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REVIEW ARTICLE

# Essential updates 2022/2023: Recent advances in perioperative management of esophagectomy to improve operative outcomes

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## Abstract
In the era of minimally invasive surgery, esophagectomy remains a highly invasive procedure with a high rate of postoperative complications. Preoperative risk assessment is essential for planning esophagectomy in patients with esophageal cancer, and it is crucial to implement evidence-based perioperative management to mitigate these risks. Perioperative support from multidisciplinary teams has recently been reported to improve the perioperative nutritional status and long-term survival of patients undergoing esophagectomy. Intraoperative management of anesthesia and fluid therapy also significantly affects short-term outcomes after esophagectomy. In this narrative review, we outline the recent updates in the perioperative management of esophagectomy, focusing on preoperative risk assessment, intraoperative management, and perioperative support by multidisciplinary teams to improve operative outcomes.

KEYWORDS
enhanced recovery after surgery, esophagectomy, morbidity, perioperative care, risk assessment

## 1 | INTRODUCTION

Esophageal cancer is the sixth most common cause of cancer-related mortality worldwide and has a poor prognosis.[1] In Japan, most esophageal cancers are squamous cell carcinomas (ESCC) of the thoracic esophagus. According to the esophageal cancer practice guidelines 2022 edited by the Japan Esophageal Society, the standard treatment for superficial ESCC is subtotal esophagectomy with two- or three-field lymphadenectomy, and for resectable advanced ESCC it is subtotal esophagectomy following preoperative chemotherapy.[2,3] Subtotal esophagectomy followed by esophagogastric anastomosis in the neck (McKeown esophagectomy) requires surgery across the neck, chest, and abdominal areas; is highly invasive; and is associated with a high rate of postoperative complications, including pneumonia, anastomotic leakage, and recurrent laryngeal nerve (RLN) palsy.[4] In Western countries, where adenocarcinoma of the lower esophagus and gastroesophageal junction is more common, Ivor–Lewis surgery, which involves esophagogastric anastomosis within the thoracic cavity without neck manipulation, is a typical procedure.[5] Although RLN palsy is rare, anastomotic leakage and pneumonia are the major postoperative complications of Ivor–Lewis esophagectomy.[6] These can lead to postoperative nutritional disorders and a decrease in quality of life (QOL), and are reportedly related to long-term prognosis.[7] Therefore, preoperative risk assessment and prevention of postoperative complications remains challenging.

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In recent years, thoracoscopic minimally invasive esophagectomy (MIE) and robot-assisted MIE (RAMIE) have become common in the treatment of esophageal cancer, with an expected effect in preventing postoperative complications.[8] However, pneumonia and anastomotic leakage still occur at high rates and are considered significant factors for poor long-term prognosis.[9–13] In addition to these major complications, a recent study reported that multiple minor complications negatively affect survival.[14] Therefore, safe surgery without major postoperative complications or multiple minor complications is the principal goal of esophageal cancer treatment, even with minimally invasive procedures.

Meanwhile, the utility of multidisciplinary treatment combining surgery and preoperative chemotherapy, with or without radiotherapy, has been reported, emphasizing the importance of maintaining nutritional status during a prolonged treatment period.[8] However, advanced esophageal cancer often causes dysphagia and passage disorders, leading to significant weight loss. Additionally, it takes time to improve food intake after subtotal esophagectomy, making patients prone to malnutrition. Therefore, to improve the prognosis nutritional support and infection control through team-based medical care are required.

In this narrative review we outline recent updates in the perioperative management of esophagectomy, especially McKeown esophagectomy, focusing on preoperative risk assessment, intraoperative management, and perioperative support by a multidisciplinary team (MDT) to improve operative outcomes.

## 2 | RISK STRATIFICATION FOR ESOPHAGECTOMY

Preoperative risk assessment is essential for planning esophagectomy in patients with esophageal cancer, and it is crucial to implement evidence-based perioperative management to mitigate these risks. Several risk models for mortality and morbidities of esophagectomy have been developed using nationwide databases such as the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) in the USA where Ivor–Lewis esophagectomy is predominant,[15–17] and the National Clinical Database (NCD) in Japan, where the vast majority of esophagectomies are the McKeown procedure[18–20] (Table 1), and online surgical risk calculator systems have been established using these risk models.

Perioperative predictors of morbidity and mortality after esophagectomy were first reported in 2010 using the ACS-NSQIP data for esophagectomies between the years 2005 and 2008.[15] In 2022, Lorenzo, et al analyzed 2538 esophagectomy patients using the 2016–2018 ACS-NSQIP datasets to determine the impact of diabetes on postoperative complications, and reported that insulin-dependent diabetes doubles the risk of all major complications compared to nondiabetics, and the risk of complications further doubles for minimally invasive procedures compared to open esophagectomy.[32] In 2023, Townsend et al analyzed 2544 patients using the 2016–2018 ACS-NSQIP datasets, and reported that age, operation time, nonwhite race, underweight body mass index (BMI), and smoking were independently associated with an increased risk of developing a postoperative complication following esophagectomy.[33] Conroy et al also reported in 2023 that patients with a BMI >35 have a higher rate of anastomotic leak using the ACS-NSQIP data between 2016 and 2019.[34]

The first report using NCD data was published in 2014, in which the preoperative clinical variables of 5354 patients who underwent esophagectomy in 2011 were used to predict 30-d and operative mortalities.[18] In 2020, risk models for major morbidities, including pneumonia, anastomotic leakage, and surgical site infection (SSI), were developed using NCD data of 10,862 patients who underwent esophagectomy between 2011 and 2012.[19] Based on these results, the NCD developed a risk calculator for short-term outcomes after esophagectomy, which is available to all participating hospitals as a feedback function on the NCD website. The relationship between hospital volume and risk-adjusted mortality and the survival advantage of undergoing esophagectomy at an Authorized Institute for Board Certified Esophageal Surgeons was reported using NCD data in Japan.[21,26] In 2023, Sasaki et al revised the risk models for mortality and major morbidities using NCD data registered between 2012 and 2017 in which the clinical tumor stage was added as a preoperative variable.[20] Murakami et al developed a risk model of operative mortality for elderly patients ≥75 y undergoing esophagectomy using the NCD data registered in 2012–2013[23] (Table 1).

Respiratory complications, including pneumonia, are the most frequent postoperative complications following esophageal cancer surgery and are the leading causes of surgery-related deaths.[18] These complications can negatively affect postoperative QOL and oncological outcomes.[9–11,35] The risk of pneumonia in patients undergoing McKeown esophagectomy could be predicted based on 17–23 preoperative factors registered in the NCD, including those related to respiratory disorders and a history of heavy smoking, as well as preoperative nutritional status such as weight loss and low serum albumin.[19,20] In the revised risk models by Sasaki et al, the c-index for the prediction of pneumonia was as low as 0.610 (95% confidence interval [CI], 0.582–0.637).[20] These results were comparable to those of a previous report using NCD data registered in 2011–2012, in which the c-index for pneumonia was 0.632 (95% CI, 0.599–0.665),[19] suggesting the difficulty in predicting postoperative pneumonia using preoperative clinical factors alone. MIE has been reported to be beneficial in reducing postoperative respiratory complications compared to conventional open esophagectomy,[24,25,36] and RAMIE appears to have the potential to further improve pulmonary complications.[37,38] In 2023, Zhang et al conducted a meta-analysis comparing perioperative safety and efficacy, including the long-term survival of patients undergoing either RAMIE or MIE, and reported that RAMIE was associated with a lower incidence of pneumonia (9.61% vs 14.74%; odds ratio [OR] = 0.73; 95% CI, 0.58–0.93; $p$ = 0.01).[39] Okamura et al analyzed the NCD data of 9850 patients who underwent MIE to elucidate the impact of patient position on the occurrence of postoperative pneumonia.[28] Although prolonged ventilation and surgery-related

TABLE 1 Esophagectomy studies using the Japanese National Clinical Database.

| Author (y) | Dataset y | No. of patients | Operation | Variables | Outcome measures | Ref. no. |
|---|---|---|---|---|---|---|
| Risk models | | | | | | |
| Takeuchi (2014) | 2011 | 5354 | Esophagectomy | Preoperative clinical factors | 30-d mortality, operative mortality | 18 |
| Nishigori (2016) | 2011–2013 | 16 656 | Esophagectomy | Hospital volume | 30-d mortality, operative mortality | 21 |
| Ohkura (2020) | 2011–2012 | 10 862 | Esophagectomy | Preoperative clinical factors, operative procedure (MIE) | Pneumonia, anastomotic leakage, SSI, transfusion, blood loss over 1000 mL, unplanned intubation, prolonged ventilation over 48 h, systemic sepsis | 19 |
| Okamura (2022) | 2015–2017 | 15 801 | Esophagectomy | Preoperative HbA1c levels | Pneumonia, anastomotic leakage, SSI, reoperation within 30 d, surgery-related mortality | 22 |
| Sasaki (2023) | 2012–2017 | 32 779 | Esophagectomy | Preoperative clinical factors, clinical tumor stage | Pneumonia, postoperative artificial respiration, unplanned intubation, 30-d mortality, operative mortality | 20 |
| Murakami (2023) | 2012–2013 | 1959 | Esophagectomy, ≥75 y | Preoperative clinical factors | Operative mortality | 23 |
| Comparative studies | | | | | | |
| Takeuchi (2017) | 2011–2012 | 9584 | Esophagectomy | Preoperative clinical factors | Pneumonia, anastomotic leakage, SSI, unplanned intubation, prolonged ventilation over 48 h, sepsis, recurrent laryngeal nerve palsy, reoperation within 30 d, surgery-related mortality, etc.; OE vs MIE | 24 |
| Yoshida (2020) | 2012–2016 | 24 233 | Esophagectomy | Preoperative clinical factors, clinical tumor stage | Pneumonia, anastomotic leakage, SSI, unplanned intubation, prolonged ventilation over 48 h, sepsis, reoperation within 30 d, surgery-related mortality; OE vs MIE | 25 |
| Motoyama (2020) | 2015–2017 | 16 752 | Esophagectomy | Preoperative clinical factors, clinical tumor stage | Pneumonia, anastomotic leakage, recurrent laryngeal nerve palsy, surgery-related mortality; Board Certified Esophageal Surgeons (BCES) vs non-BCES, Authorized Institutes for BCES (AIBCES) vs non-AIBCIS | 26 |
| Kikuchi (2022) | 2016–2018 | 9786 | Esophagectomy | Preoperative clinical factors, clinical tumor stage | Pneumonia, anastomotic leakage, SSI; posterior mediastinal vs retrosternal reconstruction route | 27 |
| Okamura (2023) | 2016–2019 | 9850 | MIE | Preoperative clinical factors, clinical tumor stage | Pneumonia; left lateral decubitus vs prone position | 28 |
| Nakajima (2022) | 2018–2019 | 215 | Esophagectomy for cervical esophageal cancer | Preoperative clinical factors, clinical tumor stage, reconstructed organ | Pneumonia, anastomotic leakage, re-intubation, tracheal necrosis, postoperative hospital stay, 30-d mortality; Larynx preserved vs laryngectomy | 29 |
| Miyawaki (2023) | 2016–2019 | 807 | Esophagectomy for cervical esophageal cancer | Preoperative clinical factors, clinical tumor stage | Pneumonia, anastomotic leakage, reconstructed organ necrosis, 30-d reoperation, tracheal necrosis, 30-d mortality; Gastric tube vs free jejunum reconstruction | 30 |
| Descriptive study | | | | | | |
| Takeuchi (2023) | 2018–2021 | 23 151 | Esophagectomy | | Pneumonia, anastomotic leakage, unplanned intubation, sepsis, 30-d mortality, operative mortality | 31 |

Abbreviations: MIE, minimally invasive esophagectomy; OE, open esophagectomy; SSI, surgical site infection.

mortality occurred more frequently in the lateral decubitus position group ($n = 2637$) than in the prone position group ($n = 7213$), patient position did not significantly influence the occurrence of postoperative pneumonia.[28] Kikuchi et al performed a multivariate analysis using the NCD data of 17,478 patients who underwent McKeown esophagectomy through the posterior mediastinal (PM) or retrosternal (RS) route and revealed a lower risk of pneumonia in the RS group than in the PM group (OR, 0.86; 95% CI, 0.75–0.98; $p = 0.028$).[27] In 2023, Booka et al conducted a meta-analysis comparing PM and RS reconstruction routes and suggested a lower incidence of pneumonia in the RS than in the PM route for performing MIE.[40] Therefore, the risk of postoperative pulmonary complications, including pneumonia, should be evaluated based on preoperative variables and operative procedures, including minimally invasive procedures and reconstruction routes.

Anastomotic leakage is another serious postoperative complication after esophagectomy that impairs QOL, prolongs hospital stay, and may lead to surgery-related deaths. However, revised preoperative risk models using NCD data failed to predict anastomotic leakage with sufficient predictive performance.[19,20] In 2022 and 2023, several studies reported that the reconstruction route (PM vs RS), anastomotic procedure (circular stapled vs linear stapled), and blood flow ratio in the gastric conduit are associated with the incidence of anastomotic leakage after esophagectomy.[27,40–44] As multiple operative and anatomical factors can affect the rate of anastomotic leakage, further research involving preoperative and operative factors, with or without postoperative events, is warranted to develop useful predictive models for anastomotic leakage after esophagectomy.

SSI is a major postoperative morbidity after esophagectomy. In 2023, Matsuda et al reported the results of a recent multicenter retrospective cohort study conducted by the Japan Society for Surgical Infection.[45] In the multivariate analysis using multicenter retrospective cohort that involved 407 patients with curative stage I/II/III esophageal cancer at 11 centers between April 2013 and March 2015, SSI had a significant negative impact on relapse-free survival (hazard ratio [HR], 1.63; 95% CI, 1.12–2.36; $p = 0.010$) and overall survival (OS) (HR, 2.06; 95% CI, 1.41–3.01; $p < 0.001$).[45] In the risk models using the NCD data, the c-index for the prediction of SSI was as low as 0.564 (95% CI, 0.530–0.597),[19] suggesting the difficulty in predicting SSI using preoperative clinical factors alone, similar to other morbidities.

In 2022, Okamura et al evaluated the association between preoperative hemoglobin A1c (HbAlc) levels and short-term outcomes using the NCD data of 15,801 patients who underwent oncological esophagectomy between 2015 and 2017.[22] Although there were value-dependent associations between HbA1c values and OR for pneumonia, anastomotic leakage, SSI, and composite outcomes, a single factor would not be satisfactorily predictive for postoperative morbidities (OR ≤1.40).[22] Grantham et al performed a systematic review of preoperative risk modeling for esophagectomy.[46] Notably, an NCD study in 2023 reported that esophagectomy was performed during the COVID-19 pandemic despite limited medical resources in Japan without increasing the incidence rate of worse outcome.[31]

As cervical esophageal cancer accounts for a small proportion of all esophageal cancers, radical surgery can be performed by laryngectomy followed by reconstruction using a gastric tube or free jejunum; however, the risk assessment of postoperative morbidity and mortality differs from that of thoracic esophageal cancer. In 2022, Nakajima et al conducted a survey of the clinical outcomes of cervical esophageal carcinoma surgery using NCD data registered in 2018–2019, and reported that larynx-preserving surgery was equivalent to laryngectomy in terms of short-term surgical outcomes.[29] Miyawaki analyzed NCD data registered in 2016–2019, and reported that anastomotic leakage was higher in gastric tube reconstruction than in the free jejunum for cervical esophageal cancer (17.9% vs 6.7%, $p < 0.01$).[30]

Postoperative delirium is a common and serious postoperative complication, particularly in elderly patients or those with certain preexisting conditions.[47] It is characterized by an acute change in mental status, typically involving confusion, disorientation, altered levels of consciousness, and sometimes hallucinations.[48] Perioperative risk factors for postoperative delirium, such as older age, pulmonary diseases, surgical procedures, and postoperative complications, have been reported in patients with esophageal cancer undergoing esophagectomy.[49–52] In 2023, Sugi et al assessed risk factors for postoperative delirium among 158 elderly patients' ≥75 y undergoing elective surgery for gastroenterological cancer, and revealed that Short Physical Performance Battery score, ≤9, Mini Nutritional Assessment score ≤11, a Mini-Mental State Examination score ≤24, and regular use of benzodiazepine were independent preoperative risk factors for postoperative delirium.[53]

## 3 | PERIOPERATIVE TEAM MANAGEMENT OF PATIENTS UNDERGOING ESOPHAGECTOMY

### 3.1 | Preoperative patient support and rehabilitation

Enhanced recovery after surgery (ERAS)/Fast Track Surgery was introduced and established to promote rapid postoperative recovery.[54,55] The ERAS protocol, proposed by the ERAS group of the European Society for Clinical Nutrition and Metabolism (ESPEN), aims to prevent postoperative complications, shorten hospital stay, and improve safety by comprehensively implementing measures that enhance postoperative recovery.[54] In Japan, ERAS is gradually gaining acceptance, and the importance of perioperative management with MDT is being advocated. Currently, many institutions have introduced a clinical path and an MDT for perioperative management of esophageal cancer patients, such as the perioperative team in the Cancer Institute Hospital (PeriCan) by Watanabe et al and the perioperative management center (PERiO) by Shirakawa et al with perioperative rehabilitation (prehabilitation) programs and nutritional therapy.[56,57] Watanabe et al reported that the incidence of postoperative complications significantly decreased from 73% to

49% ($p=0.0003$), particularly postoperative pneumonia (43%–13%, $p<0.0001$) with the introduction of PeriCan[56] (Table 2). Shirakawa et al reported that the adverse event rate during chemotherapy, especially oral complications, was significantly decreased in the PERiO Intervention group started before NAC ($n=100$) compared with the PERiO Intervention group started after NAC ($n=77$) ($p=0.007$).[57] Furthermore, weight loss during the period from chemotherapy to surgery was significantly reduced in the group started before NAC ($p=0.033$)[57] (Table 2).

In April 2017, our hospital launched the Hamamatsu Perioperative Care Team (HOPE) to ensure safer perioperative management, improve long-term prognosis, and enhance the long-term QOL of patients. Patients with esophageal cancer determined for surgery receive interventions from the HOPE staff from their initial outpatient visit to the postdischarge period. The incidence rates of postoperative atrial fibrillation and pneumonia, and body weight loss at postoperative months (POM) 1, 3, 6, and 12, were significantly lower in the HOPE group than in the pre-HOPE group.[58] From 2019, a wearable fitness tracking device (WFT) was used to record the heart rate, steps, physical activity, calorie consumption, and sleep duration in patients who agreed to wear the WFT.[59] In 2022, Honke et al performed a propensity score analysis of 94 patients who underwent esophagectomy and reported that the rate of postoperative pneumonia was significantly lower (0% vs 22.6%, $p=0.005$), the postoperative hospital stay was shorter ($p=0.012$), and the prognostic nutritional index (PNI) at POM 1 was better ($p=0.034$) in the WFT group than in the non-WFT group[59] (Table 2). Although there seemed some bias that the use of WFT as indicated may be influenced by the patient's willingness to participate in the treatment, the WFT encouraged, at least in part, their motivation to exercise that could lead to the better short-term postoperative outcomes.

In 2022, Shen et al conducted a randomized controlled trial (RCT) to determine whether ERAS could improve the outcomes of a three-stage MIE.[61] Postoperative morbidity (33.3% vs 51.7%; $p=0.04$) and pulmonary complication rates (16.7% vs 32.8%; $p=0.04$) were lower in the $ERAS^+$ group ($n=60$) than in the control group ($n=58$).[61] Chen et al[62] conducted a parallel-group, single-blind, RCT to evaluate the effects of perioperative nutritional management by an MDT on nutrition and postoperative complications in patients with esophageal cancer. Patients who received perioperative nutrition management by MDT had higher total protein and albumin levels on postoperative d (POD) 3 and 7, a lower incidence of postoperative pneumonia and anastomotic fistula, and a lower incidence of hypoproteinemia on POD 3 and 7 than those who received routine diet management.[62] These studies revealed the clinical importance of ERAS and MDT management in improving the operative outcomes of patients with esophageal cancer in the era of MIE (Table 2).

In the esophageal cancer practice guidelines 2022 edited by the Japan Esophageal Society, there is a section on perioperative management, titled "Perioperative Management and Clinical Path."[3] A qualitative and quantitative systematic review was conducted on the recommendation of preoperative rehabilitation for esophageal cancer surgery, which resulted in a weak recommendation for preoperative rehabilitation to prevent postoperative complications in esophageal cancer. On the other hand, the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines Version 2.2023, and the European Society for Medical Oncology (ESMO) Clinical Practice Guidelines for diagnosis, treatment, and follow-up 2022, have little mention of perioperative management.[63,64] The NCCN guidelines recommend perioperative enteral nutrition management,[63] while the ESMO guidelines state that nutritional status and a history of weight loss should be assessed according to the European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines.[64,65]

### 3.2 Intraoperative managements

As mentioned previously, the use of minimally invasive techniques reduces postoperative complications. In addition, anesthesia management, including patient pain, consciousness, vital functions during surgery, and intraoperative fluid balance, and nursing care, such as intraoperative temperature management, can also affect the postoperative course, including infectious complications and delirium.[66,67] In 2022, Hirano et al analyzed the clinical data of 12,688 patients who underwent MIE using the Diagnosis Procedure Combination database in Japan and found that the use of epidural analgesia was associated with low in-hospital mortality and decreased respiratory complications and anastomotic leakage[68] (Table 3).

Controversies remain regarding appropriate intraoperative fluid therapy in terms of its impact on postoperative complications after esophagectomy. Previous studies have demonstrated the relationship between increased intraoperative fluid administration and worse postoperative pulmonary complications.[76-78] Mukai et al conducted a multicenter RCT to evaluate the effect of intraoperative goal-directed fluid therapy (GDT) on major morbidity and mortality in patients undergoing transthoracic esophagectomy.[72] GDT was independently associated with morbidity and mortality (HR, 0.51; 95% CI, 0.30–0.87; $p=0.013$).[72] Tang et al conducted an RCT to investigate whether stroke volume variation (SVV)-guided GDT can improve postoperative outcomes in elderly patients undergoing MIE.[73] The incidence of postoperative complications was similar between the two groups with or without the GDT protocol, including a baseline fluid supplement of 7 mL/kg/h Ringer's lactate solution and SVV optimization.[73] In 2023, Buchholz et al reported in a retrospective observational study that higher cumulative fluid balance was associated with worse postoperative outcomes in patients undergoing transthoracic esophagectomy[69] (Table 3). Further studies, including RCTs comparing GDT and restrictive intraoperative fluid administration, are warranted.

The relationship between postoperative delirium and the intraoperative management is complex and multifaceted. Intraoperative factors, including anesthetics, intraoperative blood loss, intraoperative fluid administration, longer surgical procedures, and intraoperative hypotension, can significantly influence the risk and development of postoperative delirium.[79] In 2023, a retrospective observational study by Ju et al and a prospective observational study by Wang et al showed that hypothermia during surgery can affect cerebral metabolism and

**TABLE 2** Perioperative management of patients who underwent esophagectomy.

| Author (y) | No. of patients | Patients' cohort | Operation | Intervention | Control | Outcomes | Ref. no. |
|---|---|---|---|---|---|---|---|
| Observational study | | | | | | | |
| Watanabe (2016) | 218 | Single center, retrospective | Esophagectomy | Perioperative management by MDT (PeriCan), $n=105$ | Before PeriCan, $n=113$ | Lower incidence of postoperative complications and postoperative pneumonia | 56 |
| Shirakawa (2021) | 177 | Single center, retrospective | MIE after NAC | Perioperative management by MDT (PERiO) started before NAC, $n=100$ | PERiO after NAC, $n=77$ | Lower incidence of oral complication during NAC, less weight loss during NAC | 57 |
| Kawata (2020) | 125 | Single center, retrospective | Esophagectomy | Perioperative management by MDT (HOPE), $n=63$ | Before HOPE, $n=62$ | Lower incidence of postoperative atrial fibrillation and pneumonia, less body weight loss at POM 1, 3, 6, and 12 | 58 |
| Honke (2022) | 94 | Single center, retrospective | Esophagectomy | Perioperative use of wearable fitness tracking device (WFT), $n=41$ | Non-WFT, $n=53$ | Lower incidence of postoperative pneumonia, shorter postoperative hospital stay, better prognostic nutritional index at POM 1 | 59 |
| Mayanagi (2023) | 251 | Single center, retrospective | Esophagectomy | Perioperative management with ramelteon and suvorexant | No ramelteon and suvorexant | Lower incidence of postoperative delirium | 60 |
| RCT | | | | | | | |
| Shen (2022) | 118 | Single center | MIE | Guideline-based ERAS, $n=60$ | Standard care, $n=58$ | Lower incidence of postoperative morbidities and pulmonary complication, earlier ambulation | 61 |
| Chen (2023) | 239 | Single center | Esophagectomy | Perioperative nutrition management by MDT, $n=120$ | Standard care, $n=119$ | Higher total protein and albumin levels at POD 3 and 7, lower incidence of postoperative pneumonia and anastomotic fistula, lower incidence of hypoproteinemia at POD 3 and 7 | 62 |

Abbreviations: ERAS, enhanced recovery after surgery; MDT, multidisciplinary team; MIE, minimally invasive esophagectomy; NAC, neoadjuvant chemotherapy; POD, postoperative day; POM, postoperative month; RCT, randomized controlled trial.

**TABLE 3** Studies on the intraoperative management of patients undergoing major noncardiac surgery.

| Author (y) | No. of patients | Patients' cohort | Operation | Intervention | Control | Outcomes | Ref. no. |
|---|---|---|---|---|---|---|---|
| Observational study | | | | | | | |
| Hirano (2022) | 12 688 | DPC database, retrospective | MIE | Epidural analgesia (EDA), $n = 9954$ | non-EDA, $n = 2734$ | Lower incidence of in-hospital mortality, respiratory complications and anastomotic leakage | 68 |
| Buchholz (2023) | 109 | Single center, retrospective | Esophagectomy | High intraoperative fluid balance (IFB), $n = 54$ | Low IFB, $n = 53$ | Higher incidence of anastomotic leakage, severe complications (any) and severe pulmonary complications | 69 |
| Ju (2023) | 27 674 | Single center, retrospective | Major noncardiac surgery | Severe hypothermia (<35.0°C), $n = 388$ Mild hypothermia (35.0°C–36.0°C), $n = 11\,779$ | Normothermia, $n = 15\,507$ | Higher incidence of postoperative delirium | 70 |
| Wang (2023) | 874 | Single center, prospective, 65–90 y | Major noncardiac surgery | Hypothermia (<35.5°C), $n = 336$ | Normothermia, $n = 538$ | Higher incidence of postoperative delirium | 71 |
| RCT | | | | | | | |
| Mukai (2020) | 232 | Multicenter | Esophagectomy | Intraoperative goal-directed therapy (GDT), $n = 115$ | non-GDT, $n = 117$ | Lower incidence of major morbidity, atrial fibrillation, respiratory failure and mortality, less readmission to ICU | 72 |
| Tang (2021) | 65 | Single center, >65 y | MIE | Intraoperative GDT, $n = 33$ | Conventional care, $n = 32$ | No difference in the incidence of short-term postoperative complications | 73 |
| Hu (2021) | 177 | Single center, 60–80 y | OE | Dexmedetomidine with total intravenous anesthesia (TIVA), $n = 90$ | TIVA, $n = 87$ | Lower incidence of postoperative delirium | 74 |
| Huang (2023) | 90 | Single center, >65 y | MIE | Repeated intranasal administration of 20 U (0.5 mL) insulin, $n = 30$ or 30 U (0.75 mL), $n = 30$, starting 2 d preoperatively, twice daily | Intranasal administration of 0.5 mL saline, $n = 30$ | Lower incidence of postoperative delirium in 30 U (0.75 mL) insulin group | 75 |

Abbreviations: DPC, diagnosis procedure combination; MIE, minimally invasive esophagectomy; OE, open thoracic esophagectomy; POD, postoperative day; POM, postoperative month; RCT, randomized controlled trial.

is associated with an increased risk of postoperative delirium.[70,71] Recently, two interesting RCTs were conducted in elderly patients undergoing esophagectomy. Hu et al investigated the efficacy and safety of dexmedetomidine in reducing postoperative delirium, and reported that adding perioperative dexmedetomidine to a total intravenous aesthetic safely reduced postoperative delirium and emergence agitation in elderly patients undergoing open transthoracic esophagectomy.[74] Huang et al investigated the effect of repeated intranasal administration of different insulin doses before MIE on postoperative delirium and reported that the administration of 30U of intranasal insulin twice daily, from 2d preoperatively until 10min preanesthesia on the day of surgery, significantly reduced postoperative delirium by reducing $\tau$ protein hyperphosphorylation and A$\beta$, which could synergistically block neuronal function and cause postoperative delirium in elderly patients undergoing MIE[75] (Table 3).

### 3.2 | Postoperative patient care with MDT

Postoperatively, pain control is usually administered, and early mobilization is encouraged, as it may reduce the incidence of postoperative pulmonary complications.[80,81] In 2023, Schuring et al conducted a retrospective cohort study involving 384 patients and reported the importance of 100m ambulation on POD 1 as an achievable target to start with after esophageal cancer surgery.[82] Postoperative early enteral nutrition should also be taken orally with or without oral nutritional supplements (ONS) or via the gastrointestinal fistula.[58,81]

Several previous reports, including two recent articles published by Zheng et al and Sugimura et al, have revealed the survival impact of preoperative nutritional status on the prognosis of patients undergoing esophagectomy.[83–89] In a retrospective study conducted in 2022, Haneda et al reported that the recovery of PNI levels at POM 1 was associated with better prognosis in patients with preoperative malnutrition.[90] While patients with preoperative-low PNI had significantly worse OS than those with preoperative-high PNI ($p=0.001$), there was no significant difference in OS between patients with preoperative-high PNI and those with preoperative-low PNI and postoperative-high PNI ($p=0.224$).[90] These results suggest the importance of perioperative nutritional management for improving survival.

As previously mentioned, preoperative risk assessment and intraoperative management are important for preventing postoperative delirium. In 2023, Mayanagi et al reported that perioperative management with ramelteon (8mg/day) and suvorexant (15mg/day) may play an important role in reducing postoperative delirium in elderly patients with esophageal cancer.[60]

### 3.3 | Postoperative outpatient care with MDT

Postdischarge follow-ups should be continued in collaboration with rehabilitation professionals and dietitians during outpatient visits. At our institute, continuous follow-up is performed with physical measurements at POM 1, 3, 6, and 12 for the ongoing evaluation of physical function.[58] Dietitians conduct outpatient nutritional counseling to assess home nutritional intake and provide guidance on oral intake, ONS formulations, and enteral nutrition management. A treatment diary and WFT were used from the start of the intervention until 1mo after discharge.[59]

The clinical impact of diarrhea during enteral feeding after esophagectomy has been recently reported.[91] Diarrhea during enteral feeding can put elderly patients at risk of postoperative malnutrition and poor prognosis after esophagectomy.[91] Therefore, continuous postoperative care with MDT is important in maintaining the patient's general condition, preventing malnutrition due to diarrhea during enteral feeding, and improving survival.

## 4 | CONCLUSION

Risk stratification of mortality and morbidities should be assessed using preoperative values; however, the selection of operative procedures, including MIE and RAMIE, and the reconstruction route could also significantly affect the outcomes. Intraoperative management of anesthesia and fluid therapy also significantly affects short-term outcomes after esophagectomy. Perioperative patient care with MDT is important in improving perioperative nutritional status and long-term survival of patients undergoing esophagectomy. Recent advances in the perioperative management of esophagectomy are expected to improve operative outcomes in the era of MIE and RAMIE.

### AUTHOR CONTRIBUTIONS

Hiroya Takeuchi devised the project, main conceptual ideas, and proof outline. Hirotoshi Kikuchi selected and reviewed the references and wrote the article's initial draft. Eisuke Booka, Yoshihiro Hiramatsu, and Hiroya Takeuchi contributed to the review of the references and assisted with the presentation of the article. All authors have reviewed the article.

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### ETHICS STATEMENTS

Approval of the research protocol: N/A.
Informed consent: N/A.
Registry and the Registration No. of the study/trial: N/A.
Animal studies: N/A.

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