ORIGINAL RESEARCH

Efficacy and Perioperative Safety of Robot-Assisted Minimally Invasive Esophagectomy for Esophageal Cancer

Mingquan Ma, MM; Peng Ren, MM; Haitong Wang, MM; Hongdian Zhang, MM; Lei Gong, MM; Yufeng Qiao, MM; Xiangming Liu, MM; Peng Tang, MM

ABSTRACT

Background • Esophageal cancer (EC) remains a significant global health concern. Minimally invasive surgical techniques, including robot-assisted approaches, have emerged as promising options for improving outcomes and patient recovery in EC management.

Objective • This study aims to evaluate the clinical utility of robot-assisted minimally invasive esophagectomy (RAMIE) in the treatment of EC.

Methods • A total of 160 EC patients undergoing treatment at our hospital were included in this study. Patients were randomly assigned to either the research group, receiving RAMIE, or the control group, undergoing thoracoscopic minimally invasive esophagectomy (MIE). Surgical outcomes, postoperative recovery, complication rates, and changes in inflammatory factors (IFs) such as malondialdehyde (MDA), superoxide dismutase (SOD), and glutathione peroxidase (GSH-Px) levels were compared between the two groups. Additionally, prognostic survival and EC recurrence rates were assessed at a 1-year follow-up.

Results • The research group demonstrated longer operative times, a higher number of dissected lymph nodes, reduced intraoperative bleeding, and quicker postoperative recovery compared to the control group, with significantly fewer complications ($P < .05$). Furthermore, the research group exhibited lower levels of postoperative IFs and MDA, along with higher levels of SOD and GSH-Px, compared to the control group ($P < .05$). There was no significant difference between the two groups in terms of prognostic survival and EC recurrence rates ($P > .05$).

Conclusion • RAMIE demonstrates superior efficacy in enhancing therapeutic outcomes and accelerating postoperative recovery in patients with EC, thus establishing its value in EC treatment protocols. RAMIE is suggested as a valuable therapeutic option and warrants clinical adoption for EC management. (*Altern Ther Health Med.* [E-pub ahead of print.])

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INTRODUCTION

Esophageal cancer (EC) stands as one of the most prevalent gastrointestinal malignancies, ranking sixth in overall cancer incidence.[1] Statistics reveal approximately 1.4 million new cases of EC diagnosed worldwide each year, with an estimated 300 thousand patients ultimately succumbing to the disease.[2] Moreover, recent shifts in dietary habits have contributed to a consistent rise in EC incidence, with the global rate in 2020 soaring to 4.3 times higher than that recorded in 2000.[3]

EC often exhibits significant concealment during its initial stages, characterized by nonspecific clinical features in the majority of patients.[2,3] Consequently, the emergence of symptoms like dysphagia and sternal pain typically signals disease advancement to the middle and late stages, thereby heightening treatment complexity and substantially augmenting patient mortality risk.[4] Clinically, malignant neoplastic diseases are primarily managed through surgical intervention, often supplemented with adjuvant therapies such as radiotherapy and chemotherapy.[3-5]

Traditional radical surgery for EC often induces considerable trauma, imposes significant stress on patients, and is associated with numerous postoperative complications, hindering their recovery.[5] The advancements in science, technology, and medical techniques have led to the emergence of robot-assisted minimally invasive esophagectomy (RAMIE) as a pivotal aspect of modern EC treatment.[6]

In addition to sharing advantages similar to traditional thoracoscopic minimally invasive esophagography (MIE), RAMIE facilitates surgeons in obtaining a clear visualization of patients' esophageal internal conditions through 3D imaging.[7] Furthermore, RAMIE offers the benefits of hand tremor filtration and robotic arm flexibility, aiding surgeons in performing EC radical surgery with greater precision and efficiency.[8] While recent studies have confirmed RAMIE's significant positive impact and high safety in treating various chest tumors,[9,10] its application in EC treatment remains relatively underreported. Meanwhile, there is a significant lack of applied research on RAMIE for EC patients in China, largely due to variations in medical standards across different regions.

Since 2020, our hospital has actively adopted RAMIE and accumulated a substantial case volume. Therefore, this study systematically assesses the application of RAMIE in EC treatment, aiming to furnish updated reference materials and guidance for future clinical approaches to managing EC. Our findings offer valuable insights into its efficacy and safety. for updated guidance in clinical practice by providing comprehensive evaluation and informing future treatment strategies.

MATERIALS AND METHODS

Study Design

This study employed a comparative design involving 160 EC patients admitted to our hospital between March 2020 and August 2021. Patients were randomly assigned to either the research group, undergoing RAMIE, or the control group, receiving thoracoscopic MIE. Approval for the study was obtained from the Ethics Committee of Tianjin Medical University Cancer Institute and Hospital, and informed consent was obtained from all participants prior to their inclusion in the study.

Inclusion and Exclusion Criteria

Inclusion criteria were as follows: (1) All patients included in the study were pathologically confirmed to have EC;[11] (2) patients meeting the surgical indications; (3) had complete clinicopathological data; and (4) underwent surgery performed by the same surgical team.

Exclusion criteria were as follows: (1) Patients with preoperative clinical stage IV EC; (2) those requiring conversion to thoracotomy intraoperatively due to tumor invasion of adjacent thoracic structures such as the aorta, trachea or lung; (3) those with severe cardiopulmonary insufficiency incompatible with anesthesia and surgery; (4) patients with epilepsy; (5) mental disorders; (6) or communication barriers were excluded from the study.

Surgical Procedure

After general anesthesia (combined anesthesia), patients underwent intubation with a double-lumen endotracheal tube. The research group received RAMIE, and the control group received thoracoscopic MIE surgical intervention.

Research Group. The bedside robotic manipulator system was positioned as follows: No.1 manipulator in the third intercostal space of the axillary midline, No.2 manipulator in the ninth intercostal space of the axillary posterior line, lens aperture in the sixth intercostal space of the midaxillary line, and the assistant hole in the fourth intercostal space of the anterior axillary line. Sequential separation of the venous arch and thoracic esophagus was performed, along with dissection of mediastinal lymph nodes and bilateral para-recurrent laryngeal nerve lymph nodes. Subsequently, the patient was repositioned supine for abdominal surgery, during which the stomach was fashioned into a tubular shape approximately 4cm wide and anastomosed at the neck using a stapler.

Control Group. In the control group, a 1.5cm thoracoscopic incision was made in the sixth intercostal space of the axillary midline, and a 12mm torca was inserted as the observation hole. The rest of the surgical procedure was the same as the research group.

Postoperative Care and Monitoring in the ICU. After the surgical procedure, patients were promptly transferred to the intensive care unit (ICU) for close postoperative monitoring and observation. This standard protocol ensures vigilant surveillance of patients' vital signs, surgical outcomes, and overall recovery progress. Within the ICU, specialized medical personnel administer tailored care and interventions to optimize patient recovery and mitigate potential postoperative complications.

Blood Sample Collection and Analysis

Fasting venous blood samples were obtained both before and 3 days post-surgery. After centrifugation, serum was collected to assess levels of inflammatory factors (IFs) interleukin-1β/6 (IL-1β/6) and tumor necrosis factor-α (TNF-α), as well as oxidative stress markers malondialdehyde (MDA), superoxide dismutase (SOD), and glutathione peroxidase (GSH-Px). Enzyme-linked immunosorbent assay (ELISA) kits, procured from Beijing TransGen Biotech, were utilized according to manufacturer recommendations for accurate measurement.

Prognostic Follow-Up

All patients underwent a one-year follow-up period, with regular reviews scheduled every two months. During these follow-up appointments, prognostic survival rates and incidences of EC recurrence were meticulously analyzed and documented.

Outcome Measures

Perioperative Inflammation and Oxidative Stress. The levels of inflammatory factors IL-1β/6 and TNF-α, as well as oxidative stress markers MDA, SOD, and GSH-Px, were measured both pre-and post-operatively to evaluate perioperative inflammation and oxidative stress.

Surgical and Postoperative Parameters. Various surgical and postoperative parameters were carefully recorded and analyzed. Operation-related metrics, including operation time, number of dissected lymph nodes, intraoperative bleeding, and instances of intraoperative conversion to thoracotomy, were documented. Additionally, postoperative variables such as the duration of chest drainage, feeding duration, length of hospital stay, and incidence of postoperative complications were comprehensively assessed.

Prognosis Assessment. Prognostic outcomes, including survival rates and the recurrence of EC, were carefully assessed to estimate the overall prognosis of patients undergoing treatment.

Statistical Analysis

Data analysis was performed using SPSS version 23.0 software. Count data were expressed as percentages [n (%)] and compared between groups using the chi-square test (χ^2). Measurement data were presented as mean ± standard deviation ($\bar{x} \pm s$), and between-group and within-group comparisons were conducted using the independent t-test and paired t test, respectively. Survival rates were calculated using the Kaplan-Meier method and compared using the Log-rank test. A value of $P < .05$ was considered statistically significant.

RESULTS

Comparison of Pathological Data between Two Groups

Comparison of patients' age, sex, pathological stage, and EC site between the research group and control group revealed no statistically significant differences ($P > .05$), refer to Table 1. This result indicates the comparability of the two groups in terms of baseline characteristics and pathological features.

Surgical Outcome Analysis

The statistical analysis of surgical outcomes revealed that only one patient in the control group required conversion to thoracotomy. In the research group, the operation time, intraoperative bleeding, and the number of dissected lymph nodes were 341.74±50.46 minutes, 114.59±36.35 milliliters, and 23.81±6.90, respectively. Notably, the operation time and number of lymph nodes dissected were significantly higher in the research group compared to the control group, whereas the intraoperative bleeding was significantly lower ($P < .05$), see Figure 1.

Comparison of Postoperative Parameters

In the research group, the duration of postoperative chest drainage, feeding, and hospitalization were 7.76±1.84 days, 6.44±1.23 days, and 17.33±2.16 days, respectively. These durations were significantly shorter compared to those observed in the control group ($P < .05$), see Figure 2. Furthermore, the incidence of postoperative complications was 10.00% in the research group, which was also significantly lower than that in the control group ($P < .05$), Table 2.

Comparison of Postoperative Inflammatory Reaction

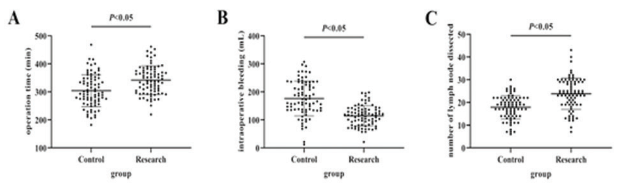
In comparing inflammatory factors (IFs), no significant inter-group differences were observed in preoperative test results ($P > .05$). However, postoperatively, levels of IL-1β, IL-6, and TNF-α increased in both groups, with significantly lower levels observed in the research group compared to the control group ($P < .05$), see Figure 3.

Table 1. Comparison of Pathological Data

Data	Control Group (n=80)	Research Group (n=80)	t (or χ^2)	P value
Age	62.83±6.10	61.45±6.30	1.403	.163
Sex			0.681	.409
Male	49 (61.25)	54 (67.50)		
Female	31 (38.75)	26 (32.50)		
Location of The Tumor			1.040	.594
Upper	9 (11.25)	13 (16.25)		
Middle	68 (85.00)	62 (77.50)		
Lower	6 (7.50)	5 (6.25)		
Type of Tumor			1.006	.605
Adenocarcinoma	0 (0.0)	1 (1.25)		
Squamous Carcinoma	79 (98.75)	78 (97.50)		
Other	1 (1.25)	1 (1.25)		
Degree of Differentiation			0.975	.614
Hypo-Differentiated	10 (12.50)	8 (10.00)		
Moderately-Differentiated	48 (60.00)	54 (67.50)		
Highly-Differentiated	22 (27.50)	18 (22.50)		

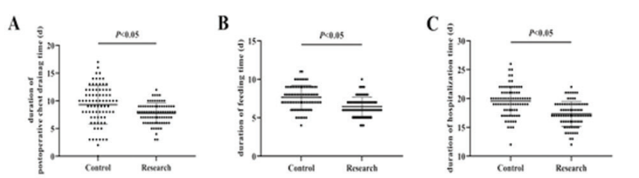
Note: Data presented as mean ± standard deviation or frequency [n (%)]. P values are calculated using independent samples t test or chi-square test, as appropriate. The statistical significance threshold was set at $P < .05$.

Figure 1. Comparison of Surgical Situations



Note: Figure 1A: Comparison of Operation Time; Figure 1B: Comparison of Intraoperative Bleeding; Figure 1C: Comparison of Number of Lymph Node Dissections between the research group and the control group. The research group exhibited a longer operative time and a greater number of lymph node dissections while experiencing lower intraoperative bleeding compared to the control group.

Figure 2. Comparison of Postoperative Conditions



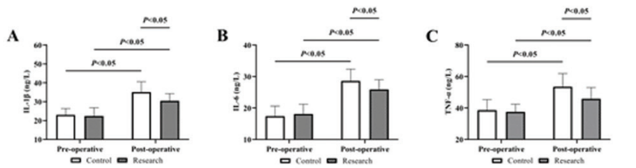
Note: Figure 2A: Duration of Postoperative Chest Drainage Time; Figure 2B: Feeding Time; Figure 2C: Hospitalization Time, between the research group and the control group. All values in the research group were lower than those in the control group.

Table 2. Postoperative Adverse Reactions

Adverse Reactions	Control Group (n=80)	Research Group (n=80)	χ^2	P value
Hoarseness	3 (3.75)	2 (2.50)		
Pneumonia	4 (5.00)	3 (3.75)		
Anastomotic fistula	3 (3.75)	0 (0.0)		
Arrhythmia	2 (2.50)	1 (1.25)		
Atrial Fibrillation	1 (1.25)	0 (0.0)		
Pleural effusion	2 (2.50)	1 (1.25)		
Cutaneous infection	1 (1.25)	0 (0.0)		
Pneumothorax	2 (2.50)	1 (1.25)		
Total incidence	22.50%	10.00%	4.592	.032

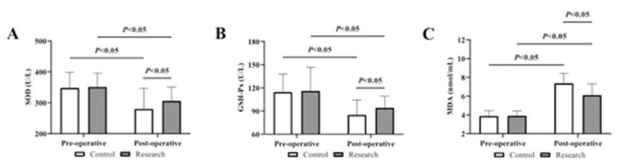
Note: Data presented as frequency [n (%)]. P values calculated using chi-square test (χ^2). The statistical significance threshold was set at $P < .05$.

Figure 3. Comparison of Inflammatory Factors



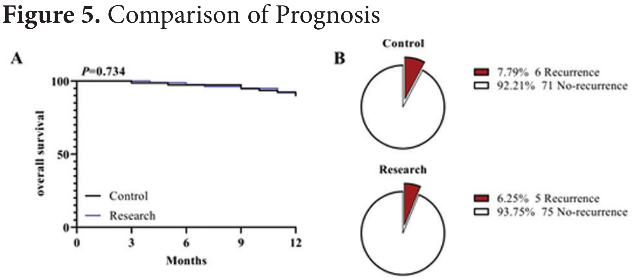
Note: Figure 3A: Interleukin-1β (IL-1β) Levels; Figure 3B: Interleukin-6 (IL-6) Levels; Figure 3C: Tumor Necrosis Factor-α (TNF-α) Levels between the research group and the control group. Postoperative inflammatory factors were lower in the research group than in the control group.

Figure 4. Comparison of Oxidative Stress Responses



Note: Figure 4A: Superoxide Dismutase (SOD) Levels; Figure 4B: Glutathione Peroxidase (GSH-Px) Levels; Figure 4C: Malondialdehyde (MDA) Levels between the research group and the control group. Postoperative SOD and GSH-Px levels were higher, and MDA levels were lower in the research group than in the control group.

Figure 5. Comparison of Prognosis



Note: Figure 5A: Prognostic Survival Curves; Figure 5B: Prognostic Recurrence Rates, respectively, between the research group and the control group. There was no significant difference in prognosis between the two groups.

Comparison of Oxidative Stress Reaction

Upon comparison of oxidative stress responses, no significant differences were observed in preoperative stress levels between the research group and control group ($P > .05$). However, postoperatively, levels of MDA increased in both groups, with notably higher levels detected in patients in the control group ($P < .05$). Conversely, levels of SOD and GSH-Px decreased postoperatively, with lower levels observed in the research group compared to the control group ($P < .05$), Figure 4.

Follow-Up and Prognosis Assessment

All patients in the research group and 77 patients in the control group were successfully followed up. Upon comparison, no significant difference was observed between the two groups in terms of overall survival rate and EC recurrence rate ($P > .05$), see Figure 5.

DISCUSSION

RAMIE represents a new frontier in thoracic surgery, offering significant advancements in surgical techniques. After years of clinical practice, RAMIE has demonstrated comparable surgical indications to traditional thoracoscopic MIE. However, its distinct advantages are particularly evident in challenging surgical scenarios and confined anatomical spaces. Therefore, RAMIE has garnered increasing adoption by hospitals seeking to tackle complex operations and enhance surgical precision.[12]

RAMIE offers several advantages, including high-definition stereoscopic 3D vision magnified by more than 10 times, flexible mechanical arms, and hand tremor filtration. These features ensure the safety and feasibility of thoracic surgery for various diseases. RAMIE enables clear exposure of lymph nodes in different regions of the pulmonary hilum and mediastinum, facilitating extensive lymph node dissection. This enhances the accuracy of the operation, reduces the risk of intraoperative bleeding and perioperative complications, and ultimately shortens hospitalization time.[13]

In the era of high-tech and information technology, RAMIE emerges as a modality that aligns well with the contemporary healthcare landscape. This is evident in light of the escalating clinical demand and heightened health awareness among patients.[14] In the current medical landscape of China, RAMIE is still at a developmental stage, and there is limited research available on the subject.[15] Furthermore, there is a notable absence of guidance regarding technical challenges, such as coordinating multiple robotic arm operations during surgery and the absence of tactile feedback for surgeons during the procedure.

This study systematically evaluated the therapeutic effect of RAMIE on EC. Initially, upon comparing the operative conditions, it was observed that the operation time in the research group was significantly prolonged, likely attributable to the complexity of the RAMIE procedure. However, despite this prolonged duration, the research group exhibited an increased number of dissected lymph nodes, reduced intraoperative bleeding, and shortened postoperative rehabilitation time. These findings suggest a more substantial therapeutic efficacy and less trauma associated with RAMIE in EC management. This finding aligns with the treatment outcomes observed in studies investigating the effectiveness of RAMIE in treating lung cancer, as demonstrated by Berzenji et al.[16]

We speculate that this outcome may be attributed to the enlarged surgical field of view offered by RAMIE, which proves particularly beneficial for intraoperative anatomy. This enhanced visualization allows for a more precise dissection of tissues around the esophagus along critical structures such as the trachea, thoracic duct, aorta, and vagus nerve.[17] Meanwhile, RAMIE demonstrates more pronounced advantages in confined areas such as the mediastinum and bilateral recurrent laryngeal nerves. It allows for the execution of more intricate minimally invasive procedures[18] while mitigating damage to surrounding normal tissues during surgery, thereby reducing blood loss.

Furthermore, the lower incidence of postoperative complications in the research group supports this perspective, suggesting that RAMIE offers enhanced safety in the treatment of EC. In the comparison of inflammation and oxidative stress reactions, it was observed that both groups of patients experienced significantly heightened postoperative inflammation and oxidative stress responses. It is a typical physiological response following invasive mechanical procedures and partial tissue resection. However, the postoperative inflammatory and oxidative stress reactions were found to be less severe in the research group.

This result indicates that patients undergoing RAMIE experience less internal tissue damage and maintain a more stable internal environment. This advantage not only facilitates quicker functional recovery post-surgery but also diminishes the likelihood of postoperative infection and other complications, thereby reinforcing our findings. Wang et al.[19] also found that RAMIE helps alleviate postoperative stress responses in patients with gastric cancer and supports their rehabilitation, which is consistent with our findings.

In addition, clinical emphasis has been placed on the importance of including bilateral para-recurrent laryngeal nerve lymph nodes in the mediastinal lymph node dissection for EC treatment.[20] However, during MIE surgery, probing bilateral para-recurrent laryngeal nerve lymph nodes presents significant challenges,[21] whereas the utilization of RAMIE aids physicians in accurately visualizing these lymph nodes.[22] However, this study did not observe any significant difference in patient prognosis, which could be attributed to the short follow-up period and limited number of subjects in the study.

In a previous study, researchers observed that RAMIE led to an improvement in the 5-year survival rate among patients with gastric cancer.[23] However, the subjects in our study were only followed up for 1 year. Overall, we have observed that RAMIE exhibits superior efficacy compared to traditional thoracoscopic MIE, leading to improved therapeutic outcomes and enhanced postoperative safety for patients. These findings underscore the significant clinical application value of RAMIE in the management of esophageal cancer. Our results serve as a reliable reference for the future adoption and implementation of RAMIE as a preferred surgical approach.

Study Limitation

While our study provides valuable insights into the therapeutic effects of RAMIE on EC, several limitations warrant acknowledgment. Firstly, the relatively short follow-up period of one year restricts our ability to assess long-term outcomes, such as overall survival and recurrence rates. Thus, a more extended follow-up period is necessary to validate the prognostic effects of RAMIE comprehensively. Secondly, the limited sample size and single-center design may introduce bias and limit the generalizability of our findings. Future studies with larger multicenter cohorts are needed to confirm our results.

Moreover, the absence of a control group receiving a different treatment modality hinders direct comparison and assessment of the relative efficacy of RAMIE. Finally, the operational experience of RAMIE was not thoroughly analyzed in this study, which could provide valuable insights into optimizing surgical techniques and outcomes. Therefore, future research should aim to address these limitations to further elucidate the role of RAMIE in EC treatment.

CONCLUSION

In conclusion, this study demonstrates that RAMIE significantly enhances the therapeutic efficacy of EC patients, leading to faster postoperative rehabilitation and improved surgical safety. Despite the longer operation time associated with RAMIE, the procedure results in increased lymph node dissections and decreased intraoperative bleeding, indicating its efficacy and reduced trauma compared to traditional methods. RAMIE also exhibits advantages in managing complications such as hoarseness, pneumonia, and anastomotic fistula. While further research with longer follow-up periods is warranted to confirm its prognostic effects, the findings underscore the clinical value of RAMIE in treating EC. Additionally, ongoing efforts to refine surgical skills and broaden operator experience are essential for the wider adoption of RAMIE in clinical practice.

COMPETING INTERESTS

The authors report no conflict of interest.

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None.

AVAILABILITY OF DATA AND MATERIALS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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