



Hybrid minimally invasive esophagectomy for esophageal cancer: less is more

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In a recently published multi-center randomized controlled trial (*New England Journal of Medicine* 2019;380:152-162) Christophe Mariette and colleagues compared open transthoracic esophagectomy to hybrid esophagectomy (open thoracic phase, laparoscopic abdominal phase) for patients with resectable cancer of the middle or lower third of the esophagus (MIRO trial) (1). The primary end point of this trial was the occurrence of intraoperative or postoperative complication of grade II or higher according to the modified Clavien-Dindo classification (MCD) (2) within 30 days. Patients who underwent a hybrid esophagectomy experienced a significantly reduced rate of intraoperative and postoperative major complications (36%) compared to open transthoracic esophagectomy (64%) as treatment for esophageal cancer (1). Postoperative complications consisted mainly of pulmonary complications; 18% in the hybrid procedure and 30% in the open-procedure group. However, the difference in postoperative complications did not result in a difference in median overall hospital stay between both groups.

This is the third randomized controlled trial for patients who underwent esophagectomy which compared a minimally invasive approach to open esophagectomy (3,4). In the TIME-trial, totally minimally invasive esophagectomy (MIE; thoracoscopic thoracic phase and laparoscopic abdominal phase) was compared to open

transthoracic esophagectomy. The primary endpoint in this trial was the occurrence of postoperative pulmonary infections within the first 2 weeks postoperatively. MIE resulted in a lower incidence of pulmonary infections (9%) compared to open transthoracic esophagectomy (29%) with better quality of life (3).

In the ROBOT-trial, robot assisted MIE (RAMIE; robot assisted thoracoscopic thoracic phase, laparoscopic abdominal phase) was compared to the open transthoracic esophagectomy (4). The primary endpoint was similar to the MIRO trial; the occurrence of postoperative complication of grade II or higher according to the MCD (2). RAMIE was associated with a significant lower percentage of overall postoperative, pulmonary and cardiac complications compared to open transthoracic esophagectomy with lower postoperative pain and better functional recovery and short-term quality of life (4).

The reduction in postoperative complications was in all trials mainly attributable to a reduction in postoperative pulmonary complications (1,3,4). It was hypothesized that reducing surgical trauma by a less invasive surgical approach resulted in better postoperative outcomes for esophagectomy. With similar endpoints and postoperative results, the 3 aforementioned trials might look really similar. However, there are also conceptual differences between the hybrid approach and a totally minimally invasive approach.

The outcome of the MIRO trial is therefore difficult to explain and several points of concern can be raised.

Short-term complications

Both in the TIME trial and the ROBOT trial, a totally minimally invasive approach was compared to an open transthoracic esophagectomy, whereas in the MIRO trial a hybrid esophagectomy, with an open thoracic phase using thoracotomy, was compared to the open transthoracic esophagectomy (1,3,4). With only the abdominal phase performed laparoscopically in the MIRO trial, resulting in such favorable postoperative results, one might argue that the reduction in postoperative complications was mainly attributable to the minimally invasive abdominal phase of the operation, rather than the thoracic phase of the operation. However, conflicting data are reported concerning the value of laparoscopy as a sole instrument to reduce pulmonary complications in upper GI surgery.

Data from randomized controlled trials on a total gastrectomy, give further information on the impact of a laparoscopic versus an open abdominal approach. A (laparoscopic) gastrectomy is comparable to the abdominal phase of an esophagectomy (5). However, various randomized controlled trials on laparoscopic versus open gastrectomy show no effect on postoperative (pulmonary) complications (6,7). The mechanism of reducing the complications within the hybrid MIRO trial to the same extend as with a full minimally invasive procedure is unknown and difficult to understand in light of the results of aforementioned gastric surgery studies.

There is convincing literature showing that the thoracic phase is the most important predictor of postoperative outcomes after esophagectomy. The HIVEX trial compared open transthoracic esophagectomy to open abdominal approach transhiatal esophagectomy for patients with resectable esophageal cancer (8). The incidence of postoperative pulmonary complications was much higher after a transthoracic approach (57%) compared to a transhiatal approach (27%) (8).

Oncological outcome

Even though insignificant, the MIRO trial suggests a better survival after a hybrid approach, whereas both TIME and ROBOT trial show equal survival after open and total MIE (1,3,4). However, there was a disbalance in lymph node metastasis in the hybrid group considering postoperative

pathological nodal negative disease (pN0 =62%) compared to the open group (pN0 =52%). This difference in postoperative pathological staging between the groups is most probably responsible for the better survival in the hybrid group 3 years postoperatively. The last patient was included in the MIRO trial in April 2012 (1). This means that all patients had at the time of acceptance of this article a complete follow up of 5 years. However, in this article, only 3-year survival rates were shown. The 5-year follow up data are essential and might result in a significant difference in overall survival for this secondary endpoint. Therefore, it would be very important to report the multivariable analysis considering survival after the completed follow up of 5 years.

In the appendix, the distribution of centers which included patients in the MIRO trial was pointed out. Approximately half of all patients were included in the main center in Lille. There are 8 out of 13 centers which included less than 10 patients in the MIRO trial. Centralization of esophageal surgery leads to better outcomes (9). The annual case volume of esophagectomies in the centers that included in the MIRO trial is unclear. More importantly, the distribution of open versus hybrid procedures per center is unclear. This may be a key point for the explanation of the results of this trial. Less experienced centers might have included significantly more patients in the open groups and negatively influence overall survival in the open group.

Long-term outcome

At long term, post-thoracotomy-related pain is well known and widely reported and up to 50 % of patients describe post-thoracotomy pain 1 year after the procedure, probably due to intercostal nerve damage and myofascial pain (10-12). Mid-term results of the TIME trial showed that a total minimally invasive approach (thoracoscopy and laparoscopy) is associated with better quality of life and less pain after 1 year, which is an important advantage of the minimally invasive thoracic phase of the operation (12).

In conclusion, the MIRO trial is the third randomized controlled trial for patients with esophageal cancer that shows that reducing surgical morbidity results in better postoperative outcomes. The question remains what is the best approach to perform an esophagectomy; hybrid or totally minimally invasive?

A fully minimally invasive approach will most probably show better postoperative results, especially avoiding the thoracotomy and associated problems (10,12). However, current evidence comparing these 2 approaches is limited

and no randomized studies are conducted yet. Currently, 1 randomized trial (ROMIO trial, ISRCTN59036820) is underway comparing open, hybrid and totally MIE (13). The ROMIO trial might answer the question which method is superior; the hybrid esophagectomy or totally MIE.

A hybrid esophagectomy might be a first step for surgeons who were trained in open esophagectomy aiming to switch to totally MIE. When proficiency is obtained in the laparoscopic abdominal phase, surgeons should add the thoracoscopic phase of the operation. However, proctoring remains pivotal to learn new surgical techniques in order to pass the learning curve faster without compromising postoperative and oncological results (14).

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Footnote

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

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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