A Systematic Review of Inflatable Transcervical Mediastinoscopic Oesophagectomy and McKeown Oesophagectomy in Oesophageal Cancer

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ABSTRACT

This study compared the clinical efficacy and practicality of inflatable transcervical mediastinoscopic oesophagectomy (TIME) *versus* minimally invasive 3-stage McKeown oesophagectomy (MIME) for oesophageal cancer. A comprehensive literature search from 2018 onwards was conducted in databases such as PubMed and Wiley Online Library, focusing on studies that detail these surgical methods. Primary outcomes assessed the feasibility and practicality of TIME and MIME, with secondary outcomes including post-surgical complications, using data from published sources. Results indicate that TIME is generally less invasive, associated with fewer pulmonary complications (6.43 *vs*. 15.42; p = 0.06, 95% CI: 3.71- 21.71) and shorter operative time (270.75 *vs*. 337.01 minutes; p = 0.60, 95% CI: 5,47-8.61) compared to MIME, making it preferable for patients with previous thoracic surgeries or elderly patients. TIME also shows advantages in terms of shorter hospital stays (15.37 *vs*. 24.28 days; p = 0.21, 95% CI: 5.90- 23.74), less operative bleeding (138.94 *vs*. 187.53 ml; p = 0.28, 95% CI: 4.65-12.2), and fewer postoperative complications. However, concerns remain regarding the capability of TIME for lymph node dissection (15.47 *vs*. 29.42; p = 0.05, 95% CI: 4.74-32.65) and the resection of large tumours, such as T3 and T4 tumours, where MIME is perceived to perform better. The mortality rate was insignificant for both surgical methods (0.50 *vs*. 0.20; p = 0.22, 95% CI: 1.11-5.61), demonstrating their safety for patients with oesophageal cancer. Nonetheless, both techniques are deemed safe and effective for treating oesophageal cancer, with TIME demonstrating capability in resecting T3 tumours with good post-surgical outcomes.

Key Words: *Oesophageal cancer, Minimally invasive oesophagectomy, Thoracoscopy, Mediastinoscopy, McKeown oesophagectomy.*

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INTRODUCTION

Oesophageal cancer is one of the most common malignancies globally,[1] showing significant geographic variability in its occurrence. This variability is observed not only between countries but also within specific geographic areas and among different ethnic groups, distinguishing oesophageal cancer from many other types of cancers. The global incidence of oesophageal cancer has surged by 50% in recent decades, with approximately 482,300 newly diagnosed cases and 84.3% of patients succumbing to the disease annually.[2,3] As the 6th most fatal malignancy, oesophageal cancer poses a serious oncological burden.[4,5]

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Oesophageal squamous cell carcinoma, predominantly occurring in the upper and middle portions of the oesophagus, is the predominant histology in East Asian oesophageal cancer.[6] Notably, China, where the incidence of oesophageal cancer ranks third, and the mortality rate ranks fourth among all cancers, reports more than half of the world's newly diagnosed cases.[7] In the Western world, particularly in the USA, oesophageal cancer prevalence is increasing, attributed to the growing incidence of oesophageal adenocarcinoma.[8] This increase is attributed to the growing prevalence of both gastroesophageal reflux disease and obesity.[9,10]

Traditionally, surgery remains the primary approach for treating both forms of oesophageal cancer. Presently, various multimodal therapeutic approaches, with surgery as the cornerstone, have been invented to achieve 5-year survival rates of up to 50%.[11,12] The open transthoracic and open transhiatal surgical approaches have traditionally been the preferred choices for most surgeons, despite their limitations, including higher morbidity rates and an elevated risk of pulmonary complications.[13] In recent decades, minimally invasive surgery has made significant strides in the field of oesophagectomy.

The primary objective of this surgical method is to reduce the invasiveness associated with open oesophagectomy procedures, thereby minimising trauma, respiratory complications, and post-surgical pain, and facilitating quicker post-surgical recovery. These improvements are achieved without compromising oncological efficacy.

Thoracoscopic oesophagectomy was introduced by Cuschieri in 1992,[14] marking the beginning of minimally invasive approaches. Over nearly 30 years, advancements in minimally invasive equipment and methods, coupled with refined patient selection and perioperative management, have substantially advanced the treatment of oesophageal cancer. Several minimally invasive approaches to oesophagectomy have emerged during this period, including laparoscopic transhiatal, laparoscopic thoracoscopic Ivor Lewis, minimally invasive 3-stage McKeown oesophagectomy (MIME), inflatable transcervical mediastinoscopic oesophagectomy (TIME), and robotic-assisted oesophagectomy.

The choice of surgical approach is primarily at the discretion of the surgeon, although tumor location and patient comor-bidities may influence the choice of surgical technique. A combination of mediastinoscopic and transhiatal oesophagectomy surgical techniques was first introduced by Bumm *et al*.[15] In 2015, it was modified into inflatable video-assisted mediastinoscopic transhiatal oesophagectomy.[16] In 2016, Fujiwara *et al*. pioneered a new surgical technique for dissecting upper mediastinal lymph nodes using single-port mediastinoscopy through a cervical incision,[17] as well as for lower mediastinal lymph nodes. (including the number seven group of lymph nodes) using laparoscopy, respectively. However, the adequacy of mediastinal lymph node resection remains controversial.[18] A comparison between TIME and MIME revealed that MIME resulted in the highest number of resected mediastinal lymph nodes.[19] Despite its advantage in terms of decreased postoperative pain, fewer cardiac and pulmonary complications, lower mortality rates, and improved safety for elderly patients and those with prior thoracic surgery, the TIME approach has limitations due to its limited surgical visibility and challenging dissection of mediastinal lymph nodes, particularly those in the upper mediastinum.[20] Shi *et al*. suggested that, compared with MIME, the TIME approach results in less trauma, avoids chest wall injury, and carries a reduced risk of lung infection.[21]

Thus, this review aimed to demonstrate the feasibility and safety of both TIME and MINE, and to discuss the differences between these surgical techniques, including surgical procedures, tumour-stage resection (T3 or T4), lymph node dissection, intraoperative parameters, and post-surgical complications, based on previous studies.

METHODOLOGY

Studies were retrieved from databases such as PubMed and the Wiley Online Library to assess and compare the two surgical methods. The search utilised various terms, including minimally invasive oesophagectomy and oesophagus. To ensure the accuracy of the study, incomplete, overlapping, and duplicated studies were excluded. The search was primarily conducted in PubMed and the Wiley Online Library databases, focusing on English-language studies related to TIME and MIME. In December 2023, a search for minimally invasive oesophagectomy yielded 228 results in PubMed and 186 in the Wiley Online Library database for the period 2018-2023. In total, 414 studies were identified; however, only eight met the inclusion criteria and were used for the surgical analysis (Figure 1). The inclusion criteria were studies published in indexed journals, studies describing one or both of the surgical techniques related to this topic (TIME and MIME), and studies published in the English language. Eight studies, comprising four prospective and four retrospective studies and involving a total of 684 patients, facilitated a comprehensive comparative analysis of the surgical techniques. Some of the data collected were patient characteristics (age, gender, history), surgical period (amount of blood lost, surgical time, amount of lymph nodes resected), post-surgical complications (pulmonary complications such as pneumonia, pleural effusion, and pneumothorax), recurrent laryngeal nerve paralysis (detected when patients experienced hoarseness of voice after surgery or confirmed by flexible laryngoscopy), and mortality rate (death that occurred 30-35 days after surgery). The comparative analysis was conducted using SPSS version 26.0, and the difference between the two surgical techniques was analysed with a Student's t-test. Before the analysis was conducted, a normality test was performed on the data retrieved from the published studies to determine whether the data were normally distributed. The Shapiro-Wilk test was used, and it produced a p-value of 0.589, which was greater than 0.05. This indicated that the retrieved data were normally distributed. A p-value of <0.05 was considered to be statistically significantly different.

Conducted in accordance with the 1996 Declaration of Helsinki and PRISMA 2020 guidelines, this research did not involve human participants; therefore, neither patient consent nor ethical approval was required.

RESULTS

Table I compares and assesses the two surgical methods using data from various studies. It shows that TIME is feasible for the resection of T3 category tumours. All authors acknowledge that TIME results in less surgical bleeding and a shorter surgical time, except for one study, which states that MIME is associated with less surgical bleeding and a short operative time.

Table I: Comparison of TIME and MIME surgical patients: using patient's characteristics and intraoperative parameters.

Study	Study type	Year of publication	Country's affiliation	No. of patients	Surgical method	Age	Patient history	TNM staging	No of LN dissection	Surgical time (minutes)	Blood lost (mL)
Shi *et al*[21]	A prospective study	2021	CHINA	200	TIME	66.3 ± 6.7	NR	I-24 II-55 III-21	15.8 ± 4.5	164.3 ± 47.0 265.4 ± 47.2	94.7 ± 56.7
					MIME	66.3 ± 6.1		I-16 II-59 III-25 P 0.352	20.3 ± 6.5	p <0.00	184.4 ± 65.2
						P 0.982			p <0.001		p <0.001
Guo *et al*[22]	Retrospective study	2020	CHINA	76	MIME	63.69 ± 6.03	HBP- 12 DM- 2	I-14 II-21 III-12	18.04 ± 8.86	400.2	237.50 ± 108.91
					TIME	66.71 ± 8.10 P 0.067	HBP- 8 DM- 0	I-10 II-9 III-9 P-0.692	13.32 ± 6.74 P 0.01	189 P-0.000	154.64 ± 112.10 P-0.002
Jin *et al*[23]	A Retrospective study	2018	CHINA	49	MIME	59.9 ± 7.92	NR	I-1 II-10 III-19	NR	291.50 ± 33.17 255.5 ± 13.43 P-0.000	282.67 ± 196.71
					TIME	62.50 ± 8.46 P 0.259		I-2 II-8 III-9 P-0.741			106.84 ± 51.10 P 0.000
Wang *et al*[24]	A prospective study	2023	CHINA	60	MIME	68 ± 8.47	NR	I-9 II-14 III-7	15.3 ± 4.74	264.9 ± 47.57 217.2 ± 38.6	100
					TIME			I-17 I-8 I-5	14.5 ± 5.27 P 0.556		50 p <0.001
Chen *et al*[25]	A retrospective study	2022	CHINA	129	MIME	63.3 ± 9.6	HBP- 14 P-0.82 SH- 12 P-0.38 DH- 9 P-0.34 DM- 5 P-1.00	I-16 II-25 III-29	23.1 ± 14.0	277.3 ± 61.7	293.2 ± 60.0
					TIME	66.2 ± 7.1	HBP- 13 P-0.82 SH- 16 P-0.38 DH- 13 P-0.34 DM- 5 P 1.00	I-15 II-28 III-16	18.9 ± 6.0	242.0 ± 65.8 P 0.00	225.7 ± 50.3
									P 0.03		P 0.12
Sasaki et al[26]	A retrospective study	2022	JAPAN	72	MIME	66.5	NR	0-5 I-8 II-18 III-4 IV-3	31	647.5	165
					TIME	67 P 0.6232		0-6 I-14 II-6 II-7 IV-1	16 p <.0001	550 p <.0001	240 P 0.0884
Daiko et al[27]	A prospective study	2020	JAPAN	16	TIME	Average- 81	HBP- 7 DM- 4 HD- 1 LD- 3 CD- 2 GVHD- 2	T staging T1- 8 T2- 0 T3- 8	13.5	Average-231	Average- 50
Zhu et al[28]	A prospective study	2018	CHINA	82	MIME	Mean age (year) 64.2 ± 6.9	NR	I-22 II-19 III-41 IV-0	69.6	260.0 ± 61.9	100

TIME: Inflatable transcervical mediastinoscopic oesophagectomy; MIME: Minimally invasive 3- staged McKeown oesophagectomy; NR: Not recorded; HBP: High blood pressure; SH: Smoking history; DM: Diabetes mellitus; DH: Drinking history; LN: Lymph node; HD: Heart disease; LD: Liver disease; CD: Cerebrovascular disease; GVHD: Graft versus host disease.

Table II: Comparison of TIME and MIME surgical patients, using post-surgical outcomes.

Study	Surgical methods	Pulmonary complications	Hoarseness of voice	Anastomotic leak	Arrhythmia	Post-surgical hospital stays (days)	Mortality rate
Shi *et al.*[21]	MIME	Pneumonia- 29 Pneumothorax- 2	15	NR	9	23.2 ± 7.2	NR
	TIME	Pneumonia- 7 Pneumothorax- 0	12		6	18.0 ± 7.6 p <0.001	
			P 0.680		P 0.593		
Guo *et al.*[22]	MIME	38	1	7	NR	20.38 ± 11.54	NR
		21	1	6		15.07 ± 7.54 P 0.036	
	TIME	P-0.444	P 1.00	P 0.532			
Jin *et al.*[23]	MIME	4	2		2	16.90 ± 6.19	NR
	TIME	1 P 0.636	6 P 0.043	2	1 P 1.000	13.00 ± 7.03 P 0.047	
				2 P 0.636			
Wang *et al.*[24]	MIME				4		0
		6	1	4	2 P 0.667	10	
	TIME	2 P 0.255	3 P 0.605	2 P 0.667		9 P 0.230	
Chen *et al.*[25]	MIME					16.5 ± 10.8	
		16	9	5	4	16.0 ± 13.1 P 0.81	1
	TIME	5	15	8	2		2
		p <0.03	p <0.07	p <0.23	p <0.69		p <0.59
Sasaki *et al.*[26]	MIME	10	9	7	0	20	0
	TIME	6 P 0.3746	14 P 0.0599	6 P 0.932	1 P 0.2182	21.5 P 0.4159	0
Daiko *et al.*[27]	TIME	3	5	1	NR	Average-15	0
Zhu *et al.*[28]	MIME	3	5	4	NR	63 (76.8%)	0

NR: Not recorded; MIME: Minimally invasive 3-stage McKeown oesophagectomy; TIME: Inflatable transcervical mediastinoscopic oesophagectomy.

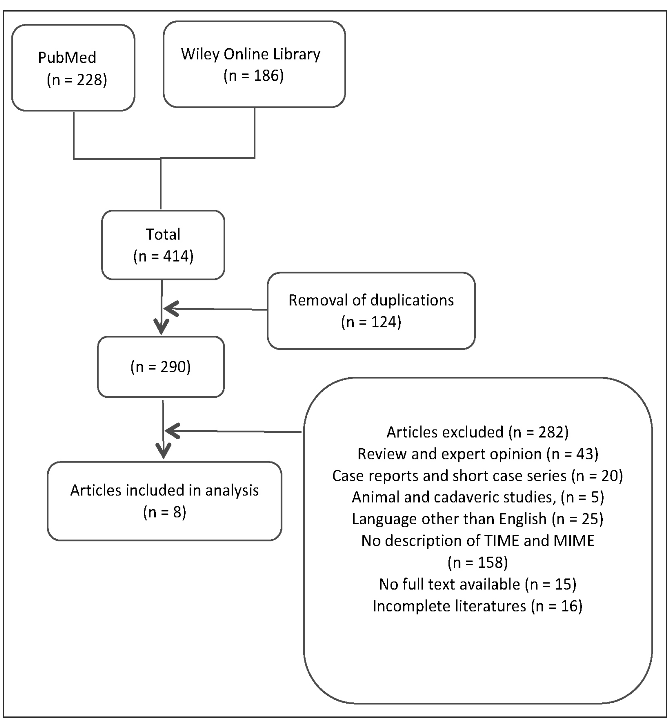

Figure 1: A flowchart of the search strategy.

All studies categorised T3 tumours under the TIME surgical method, demonstrating their resectability (Table I). Blood loss and operative time were lower in TIME than in MIME; however, lymph node resection was also lower in TIME (Table I).

Since the adoption of MIME techniques, medical literature has extensively examined various intraoperative parameters, such as operative time and blood loss. It has been reliably shown that the total surgical time is longer for MIME than for TIME. This study disclosed average surgical time to be 270.95 minutes for TIME *vs*. 337.01 minutes for MIME ($p = 0.60$, 95% CI: 5.47-8.61), which shows that MIME surgical time is longer than TIME, and these findings are consistent with the studies conducted by Shi *et al*., Guo *et al*., and Jin *et al*.[21-23] Only Wang *et al*. reported differently, potentially attributed to the learning curve of surgeons mastering a new and intricate technique.[24] Additionally, with respect to blood loss, this study disclosed an average blood loss of 138.94 mL for TIME patients compared with 187.53 mL for MIME patients ($p = 0.28$, 95% CI: 5.47- 8.61), showing that TIME patients experienced less blood loss than MIME patients. These findings are consistent with those reported by Shi *et al*., Guo *et al*., Jin *et al*., and Chen *et al*.[21-23,25]

Studies comparing the number of lymph nodes harvested in TIME *versus* MIME reveal that MIME patients undergo more extensive resection compared to those undergoing TIME. Shi *et al*.,[21] Guo *et al*.,[22] Chen *et al*.,[25] and Sasaki *et al*.[26] reported a higher number of resected lymph nodes in MIME patients. On the other hand, Wang *et al*.[24] revealed a larger number of harvested lymph nodes in TIME patients (15.3 *vs*. 14.6, p = 0.55). This study showed that MIME has a greater number of resected lymph nodes than TIME (29.42 *vs*. 15.47, p = 0.05, 95% CI: 4.74-32.65).

Table II describes the post-surgical outcomes of the two surgical methods. Pulmonary complications were fewer in TIME compared to MIME. Recurrent laryngeal nerve paralysis was reported to be more frequent with TIME, except in studies by Shi *et al*. and Guo *et al*., who reported lower and equal rates, respectively, compared to MIME.[21,22] The mortality reported for both surgical methods was insignificant.

All authors revealed a reduction in pulmonary complication rates in TIME patients compared with MIME patients (6.43 *vs*. 15.42, p = 0.06, 95% CI: 3.71-21.71). These outcomes are thought to be attributable to complete lung collapse and the avoidance of a thoracotomy incision, typically encountered in TIME.

Another potentially severe complication observed after surgery is an anastomotic leak, which may result in localised infection, sepsis, and potentially death. The overall anastomotic leak rate among patients was 7.89%. Three studies suggested that TIME is associated with a lower anastomotic leak rate than MIME,[22,25,26] while one study suggested the opposite,[24] and another study[23] recorded equal rates of anastomotic leaks for both surgical methods (Table II). The comparison of TIME to MIME (3.65% *vs*. 4.23%; mean value = 2.40 *vs*. 3.80; p = 0.50, 95% CI 2.66-5.46) indicated a tendency for higher rates of anastomotic leaks following MIME; however, the difference between the two surgical techniques was insignificant. Some surgeons argue that anastomotic leaks are influenced more by the surgeon's expertise than by the choice of surgical technique.

Damage to the recurrent laryngeal nerve may occur during the thoracic and cervical dissections of the oesophagus. Data retrieved from the aforementioned studies (Table II) showed low rates of recurrent laryngeal nerve injury. Some have hypothesised that MIME may lower the incidence of nerve injury by facilitating neck dissection through carbon dioxide insufflation, thereby enhancing visualisation of the recurrent laryngeal nerve, which is crucial in both TIME and MIME procedures. However, previous studies comparing TIME and MIME patients were inconclusive. Data reported in those studies showed a lower rate of palsy in MIME patients than TIME patients (6 *vs*. 8; p = 0.64, 95% CI: 4.32-8.32).

According to the data compiled from the studies (Table II) on TIME *vs*. MIME, most reports indicate that MIME is associated with a longer hospital stay compared to TIME, except Sasaki *et al*.,[26] who reported a shorter hospital stay for MIME compared to TIME (20 *vs*. 21.5 days). The findings regarding the duration of hospital stay are inconsistent, likely due to variations in practice patterns rather than the actual impact of surgical technique. The duration of general hospital stay across these studies was more evenly distributed, revealing shorter stays for TIME patients. According to the data retrieved, TIME patients stayed an average of 5-8 days fewer than MIME patients (15.37 *vs*. 24.28 days; p = 0.21, 95% CI: 5.90-23.74).

Although TIME and MIME patients have shown minimised blood loss, shorter hospital stays, and reduced rates of postoperative complications, few studies have demonstrated a disparity in mortality rates between the two surgical techniques. The mortality rates reported in the study's results were 0.50 for TIME and 0.25 for MIME, demonstrating no significant differences (p = 0.22, 95% CI: 1.11-5.61). Four of the included studies reported zero mortality,[25-28] while one study[24] recorded 1 death in the MIME group and 2 in the TIME group, and three studies did not report mortality rates.[22-24] Data retrieved from these studies suggest the safety and feasibility of both surgical methods, as evidenced by the low mortality rate observed in patients undergoing both procedures.

DISCUSSION

Some arguments have been made regarding the effectiveness of TIME in achieving sufficient lymph node dissection and its ability to resect T3 and T4 tumours due to limitations in surgical space. According to the retrieved data, TIME results in fewer lymph node resections, reduced blood loss, and a shorter operative time compared with MIME. In the case of postoperative complications, MIME has the upper hand with fewer cases of recurrent laryngeal nerve palsy and a lower mortality rate; however, it showed inferior results regarding pulmonary complications, length of hospital stays, and anastomotic leak rate compared to TIME. In this study, out of 684 patients, 327 patients (54.3% of the study population) suffered from postoperative complications, highlighting the high risk associated with oesophagectomy as a surgical method. However, the recorded mortality rate, which represents 0.75% of the study population, indicates the safety and feasibility of both TIME and MIME techniques for oesophageal cancer patients. Although this study's data show the feasibility of using TIME to resect T3 tumours, performing such a surgical technique remains difficult due to the narrow surgical space. Zhu *et al*. described a surgical technique involving the use of a mediastinal retractor placed at the third or fourth intercostal space of the left margin of the sternum. After a small operative space is created, a sternal suspension retractor hook is inserted behind the sternum, and the sternum is lifted. This helps create more space through the mediastinal pathway, thereby enhancing the surgical view and reducing blood loss.[29] However, TIME is still lagging behind MIME in the surgical space related to tumour size resection.

The TIME surgical procedure requires patients to remain in a supine position throughout the procedure, unlike MIME, which requires repositioning the patients from a lateral, semi-prone, or prone decubitus position (for thoracic resection) to a supine position (for abdominal resection).[30,31] This gives the TIME surgical technique the advantage of short operating time, as seen in this study. Moreover, two-lung ventilation is maintained throughout the procedure, enhancing patient comfort and reducing the risk of pulmonary complications, as seen in this study and supported by a retrospective study performed by Lin *et al*., which revealed that hypoxaemia and pulmonary complications occurred significantly less in the two-lung ventilation group in the TIME procedure, compared to the one-lung ventilation group during the MIME procedure.[32] Additionally, TIME avoids thoracic incisions, which can cause pain and limit patients' ability to cough or take deep breaths, potentially leading to lung non-expansion.[25] These factors contributed to the lower pulmonary complication rates observed with TIME in this study. The TIME surgical technique is more minimally invasive than MIME, as demonstrated by the number of incisions (MIME: cervical, thoracic, and abdominal incisions *vs*. TIME: cervical and abdominal incisions) and the body cavities disrupted (MIME: thoracic and abdominal *vs*. TIME: abdominal cavity). This can lead to earlier ambulation and faster patient recovery, thereby leading to a shorter hospital stay for TIME compared with MIME, as observed in this study.

Lymph node resection has been a controversial limitation of the TIME surgical technique. Recently, Daiko *et al*. introduced a bilateral TIME oesophagectomy technique.[27] This allows resection of the right recurrent laryngeal lymph node and the 4 and 2 groups of lymph nodes. However, TIME lags behind MIMF in the number of lymph node resections. Additionally, although successful surgical manipulation in a narrow space requires considerable skill, the learning curve for TIME is hypothetically steeper than that of MIME. However, both TIME and MIME stand as remarkable surgical techniques, contributing significantly to the well-being of surgeons and patients. Their impact is evident in the reduction of stress and burden, resulting in shorter postoperative stays, a decreased need for painkillers postoperatively (as observed in open surgeries), and higher levels of patient satisfaction.

This study has some limitations. First, the search coverage may not have been sufficiently extensive. Second, the eight studies included in this systematic review's results section comprise data from studies conducted in only two countries (China and Japan). Third, the latest surgical method, robotic-assisted minimally invasive oesophagectomy (RAMIE), which involves the da Vinci robotic system to perform both TIME and MIME, was not discussed in this study.

CONCLUSION

The minimally invasive oesophagectomy technique, introduced 25 years ago, has been documented in many high-volume centres. Despite its reported benefits, it has not gained widespread acceptance due to its steep learning curve and the high level of expertise needed, especially in TIME. These factors may contribute to the gradual incorporation of MIME into practice. Nevertheless, both TIME and MIME, as supported by existing studies, have demonstrated safety and effectiveness in resecting oesophageal tumours. They yield favourable surgical outcomes and hold potential to augment post-surgical patients' quality of life. Consequently, these surgical techniques should be prioritised when patients meet the necessary surgical requirements.

COMPETING INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
ICO, SZ: Wrote the original draft of the manuscript.
YQ: Help with the validation or verification of the references.
SZ, GH: Revised and edited the manuscript.
All authors approved the final version of the manuscript to be published.

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