with a multicentre, randomized trial comparing open oesophagectomy with minimally invasive oesophagectomy in patients with resectable oesophageal cancer.

Before the design of this randomized TIME trial, we thought we had enough experience in MIO surgery, because we had started in 1995 practicing both the transhiatal and the thoracoscopic oesophagectomy for cancer al (10,11). We designed this multicentre, open-label, randomized controlled trial for comparison of MIO and OO in 2008 (12). The study was called the TIME trial (Traditional Invasive *vs*. Minimally invasive Esophagectomy). The TIME trial compares the traditional transthoracic oesophageal resection (right thoracotomy and laparotomy) with MIO (right thoracoscopy in prone and laparoscopy) followed by intrathoracic or cervical anastomosis. Patients with resectable intrathoracic and gastro-oesophageal junction type I Siewert were randomized for either (I) MIO in prone position or (II) OO followed by intrathoracic or cervical anastomosis. All patients were treated by neoadjuvant treatment according to the center protocol (13). Our hypothesis was that patients undergoing MIO will have less morbidity, a shorter duration of the intensive care unit (ICU) admission and a better quality of life than following the traditional approach (OO).

The primary endpoint of the study concerned the respiratory complications, especially the postoperative bronchopneumonia confirmed by thorax X-ray or CT scan, and positive sputum culture.

Secondary endpoints were operation-related events,

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Submitted Jul 20, 2012. Accepted for publication Aug 21, 2012.
Available at www.jthoracdis.com

ISSN: 2072-1439

complications, ICU and hospital stay, quality of life as determined by questionnaires (SF-36, EORTC C30 and OES18), and the quality of specimen resected (length of specimen, number and location of lymph nodes resected, and circumferential resection margins). Also, hospital mortality and readmissions were recorded. Furthermore, survival rates will be analysed.

Power of the study was calculated according to the published literature and our experience at the VU University medical centre. We took into consideration that a difference in respiratory infections of 28% can be found between the traditional open procedure (57%) and the MIO procedure (29%) (14). To demonstrate this difference of 28%, using a alpha =0.05 and beta =0.80, two groups of 48 patients were required. Estimating that approximately 20% of the eligible patients would not undergo the allocated intervention (e.g., metastases during neoadjuvant therapy, irresectable tumors), approximately 60 patients per group were asked to participate.

Preoperative programs-including physiotherapy, psychological assistance and adequate nutritional support-were used in all patients to enhance their recovery.

Subsequently, the trial (registered with the Netherlands Trial Register, NTR TC 2,452) was carried out. Between June 2009 and March 2011, 144 patients became eligible for randomisation. Of these 29 were excluded for different reasons. A total of 115 patients underwent randomisation in five European centres: VUmc University Medical Centre and the Academic Medical Center both in Amsterdam, the Netherlands; the Canisius Willehmina Ziekenhuis in Nijmegen, the Netherlands; Hospital Universitari dr. Josep Trueta in Girona, Spain; and I.R.R.C.S. Policlinico San Donato in Milan, Italy. Finally 56 patients were analyzed in the open group and 59 in the MIO group.

Baseline demographic and clinical characteristics of the intention-to-treat population was not different between the two groups.

The pulmonary infection rate within the first two weeks was 29% (16 patients) in the OO group and 9% (5 patients) in the MIO group, P=0.005. The overall in hospital incidence of pulmonary infections was 34% (19 patients) in the OO group and 12% (7 patients) in the MIO group, P=0.005.

Explanation for this lower incidence of pulmonary infections found in the MIO group could be explained by several factors, which taken together all might reduce the development of pneumonia. We held the following suppositions. Use of the prone position in comparison with the open thoracotomy in lateral position could be one of the underlying factors for prevention of atelectasis and pneumonia. In contrast with the lateral decubitus position, in prone position the mediastinum hangs in its usual midposition and the chest and abdomen are free of compression. A second advantage may be the avoidance of a total collapse of the lung during MIO in prone position. For the thoracoscopy in prone, patients receive a single tube intubation and the right lung is only partially collapsed by gravity and by the employed intrathoracic insufflation of CO_2 to a maximum pressure of 8 mmHg. This permits an optimal visualization of the mediastinum with preserved ventilation and oxygenation in contrast to the required one-lung ventilation for OO. Moreover, absence of one-lung ventilation reduces arterio-venous shunt with better preserved oxygenation (6). Another important underlying factor for the higher rate of pulmonary infection in OO may be the thoracotomy wound itself. Not only the development of atelectasis as result of the totally collapsed lung plays a role but also the post-operative discomfort, produced by the wound, causes an increased rate of pulmonary infections. All these factors together could explain the reduced rate of pulmonary infection found in the MIO group in comparison with the OO group. In addition, MIO preserved the quality of life better than the OO. After 6 weeks all the questionnaires, the SF 36, the EORTC C30 and the specific OES 18 questionnaire with exception of the mental component were better in the MIO than in the OO group.

Hospital stay was significantly shorter in the MIO group (14 versus 11 days, P=0.044). The short hospital stay in the MIO group reflects a faster post-operative recovery. Other postoperative data including pathology parameters, major postoperative complications (anastomotic leakage, 7% in the OO and 12% in the MIO, P=0.390) and mortality (1.8% versus 3.4%) were not significantly different. Important are the pathology parameters, the total lymph nodes retrieved, resection margins, pStage and the numbers of no residual tumour or lymph node metastasis, indicating the safety of the resection were equal between both groups. Interesting was the different rate for vocal cord paralysis, 14% in the OO group and only 2% in the MIO, P=0.012. Pneumatic dissection by CO_2 from thoracic cavity into the neck can simplify the dissection in the neck and reduce the recurrent nerve lesions.

In conclusion, this randomized trial comparing open oesophagectomy for cancer with minimally invasive oesophagectomy shows that MIO results in a lower incidence of pulmonary infections, a shorter hospital stay, and a better short term quality of life without compromise of the quality of the resected specimen.

Acknowledgements

Disclosure: The authors declare no conflict of interest.

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Cite this article as: Cuesta MA, Biere SS, van Berge Henegouwen MI, van der Peet DL. Randomised trial, Minimally Invasive Oesophagectomy versus open oesophagectomy for patients with resectable oesophageal cancer. J Thorac Dis 2012;4(5):462-464. DOI: 10.3978/j.issn.2072-1439.2012.08.12