# *Robot-Assisted Esophagectomy After Neoadjuvant Chemoradiation—Current Status and Future Prospects*

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REVIEW ARTICLE

# Robot-Assisted Esophagectomy After Neoadjuvant Chemoradiation—Current Status and Future Prospects

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**Abstract**

Multimodality treatment with neoadjuvant chemoradiation followed by surgery has become the standard of care for esophageal cancer. In the recent years, there has been a shift in focus of surgical approach from open esophagectomy to minimally invasive esophagectomy. Robot-assisted esophagectomy is being performed more often in centers across the world. However, there is limited data on role of robot-assisted esophagectomy in patients who have received neoadjuvant chemoradiation. Initial reports have shown that integrating neoadjuvant therapy to robot-assisted esophagectomy is feasible and safe. With the growing popularity of robot-assisted surgery worldwide among both surgeons and patients, understanding the impact of neoadjuvant chemoradiation on the procedure and its oncological outcome seems worthwhile. In the present study, we present a review of available literature on the feasibility and safety of robot-assisted minimally invasive esophagectomy in esophageal cancer patients after neoadjuvant chemoradiation.

**Keywords** Carcinoma esophagus · Neoadjuvant chemoradiation · Robot-assisted esophagectomy · Video-assisted thoracoscopic esophagectomy · Minimally invasive esophagectomy

## Introduction

Esophagectomy is the mainstay of treatment in appropriately selected patients with resectable esophageal cancer [1]. Esophagectomy is however a technically challenging procedure and may have significantly high postoperative morbidity and mortality [2, 3]. Surgery as a single modality achieves R0 resection rates between 59 and 92% with 5-year overall survival ranging from 34 to 41% only [4–6]. Multimodality management with preoperative concurrent chemoradiation followed by surgery has shown to have significant benefit in terms of overall survival in selected patients [4, 7, 8]. The CROSS trial was a landmark randomized controlled trial which showed benefit of adding neoadjuvant chemoradiation before esophagectomy in selected patients with resectable esophageal cancer. Neoadjuvant therapy resulted in improved R0 resection rate from 69 to 92% with statistically significant improvement in both disease free and overall survival, without any impact on postoperative morbidity or mortality [4]. Currently neoadjuvant chemoradiation followed by esophagectomy is the standard of care especially for middle third esophageal cancers.

Recently, there has been a paradigm shift in surgical approach to esophagectomy from open transthoracic esophagectomy to minimally invasive video-assisted thoracoscopic (VATS) esophagectomy and robot-assisted esophagectomy being the latest innovation. Integrating neoadjuvant therapy to robot-assisted esophagectomy seems feasible, but the data on outcomes are scarce. We present a review of literature available on role of robot-assisted minimally invasive esophagectomy (RAMIE) after neoadjuvant chemoradiation (nCRT).

## Video-Assisted Thoracoscopic Esophagectomy

A right thoracotomy approach has been the most popular method for performing esophagectomy for resection of esophageal carcinoma. However, conventional open transthoracic approaches have been attributed with increased incidence of respiratory complications necessitating greater need for

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mechanical ventilation in postoperative period and prolonged ICU and hospital stay [9]. Minimally invasive surgery was introduced in 1990s in oncologic surgery as a means to reduce the surgical trauma and immunologic stress which were thought to potentially reduce postoperative complications and overall surgery-related morbidity [10]. Minimally invasive esophagectomy has been conventionally performed by video-assisted thoracoscopic approach combined with laparoscopic abdominal dissection for gastric mobilization or a combination of hybrid techniques. Video-assisted thoracoscopic (VATS) esophagectomy has potential benefits over conventional open surgery including reduced blood loss, decreased incidence of pulmonary complications, faster postoperative recovery, and shorter ICU and hospital stay [11, 12] Several studies have shown substantially high perioperative mortality varying from 4.8 to 16% with conventional open esophagectomy [13]. Minimally invasive surgery has made it feasible to offer radical curative surgery to more number of patients those who would have been unfit for esophageal resection by thoracotomy, e.g., elderly patients and patients with significant cardiac and pulmonary comorbidities [14]. Various research groups have shown minimally invasive esophagectomy to be safe in terms of improving short-term morbidity and perioperative mortality and similar oncological results compared with conventional open esophagectomy. The safety and efficiency of VATS surgery for esophageal carcinoma in comparison with conventional open surgery have been documented in several systematic reviews and meta-analysis with shortened ICU and hospital stay, enhanced recovery in postoperative period, and similar 3-year survival [15–18]. Initially there was some reservation among surgeons in implementing VATS esophagectomy in patients after nCRT due to concerns of lack of tactile sensation, postradiation changes leading to difficult mediastinal dissection and possibility of increased postoperative complications. However, a recent meta-analysis did not show any significant adverse effects on postoperative outcome with nCRT followed by VATS surgery [19].

Cuschieri et al. [20] and Luketich et al. [14] were the first to suggest feasibility and safety of VATS esophagectomy following nCRT. Liu et al. compared outcomes of 44 patients undergoing VATS esophagectomy after nCRT with 63 patients who underwent VATS surgery directly without chemoradiation. The authors did not find any difference in operative time, intraoperative bleed, extent of lymphadenectomy, duration of ventilation period, postoperative stay in hospital, incidence of postoperative complications, and R0 resection rate in the two groups. This study established the feasibility and safety of VATS esophagectomy in patients with nCRT with enhanced postoperative patient recovery [21]. The first randomized control trial (TIME Trial) which compared open esophagectomy with VATS esophagectomy after neoadjuvant treatment showed overall better postoperative morbidity with VATS esophagectomy while maintaining desired short-term oncologic outcomes [11]. In a meta-analysis, the short-term oncologic efficacy, as defined by R0 resection rate and extent of lymphadenectomy, was found to be superior with thoracoscopic surgery compared with open esophagectomy [22].

There are very few studies on long-term oncological results and survival data of VATS esophagectomy after nCRT, results in most studies being obscured by heterogeneity of different neoadjuvant regimens and surgical approaches. Spector et al. evaluated the feasibility and safety of three-hole minimally invasive esophagectomy (3HMIE) in patients who received neoadjuvant chemoradiation. The authors compared perioperative and long-term outcomes in 78 patients undergoing preoperative chemotherapy and radiotherapy with patients undergoing direct surgery. Overall operative time, estimated blood loss, proximal and distal margin length, and total hospital stay were not different in the two groups. 3HMIE was found to be feasible with low mortality and acceptable morbidity in locally advanced esophageal cancer who have been treated with neoadjuvant chemoradiation [23]. In a similar study, Lubbers et al. evaluated 161 patients who received neoadjuvant carboplatin and paclitaxel concurrent with 41.4 Gy radiation therapy followed by total minimally invasive VATS esophagectomy at an interval of 6 weeks. The authors noted an R0 resection rate of 97% with in hospital mortality rate of 3.7%. At a median follow-up of 24 months (range 13–38 months), overall survival was 79% and 51% at 1 and 5 years, respectively. The authors concluded that minimally invasive esophagectomy was safe with low morbidity and mortality and acceptable overall survival in patients with nCRT [24].

In spite of documented advantages of minimally invasive VATS surgery over open esophagectomy, VATS surgery had several limitations, double dimensional view, lack of hand eye coordination, use of straight stick instruments with restricted range of movement, and longer learning curve with some surgeons. Although laparoscopic and thoracoscopic surgical systems are now available with 3D vision, they have not gained popularity with most minimally invasive surgeons. Robotic surgery has gained more popularity over 3D laparoscopic surgery due to its inherent advantages.

## Robot-Assisted Minimally Invasive Esophagectomy

Although Da Vinci® robotic surgical system was first used in minimally invasive urologic and pelvic surgery in 2000, R. van Hillegersberg and his team were the first to perform robot-assisted thoraco-laparoscopic lymphadenectomy in 21 patients. The total operative time for robot-assisted thoracoscopic mobilization was 180 min, median blood loss was 400 ml, and median number of lymph nodes dissected was 20 [25]. The adoption of RAMIE thereafter had more acceptance among esophageal surgeons as it reduced the limitations of conventional thoracoscopic esophagectomy. Robot-assisted esophagectomy has a definite advantage over conventional thoracoscopic esophagectomy in providing a stable three-dimensional (3D) view, 10 times magnification of surgical field, better hand eye coordination, and improved dexterity with endo-wristed instruments. The advantage of steady and magnified field of view was better appreciated while operating in areas close to moving structures in the thorax due to pulsatile effects of heart and aorta and respiratory movements. It was also experienced that upper mediastinal dissection and lymph node dissection superior to carina and along recurrent laryngeal nerves were better approached with robotic assistance than with conventional thoracoscopic surgery [26]. RAMIE also had a shorter learning curve compared with conventional thoracoscopic surgery.

Van der Sluis et al. were the first to conduct a randomized controlled trial (the ROBOT trial) comparing the role of robot-assisted minimally invasive esophagectomy (RAMIE) as an alternative to open transthoracic esophagectomy (OTE). In their study, overall surgery related complications occurred less frequently with RAMIE compared with OTE (59% vs 80%; $p = 0.02$). At a median follow-up of 40 months, the short-term and long-term oncological outcomes were comparable in both surgical groups. The results of ROBOT trial demonstrated better quality of life, lower complication rates, and better oncologic outcomes with RAMIE compared with conventional open esophagectomy regardless of clinical stage [27, 28].

Several other retrospective series have shown comparable oncological outcomes and complication rates between RAMIE and conventional VATS esophagectomy [29]. Haiqi et al. retrospectively compared short-term outcomes in patients undergoing RAMIE and conventional video-assisted minimally invasive esophagectomy (VAMIE). The authors did not find any statistically significant difference with respect to number of lymph nodes dissected, postoperative hospital stay, and overall postoperative complications in the two groups, thereby demonstrating the safety and feasibility of RAMIE [30].

One of the main advantages of RAMIE over conventional thoracoscopic surgery is in upper mediastinal lymph node dissection. Multiple studies have demonstrated superiority of RAMIE over VATS esophagectomy with higher mediastinal lymph node yield especially along recurrent laryngeal nerves [30–34]. The survival benefit of extended lymphadenectomy has not been clearly defined in patients undergoing esophagectomy after neoadjuvant chemoradiation. Park et al. retrospectively compared oncological outcomes in patients undergoing RAMIE and VATS esophagectomy. Five-year survival was comparable in the two groups, 69% in RAMIE and 59% in VATS ($p$ = ns). Five-year freedom from locoregional recurrence was also not different in the two groups, 88% in RAMIE and 74% in VATS ($p$ = ns). It was therefore hypothesized that RAMIE would result in at least similar oncological outcome and long-term quality of life compared with conventional thoracoscopic minimally invasive esophagectomy [31].

## Robot-Assisted Minimally Invasive Esophagectomy After Neoadjuvant Chemoradiation

The hesitation of considering robotic esophagectomy after nCRT was mainly attributed to lack of data on feasibility and safety, oncological outcomes, and learning curve associated with the procedure. Other areas of concern with robotic surgeons were presence of initial bulky tumor with metastatic regional lymph nodes with poor response to nCRT or gross local invasion to adjacent mediastinal structures. There has been limited series on the role of RAMIE after neoadjuvant treatment with scarce data on long-term results.

Sarkaria et al. from Memorial Sloan Kettering Cancer Center conducted a prospective observational study on 21 consecutive cases suitable for RAMIE with combined thoraco-laparoscopic robot-assisted minimally invasive esophagectomy. Seventeen patients underwent robotic-assisted Ivor Lewis esophagectomy and four patients underwent robotic McKeown esophagectomy. Sixteen patients (76%) received preoperative treatment, preoperative chemoradiation in 14, and chemotherapy alone in 2 patients. Median hospital stay was 10 days with median lymph nodes dissected being 20. Major complications, extent of lymphadenectomy, and complete resection rate were comparable with other series with open and VATS surgery. The authors observed that complete thoraco-laparoscopic RAMIE was possible even in cases with nCRT. Although lack of haptic feedback is considered as a limitation of robotic approach, the authors did not find this to be a significant drawback taking into consideration that nearly 67% patients received neoadjuvant chemoradiation [35].

Van der Sluis et al. evaluated 108 patients with potentially resectable esophageal cancer undergoing robotic esophagectomy. Majority of patients had T3/T4 disease (74%). Sixty-five percent of patients received neoadjuvant treatment (preoperative chemotherapy in 57%, nCRT in 7%, and radiation alone in 1%). Patients with adenocarcinoma received epirubicin + cisplatin + capecitabine while patients with squamous cell carcinoma received radiation therapy to a dose of 41.4 Gy with concurrent carboplatin + paclitaxel. R0 resection could be achieved in 95% patients with median number of lymph nodes retrieved being 26. At a median follow-up of 58 months, 5-year survival was 42%. RAMIE was found to be oncologically effective with high R0 resection rate in patients receiving induction treatment and provided good local control [36].

Okusanya et al. from University of Pittsburgh Medical Centre retrospectively analyzed 25 patients undergoing RAMIE. Twenty-three patients underwent robotic-assisted Ivor Lewis esophagectomy, while two patients underwent robotic McKeown esophagectomy. Fourteen patients (56%) received nCRT prior to surgery, while 4 received preoperative chemotherapy alone. Median hospital stay was 8 days, while median ICU stay was 2 days only. Median lymph nodes dissected was 26 (range 11–78). R0 resection could be achieved in 24 patients (96%), while 4 patients had complete pathological response after nCRT. Compared with other series of VATS esophagectomy in the same institute, patients with RAMIE had similar 30-day mortality, major complications, median lymph nodes harvested, R0 resection rate, and rate of conversion to open surgery [37].

Goel et al. studied the feasibility of RAMIE after nCRT in 27 cases with locally advanced esophageal cancers. All patients received nCRT to a dose of 50.4Gy/25 Fr with concurrent weekly cisplatin with clinic radiological assessment at 6 weeks interval. Patients underwent robot-assisted McKeown esophagectomy with gastric conduit mobilization and esophagogastric anastomosis in the left neck. Surgical procedure was well tolerated with only one 30-day perioperative mortality. Median number of lymph nodes dissected was 18, and R0 resection could be achieved in 96.3% patients. The study suggested that robot-assisted thoracic mobilization of esophagus was feasible and safe after neoadjuvant chemoradiation in middle third esophageal cancers and also had a shorter learning curve compared with conventional VATS esophagectomy. The procedure had lower ICU stay and postoperative complications with optimal oncological results [38].

Shridhar et al. retrospectively reviewed 89 patients with robotic-assisted Ivor Lewis esophagectomy (RAIL) with 77 patients (87%) having received nCRT. Compared with patients with upfront surgery, there was no difference in mean estimated blood loss, mean operative times, postoperative complications, length of ICU, and hospital stay in patients with nCRT. There were no mortalities in either group. The R0 resection and mean lymph nodes harvested were similar with nCRT group with pCR in 31%. The authors concluded that robotic-assisted Ivor Lewis esophagectomy could be safely performed following neoadjuvant chemoradiation [39].

Coker et al. retrospectively reviewed 23 patients who underwent robotic-assisted transhiatal esophagectomy (RATE). Eighty-three percent of patients (19/23) received nCRT, while 1 patient had preoperative chemotherapy alone. More than 90% of patients had R0 resection with average lymph nodes yield being 15. There were no conversions to open surgery. The authors concluded that in patients with more advanced tumors who had undergone preoperative chemoradiation, RATE could be performed with minimal blood loss, shorter operative time, similar morbidity, and overall survival with significant advantage in terms of nodal dissection [40].

Yun et al. performed a retrospective analytical study in patients undergoing RAMIE with and without nCRT and assessed the overall impact of nCRT on postoperative complications. In their series, 219 patients with esophageal carcinoma underwent RAMIE (35 patients received nCRT), and the results were compared with 289 patients who underwent conventional open esophagectomy (111 patients had nCRT). Patients with nCRT received oxaliplatin + titanium silicate-1 with concurrent external beam radiation (46 Gy/23 Fr over 5–6 weeks). Four weeks after concluding therapy, repeat PET-CT scans were performed for restaging. All patients were then offered esophagectomy, except for patients with distant metastasis to major organs (liver, lung, spine, brain, etc.) or who refused surgery. R0 resection was similar in patients undergoing RAMIE or open esophagectomy after nCRT (94.3% vs 94.6%), and there was no statistically significant difference in the numbers of lymph nodes sampled in the two groups with comparable postoperative morbidity rates. The authors concluded that in patients who received nCRT, patients undergoing RAMIE and open esophagectomy had similar operative time, blood loss, and early recurrence rate. The administration of preoperative chemoradiation did not have any impact on postoperative morbidity in patients who underwent RAMIE [41] (Table 1).

Currently, there are three main surgical approaches for resectable esophageal cancers, open transthoracic esophagectomy, conventional thoracoscopic esophagectomy, and robot-assisted esophagectomy. Although previous studies have demonstrated better short-term outcomes with robot-assisted minimally invasive esophagectomy compared with open surgery, there is no prospective data to compare these two approaches. RAMIE trial is an ongoing multicenter prospective randomized non-inferiority phase III clinical trial to investigate whether robot-assisted esophagectomy would be a safe alternative compared with conventional thoracoscopic esophagectomy for resectable squamous cell carcinoma. All patients would receive preoperative therapy followed by restaging to define feasibility for surgical resection. The primary endpoint of the study is 5-year overall survival, and secondary endpoints are 3,year survival, 5-year disease-free survival, and quality of life after surgery. The study is based on the hypothesis that robot-assisted esophagectomy will result in at least similar oncologic outcomes and longer quality of life, shorter operative time with lesser complications, hospital stay, and blood loss compared with conventional VATS surgery [42].

**Table 1** A retrospective analytical study in patients undergoing RAMIE with and without nCRT and assessed the overall impact of nCRT on postoperative complications

| Authors | Number of patients | No of patients with nCRT | Surgery performed | R0 resection rates | LN harvested (median) | Results |
|---|---|---|---|---|---|---|
| Sarkaria et al. [35] | 21 | 14 nCRT<br>2 nCT | 17—IL<br>4—MK | 81% | 20 | Similar overall major morbidity and mortality, anastomotic leak rate with OE and MIE |
| Okusanya et al. [36] | 25 | 14 nCRT<br>4 nCT | 23—IL<br>2—MK | 96% | 26 | Similar 30-day mortality and clinically significant anastomotic leak rates |
| Goel et al. [37] | 27 | 27 nCRT | 27—MK | 96.3% | 18 | Similar operative times, similar ICU stay, overall low morbidity and mortality |
| Shridhar et al. [38] | 89 | 67 nCRT | All—RAIL | 100% | $20.2 \pm 8.4$ (CRT) vs $21.7 \pm 11$ (no CRT) $p = 0.5$ | No increase in adverse effects in nCRT compared with those who did not receive nCRT |
| Coker et al. [39] | 23 | 19 nCRT<br>1 nCT | All—RATE | 100% | 15 | Minimal blood loss, shorter operative time, similar morbidity and survival compared with OE |
| Yun JK et al. [40] | 219 | 35 nCRT | 18—IL<br>17—MK | 94.3% | $37.9 \pm 15.3$ | Comparable early mortality, early recurrence and postoperative morbidity, compared to OE |

*IL* Ivor Lewis esophagectomy, *MK* McKeown esophagectomy, *OE* open esophagectomy, *MIE* minimally invasive esophagectomy, *RATE* robotic-assisted transhiatal esophagectomy, *RAIL* robotic-assisted Ivor Lewis esophagectomy, *nCRT* neoadjuvant chemoradiation, *nCT* neoadjuvant chemotherapy

## Conclusion

The surgical management for esophageal cancer has evolved over recent years, with a paradigm shift to minimally invasive approach. Robot-assisted esophagectomy has shown to be promising over conventional thoracoscopic esophagectomy, but no studies have proven its superiority over open or standard thoraco-laparoscopic approach. Few studies have incorporated robotic-assisted esophagectomy after nCRT establishing its feasibility but needs further large-scale randomized controlled trials to study its long-term oncologic outcomes.

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