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Minimally Invasive Esophagectomy for Achieving R0

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ABSTRACT

Background: Minimally invasive esophagectomy (MIE) is becoming increasing popular. Since it was introduced, there has been debate about its safety and efficacy when compared with open esophagectomies (OE). We sought to compare the oncologic outcomes of MIE and OE in this study specifically with regards to margin status and nodal retrieval.

Methods: Ninety-three patients that underwent MIE (76/93) or OE (17/93) for esophageal cancer at out institution between January 2013 and September 2018 were retrospectively reviewed. Histological type, pathological tumor grading, clinical tumor staging (cTNM), pathological tumor staging (pTNM), post-neoadjuvant tumor staging (ypTNM), and lymph node retrieval were obtained and compared.

Results: The results show a statistically significant improvement in resection margins (R0) in the MIE group when compared with the OE group. Other oncologic parameters including clinical staging, pathologic staging, tumor grade, neoadjuvant therapy (NAT), and nodal retrieval were not statistically significantly different between the open and MIE groups.

Conclusion: The improvement in short-term surgical outcomes in MIE is well established. This study demonstrates that MIE can have superior surgical oncologic outcomes compared to OE, this was specifically an improved R0 margin rate with MIE compared to OE. These results further support the use of MIE in the treatment of esophageal cancer.

Key Words: Esophageal Cancer, Open Esophagectomy, Minimally Invasive Esophagectomy, Robotic-assisted Esophagectomy, Oncologic Outcome.

INTRODUCTION

With an incidence rate of 4.5/100,000 and an overall 5-year survival rate of 20%, esophageal cancer continues to be one of the leading causes of cancer morbidity and mortality in the United States.[1] The American Cancer Society estimates 18,440 new cases and 16,170 esophageal cancer deaths in 2020. Esophageal cancer accounts for 1% of all cancers diagnosed in the United States and has a male preponderance.[1] The most common histological type is Squamous Cell Carcinoma (SCC) worldwide and Adenocarcinoma in the United States. Obesity and Barrett's esophagus are thought to be the predisposing factors in the USA. A decrease in smoking has led to a drop in Squamous Cell cancer.[2] Over the last five decades, the overall survival rate for esophageal cancer patients has improved from 5% to 20% with localized cancer cases having a 5-year survival rate of up to 47%.[1]

As minimally invasive esophagectomy (MIE) is becoming increasing popular, it is important to establish the difference in oncologic and surgical outcomes between MIE and open esophagectomies (OE) to allow for a better evidence-based choice of approach for each patient. Data assessing the learning curves, oncologic outcomes, and surgical outcomes of MIE vs OE favor MIE after the learning curve is surpassed. The aim of this study is to further explore the differences in oncologic outcomes between MIE & OE.

Patients with esophageal cancer are often quite sick and have coexistent medical conditions. The use of MIE techniques can result in decreased pain and possibly a quicker recovery.[3,4] We hypothesize that MIE may have the additional benefit of improved oncologic measures. We sought to compare the oncologic outcomes of MIE vs OE of esophageal cancer patients undergoing esophagectomies with curative intent at our institution.

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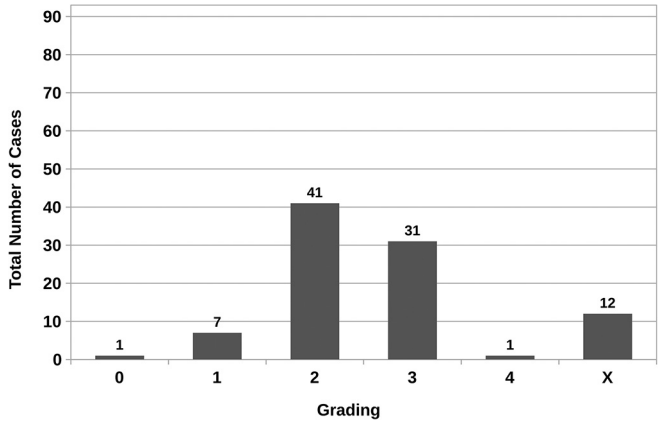

Figure 1. Distribution of Tumor Grading.

MATERIALS AND METHODS

The study includes 93 patients who underwent esophagectomies for esophageal cancer with curative intent between January 2013 and September 2018 at Methodist Health System. The types of esophagectomies were grouped into MIE (76/93) and OE (17/93). Patients selected for OE were those with multiple previous abdominal surgeries and/or inability to tolerate laparoscopy. The MIE group includes laparoscopic transhiatal esophagectomy and robotic assisted transhiatal esophagectomy (RAMIE). All esophagectomies were transhiatal and performed by one surgeon.

The following is a description of the transhiatal approach performed. An OE is started with an upper midline incision. Ports are placed and the robot is docked (for robotic) with the patient in steep reverse Trendelenburg. The usual dissection of the stomach is performed, although the senior author prefers to approach the greater curvature dissection first prior to the Pars Flaccida approach. The esophagus is encircled at the diaphragm and the left gastric vessels are taken with the stapler. Transhiatal dissection is then performed up to the mid chest. At this point, if this were the laparoscopic or robotic approach, all trocars are removed, the liver retractor is removed, and a limited upper midline incision is made. The co-surgeon proceeds with a left anterior sternocleidomastoid incision and the transhiatal dissection is then completed until the esophagus is completely free. A wide Kocher maneuver is then performed followed by a pyloroplasty in the manner of Heineke-Mikulicz. The esophagus is transected in the neck. The proximal stomach is stapled and the staple line is oversewed. The esophagogastric anastomosis is created using a stapled technique with oversewing of the enterotomies. Feeding jejunostomy is placed in all patients.

The study protocol was approved by the hospital's institutional review board and the need for informed consent from patients was waived due to the retrospective nature of the study.

The pre-operative workup for patients included a computed tomography scan and esophagogastroduodenoscopy. Positron emission tomography and upper gastrointestinal series were obtained in selected patients. The clinical (cTNM), pathologic (pTNM), and post-neoadjuvant (ypTNM) staging of both squamous cell carcinoma and adenocarcinoma was based on the American Joint Committee on Cancer 8th edition guidelines for staging cancers of the esophagus and esophagogastric junction.

The variables evaluated in this study were resection margin (R0), tumor grade, clinical tumor staging, pathologic tumor staging, neoadjuvant therapy, post neoadjuvant tumor staging, and lymph node retrieval. Surgical variables evaluated were length of stay (LOS), estimated blood loss (EBL), complications classified using the Clavien-Dindo score, and mortality rates.

RESULTS

There were 82 male patients (82/93 88.2%) and 11 female patients (11/93 11.8%) with a mean age of 63 years old (39 – 87 p = 0.64). 76 patients (81.7%) underwent MIE and 17 (18.3%) underwent OE. Of the MIE group, 53 patients (69.7%) underwent RAMIE and 23 (30.3%) underwent laparoscopic transhiatal esophagectomy.

Seventy-three patients (78.5%) received NAT and 20 (21.5%) proceeded with surgery without NAT. Sixty

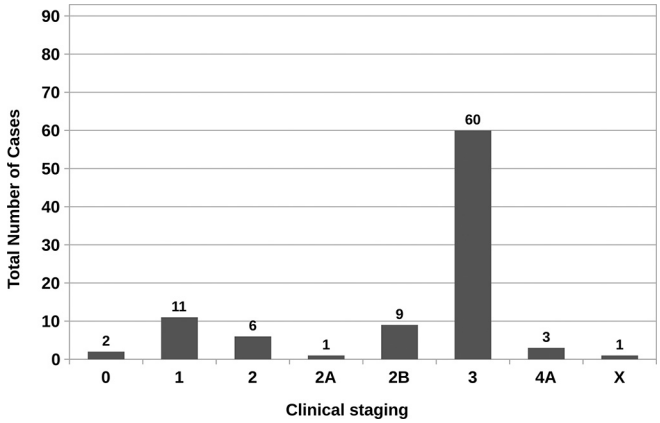

Figure 2. Distribution of Clinical Tumor Staging.

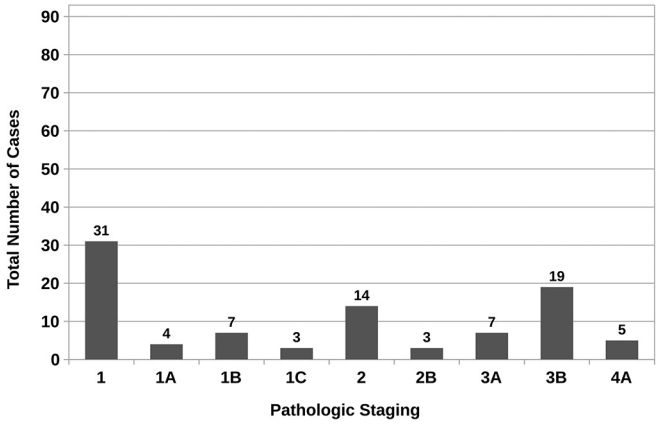

Figure 3. Distribution of Pathologic Tumor Staging.

patients (78.9%) received NAT in the MIE group and 13 patients (76.5%) received NAT in the OE group (p = 0.822). No statistically significant difference was appreciated in the histological type (adenocarcinoma vs SCC) between the MIE and OE groups (p = 0.73).

Significantly improved R0 was observed in the MIE group when compared to the OE group (92% vs 70.6%, p = 0.013). The most commonly positive margin was the radial margin in those that were R1 (45%). The average number of lymph nodes retrieved in MIE (13.43, range 2 – 30) and OE (12.29, range 3 – 26) was not significantly different between the two groups (p = 0.529). There was no statistical difference in the tumor grade (p = 0.12) (**Figure 1**), *c*TNM (p = 0.90) (**Figure 2**), or pTNM (p = 0.91) (**Figure 3**) between the MIE and OE groups. Tables 1 & 2 summarize the above-mentioned results.

In terms of operative safety profiles, the only statistically significant difference (p-value: 0.00008) was the average EBL between the MIE and OE groups where the MIE group had an average EBL of 220.9 mL (range 75 – 700) and the OE group had an average EBL of 618.8 mL (range 100 – 5000). The complications rate in the MIE group was 67.1% (51/76) and 88.2% (15/17) in the OE group with most complications being a Clavien-Dindo 1 or 2 (70.6% and 60.0% respectively). The complication rate in the R1 group was 45.5% (5/11) and 74.4% (61/82) in the R0 group with most complications being a Clavien-Dindo 1 or 2 (100% and 65.6% respectively). There were 2 mortalities in the MIE group and 1 mortality in the OE group. The mortalities occurred on postoperative days 4, 11, and 27 and were due to the patients' family wishes to withdraw care after postoperative complications. All mortalities were from the R0 group. There was no statistically significant difference between other surgical parameters. Table 3 summarizes the surgical outcomes of the MIE and OE groups and Table 4 summarizes the surgical outcomes of the R1 and R0 groups.

DISCUSSION

This study found MIE to have significantly improved R0 when compared to OE, while maintaining non-inferiority in other oncologic measures. While some studies have reported statistically significant improvement in lymph node harvest in MIE when compared with OE,[5–7] no studies have reported statistically significant improvement in R0 in MIE when compared with OE.[8–10] This would suggest that MIE had superior oncologic outcomes compared

Table 1.
Summary of Results and Respective *p*-Values

Variable	Open (n = 17)	MIE (n = 76)	*p* Value
Pathologic grade			0.128
0	0 (0%)	13 (17%)	
1	0 (0%)	7 (9%)	
2	8 (47%)	33 (43%)	
3	9 (53%)	22 (29%)	
4	0 (0%)	1 (1%)	
Clinical staging			0.902
X	1 (6%)	0 (0%)	
0	0 (0%)	2 (3%)	
1	3 (18%)	8 (11%)	
2	0 (0%)	6 (8%)	
2A	0 (0%)	1 (1%)	
2B	1 (6%)	8 (11%)	
3	12 (71%)	47 (63%)	
4A	0 (0%)	3 (4%)	
Pathologic staging			0.913
1	5 (29%)	26 (34%)	
1A	0 (0%)	4 (5%)	
1B	0 (0%)	7 (9%)	
1C	1 (6%)	2 (3%)	
2	4 (24%)	10 (13%)	
2B	1 (6%)	2 (3%)	
3A	1 (6%)	6 (8%)	
3B	4 (24%)	15 (20%)	
4A	1 (6%)	4 (5%)	
R0 Resection	12 (70%)	70 (92%)	0.013
Lymph node retrieval	12.29	13.43	0.529

MIE, minimally invasive esophagectomy.

Table 2.
Summary of R1 Margin Location Distribution

R1 Margin	Open (n = 5)	MIE (n = 6)	Total (n = 11)
Radial	1 (20%)	4 (66%)	5 (45%)
Distal	2 (40%)	1 (17%)	3 (27%)
Radial & Distal	1 (20%)	1 (17%)	2 (18%)
Radial, Distal, & Proximal	1 (20%)	0 (0%)	1 (9%)

MIE, minimally invasive esophagectomy.

to OE. The differences in surgical outcomes between the MIE, OE, R1, and R0 groups were statistically insignificant except for the average EBLs of the MIE and OE groups where the OE group had a higher average EBL. No statistically significant difference in mortality rates was noted.

The surgical management of esophageal cancer is inherently fraught with dangers as these patients tend to be quite sick and have other comorbidities on presentation. The mainstay of treatment of esophageal cancer is esophageal resection. The advent of neoadjuvant therapy has significantly improved oncologic long-term outcomes for patients. The well-established Ivor Lewis esophagectomy technique was first described in 1946.[11] Since then, surgical techniques have evolved most notably whenCuscheiri et al. first described the minimally invasive esophagectomy technique in 1992.[12] Eleven years later, the first robotic assisted minimally invasive esophagectomy was performed in 2003 by Kernstine et al.[13]

Ever since the introduction of MIE and RAMIE, there has been debate about their safety and efficacy. On the one hand, the incredible magnification enabled by RAMIE coupled with a stable 3D view offers surgeons unprecedented clarity and has enabled the identification of new previously undescribed structures such as the "meso-esophagus", a distinct fascial layer surrounding the esophageal blood supply and lymphatics.[14,15] Additionally, the precision and accuracy of RAMIE decreases injuries to the vagal branches of the right and left main bronchus which improves postoperative pulmonary outcomes.[16,17]

On the other hand, the steep learning curve associated with MIE and RAMIE continues to be a source of concern as duration of surgery, EBL, and oncologic outcomes appear to be negatively affected during the initial learning phase.[18–20] However, once the learning curve is surpassed, surgical outcomes are consistently better in MIE and RAMIE when compared with OE.[21,22] Oncologic outcomes appear to be at least equivalent with a few studies showing improved oncologic outcomes with MIE and RAMIE.[23]

The ROBOT trial reported a lower percentage of overall surgery-related and cardiopulmonary complications in the RAMIE group with lower postoperative pain, better short-

Table 3.
Summary of the Surgical Outcomes of Both Study Groups

Surgical Parameter	MIE (n = 76)	OE (n = 17)	*p*-Value
Average LOS	10.8 days (range 6 – 48)	13.4 days (range 4 – 31)	0.134
Average EBL	220.9 mL (range 75 – 700)	618.8 mL (range 100 – 5000)	**0.00008**
Mortality	2 patients*	1 patient*	0.492
Complications	51 (67.1%)	15 (88.2%)	
Clavien-Dindo Score			0.247
1	21 (41.2%)	2 (13.2%)	
2	15 (29.4%)	2 (3.9%)	
3a	2 (3.9%)	1 (6.7%)	
3b	3 (5.9%)	1 (6.7%)	
4a	8 (15.7%)	3 (20.0%)	
4b	0 (0%)	0 (0%)	
5	2 (3.9%)	1 (6.7%)	

*Mortalities were due to patients' family wishes to withdraw care after postoperative complications.MIE, minimally invasive esophagectomy; OE, open esophagectomy; LOS, length of stay; EBL, estimated blood loss.

Table 4.
Summary of the Surgical Outcomes of the R1 and R0 Groups

Surgical Parameter	R1 (n = 11)	R0 (n = 82)	*p*-Value
Average LOS	13 days (range 8 – 31)	11 days (4 – 48)	0.349
Average EBL	590.9 mL (range 100 – 3500)	316.5 (75 – 5000)	0.178
Mortality	0 patients	3 patients*	0.519
Complications	5 (45.5%)	61 (74.4%)	
Clavien-Dindo Score			0.435
1	2 (40%)	21 (34.4%)	
2	3 (60%)	19 (31.1%)	
3a	0 (0%)	3 (4.9%)	
3b	0 (0%)	4 (6.6%)	
4a	0 (0%)	11 (18.0%)	
4b	0 (0%)	0 (0%)	
5	0 (0%)	3 (5.0%)	

*Mortalities were due to patients' family wishes to withdraw care after postoperative complications.
LOS, length of stay; EBL, estimated blood loss.

term quality of life, and better short-term postoperative functional recovery without compromising oncologic outcomes when compared with OE.[7] Wang et al. performed a retrospective pair matched comparative study between MIE and OE for esophageal SCC. A total of 97 patients undergoing MIE were compared with patients undergoing OE during the same period. Significantly less bleeding and shorter LOS were observed in MIE as compared to OE, but resection margins and tumor stages were similar.[24] The uncompromised oncologic outcomes with MIE were confirmed in this study while simultaneously demonstrating improved resection margins. These results are most likely due to the increased magnification and precision offered by MIE.

The current literature shows MIE to be at least equivalent to OE in terms of oncologic outcomes and superior in terms of surgical outcomes. This study is the first of its kind to show an improved R0 rate with MIE compared to OE. This would suggest that MIE is better than OE with regards to surgical oncologic outcomes. The results of this study reinforce the currently reported MIE oncologic outcomes while showing improved resection margins. Consequently, this study supports the use of MIE in the treatment of esophageal cancer. It is important to note that learning curves must be considered as they can significantly affect surgical and oncologic outcomes. Having said that, MIE continues to have at least equivalent or improved surgical and oncologic outcomes as compared to OE when the learning curve is surpassed, and technique mastery is achieved.

There are a few limitations to this study. First, this is a single institution, retrospective, non-randomized study looking at the practice of one surgeon. The sample size is limited with disproportionate MIE versus OE groups and disproportionate pathologic stage groups making it difficult to make a generalized statement. A randomized control trial with a larger sample size is recommended for future studies.

CONCLUSION

The improvement in short-term surgical outcomes in MIE is well established. The current literature shows oncologic outcomes to be mostly equivalent between MIE and OE. This study shows that MIE appears to have significantly improved resection margins when compared with OE. These results support the use of MIE in the treatment of esophageal cancer.

References:

1. American Cancer Society. Key Statistics for Esophageal Cancer. Available at: https://www.cancer.org/cancer/esophagus-cancer/about/key-statistics.html. Accessed June 7, 2020.

2. Devesa SS, Blot WJ, Fraumeni Jr JF. Changing patterns in the incidence of esophageal and gastric carcinoma in the United States. *Cancer*.1998 Nov 15;83(10):2049-2053.

3. Berlth F, Plum PS, Chon SH, Gutschow CA, Bollschweiler E, Hölscher AH. Total minimally invasive esophagectomy for esophageal adenocarcinoma reduces postoperative pain and pneumonia compared to hybrid esophagectomy. *Surg Endosc*. 2018 Dec 1;32(12):4957-4965.

4. Khithani A, Jay J, Galanopoulos C, Curtis D, Vo A, Jeyarajah DR. Zero leaks with minimally invasive esophagectomy: a team-based approach. *JSLS*. 2009 Oct;13(4):542.

5. Yerokun BA, Sun Z, Yang CF, et al. Minimally invasive versus open esophagectomy for esophageal cancer: a population-based analysis. *Ann Thorc Surg*. 2016 Aug 1;102(2):416-423.

6. Berger AC, Bloomenthal A, Weksler B, et al. Oncologic efficacy is not compromised, and may be improved with minimally invasive esophagectomy. *J Am Coll Surg*. 2011 Apr 1;212(4):560-566.

7. van der Sluis PC, van der Horst S, May AM, et al. Robot-assisted minimally invasive thoracolaparoscopic esophagectomy versus open transthoracic esophagectomy for resectable esophageal cancer: a randomized controlled trial. *Ann Surg*. 2019 Apr 1;269(4):621-630.

8. Singh RK, Pham TH, Diggs BS, Perkins S, Hunter JG. Minimally invasive esophagectomy provides equivalent oncologic outcomes to open esophagectomy for locally advanced (stage II or III) esophageal carcinoma. *Arch Surg*. 2011 Jun 1;-146(6):711-714.

9. Tapias LF, Mathisen DJ, Wright CD, et al. Outcomes with open and minimally invasive Ivor Lewis esophagectomy after neoadjuvant therapy. *Annals Thorac Surg*. 2016 Mar 1;101-(3):1097-1103.

10. Biere SS, van Berge Henegouwen MI, Maas KW, et al. Minimally invasive versus open oesophagectomy for patients with oesophageal cancer: a multicentre, open-label, randomised controlled trial. *Lancet*. 2012 May 19;379(9829):1887-1892.

11. Lewis I. The surgical treatment of carcinoma of the oesophagus with special reference to a new operation for growths of the middle third. *Br J Surg*. 1946 Jul;34(133):18–31.

12. Cuschieri A, Shimi S, Banting S. Endoscopic oesophagectomy through a right thoracoscopic approach. *Journal of the Royal College of Surgeons of Edinburgh*. 1992 Feb;37(1):7–11.

13. Kernstine KH, DeArmond DT, Karimi M, Van Natta TL, Campos JC. The robotic, 2-stage, 3-field esophagolymphadenectomy. *J Thorac Cardiovasc Surg*. 2004;127(6):1847-1849.

14. Cuesta MA, Weijs TJ, Bleys RL, et al. A new concept of the anatomy of the thoracic oesophagus: the meso-oesophagus. Observational study during thoracoscopic esophagectomy. *Surg Endosc*. 2015 Sep 1;29(9):2576-2582.

15. Cuesta MA, van der Wielen N, Weijs TJ, et al. Surgical anatomy of the supracarinal esophagus based on a minimally invasive approach: vascular and nervous anatomy and technical steps to resection and lymphadenectomy. *Surg Endosc*. 2017 Apr 1;31(4):1863-1870.

16. Weijs TJ, Ruurda JP, Luyer MD, et al. Preserving the pulmonary vagus nerve branches during thoracoscopic esophagectomy. *Surg Endosc*. 2016 Sep 1;30(9):3816-3822.

17. Weijs TJ, Ruurda JP, Luyer MD, Nieuwenhuijzen GA, Van Hillegersberg R, Bleys RL. Topography and extent of pulmonary vagus nerve supply with respect to transthoracic oesophagectomy. *J Anat*. 2015 Oct;227(4):431-439.

18. van Workum F, Stenstra MH, Berkelmans GH, et al. Learning curve and associated morbidity of minimally invasive esophagectomy: a retrospective multicenter study. *Ann Surg*. 2019 Jan 1;269-(1):88–94.

19. Kingma BF, Ruurda JP. Comment on: "Early outcomes of robot-assisted versus thoracoscopic-assisted Ivor Lewis esophagectomy for esophageal cancer: a propensity score-matched study". *Ann Surg Onc*. 2019 May 15;26(5):1178-1181.

20. Sihag S, Kosinski AS, Gaissert HA, Wright CD, Schipper PH. Minimally invasive versus open esophagectomy for esophageal cancer: a comparison of early surgical outcomes from the Society of Thoracic Surgeons National Database. *Ann of Thor Surg*. 2016 Apr 1;101(4):1281-1289.

21. Straatman J, Van Der Wielen N, Cuesta MA, et al. Minimally invasive versus open esophageal resection: three-year follow-up of the previously reported randomized controlled trial the TIME trial. *Ann Surg*. 2017 Aug 1;266(2):232-236.

22. Mariette C, Meunier B, Pezet D, et al. Hybrid minimally invasive versus open oesophagectomy for patients with oesophageal cancer: a multicenter, open-label, randomized phase III controlled trial, MIRO trial. *J* Clin Onc.

23. van Boxel GI, Kingma BF, Voskens FJ, Ruurda JP, van Hillegersberg R. Robotic-assisted minimally invasive esophagectomy: past, present and future. *J Thor Dis*. 2020 Feb; 12(2):54.

24. Wang W, Zhou Y, Feng J, Mei Y. Oncological and surgical outcomes of minimally invasive versus open esophagectomy for esophageal squamous cell carcinoma: a matched-pair comparative study. *Int J Clin Exp Med*. 2015;8(9):15983.