

Perioperative outcomes associated with robotic Ivor Lewis esophagectomy in patient's undergoing neoadjuvant chemoradiotherapy

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Background: Neoadjuvant chemoradiotherapy (NCR) for the treatment of esophageal cancer has been associated with increased perioperative morbidity and mortality. Minimally invasive procedures utilizing robotic techniques have been shown to reduce perioperative complications and length of hospitalization (LOH). The purpose of this study is to compare perioperative outcomes between patients undergoing NCR and robotic-assisted Ivor Lewis esophagectomy (RAIL) versus upfront RAIL.

Methods: A database of esophagectomy patients was queried to identify RAIL patients. Differences in perioperative outcomes were analyzed between NCR and non NCR patients.

Results: Eighty-nine patients were identified who underwent RAIL. Seventy-seven patients (87%) had NCR and 22 patients did not (13%). The median age was 66 (range, 44-83). The median age of the patients treated with NCR was younger {69 [44-83] *vs.* 64 [46-81] years respectively, $P=0.05$ }. The patients who underwent NCR had a higher BMI than those who went straight to esophagectomy (31 *vs.* 27; $P=0.001$). There were no conversions to open laparotomy or thoracotomy in either group. There were no statistically significant differences in the mean operative times and estimated blood loss (EBL) between both groups. Complications occurred in 17 (19.1%) patients. There were no statistically significant differences in the rates of any complications between patients receiving NCR and those that did not receive NCR ($P=0.11$). There were no deaths in either group. The total number of days in hospital and total number of intensive care unit (ICU) days were also similar in both groups ($P=0.25$). There was no statistically significant difference in the mean number of lymph nodes harvested in the patients treated with NCR compared with those treated without NCR.

Conclusions: We have demonstrated that RAIL is a safe and feasible option for patients with esophageal cancer. The administration of NCR to RAIL did not result in an increase in perioperative morbidity and mortality. The number of lymph nodes harvested and the completeness of resection was also similar between patients who received NCR and those who did not. Longer follow-up is required in order to determine long term oncologic outcome.

Keywords: Robotic esophagectomy; esophageal cancer; neoadjuvant chemoradiotherapy (NCR)

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Introduction

In 2013 there will be an estimated 17,990 new cases of esophageal cancer and 15,210 deaths from the disease in the United States (1). The prognosis for patients with locally advanced esophageal cancer (defined as $\geq T2$ or node positive disease) is poor, with five-year survival rates ranging from 15-34% (2,3). Surgery alone is associated with poor long-term outcomes and definitive chemoradiation has a high locoregional recurrence rate in locally advanced esophageal cancer (4-6).

There has been conflicting evidence about the utility of neoadjuvant chemotherapy in the management of patients with locally advanced esophageal cancer (7-16). Some of these studies were limited by inadequate pre-operative staging; as well as by heterogeneity of patient population including both adenocarcinomas and squamous cell carcinomas (SCC). In spite of the conflicting evidence from some of the earlier trials, neoadjuvant chemoradiation (NCR) is currently considered the standard of care in patients with locally advanced esophageal cancer. It is currently included in the National Comprehensive Cancer Network Guidelines (NCCN) (17). In general, patients who have a response to neoadjuvant chemotherapy have improved disease free survival (DFS) and overall survival (OS) compared to patients that do not (18).

Ivor Lewis esophagectomy (ILE) is a common surgical approach for esophageal resection. The other approaches that are routinely used are the transhiatal esophagectomy (THE) and three-field esophagectomy (TFE). ILE is performed using both a right anterolateral thoracotomy incision and an abdominal incision. A significant source of the morbidity from this approach is due to the right thoracotomy. These complications include significant post-operative pain, atelectasis, pneumonia and atrial fibrillation (Afib) with pulmonary and wound complications being the most common morbidities associated with the transthoracic approach.

Minimally invasive esophageal surgery (MIE) has been increasingly used in patients undergoing surgery for esophageal cancer (19-21). Potential advantages of MIE include the decreased post-operative pain; lower post-operative wound infection, decreased pulmonary complications, and decreased length of hospitalization (LOH). Robotic ILE is a new technique in the armamentarium for MIE surgery (22,23). Robotic esophageal surgery has the ability to overcome some of the limitations of laparoscopic and thoracoscopic approaches to esophagectomy. Specifically, it allows for a broader view

of the operative field in the mediastinum, three-dimensional camera views, as well as greater range of instrument motion and articulation.

There is limited data on the impact of NCR in patients treated with robotic-assisted ILE (RAIL). We sought to examine our single institution experience with this technique in patients undergoing neoadjuvant chemo-radiation and to investigate primary operative and oncologic outcomes. To date this represents the largest series of consecutive patients treated with robotic Ivor-Lewis esophagectomy with or without NCR.

Methods

A query was performed from an Institutional Review Board (IRB) approved, prospectively maintained database of patients undergoing RAIL between October 2010 and June 2012. Perioperative morbidity and mortality were compared in the cohort of patients who received NCR *vs.* the cohort that did not receive NCR.

Endpoints and statistical analysis

The primary operative endpoints were median operating room (OR) time, estimated blood loss (EBL), intensive care unit (ICU) days following surgery, and LOH. Secondary end-points included peri-operative adverse events (AEs) less than 30 days following surgery; including pneumonia, Afib, deep vein thrombosis (DVT)/pulmonary embolism (PE), wound infection, leak, and death.

Statistical analysis was performed using SPSS[®] version 21.0 (IBM[®], Chicago, IL, USA). Continuous variables were compared using the Kruskal Wallis or the ANOVA tests as appropriate. Pearson's Chi-square test was used to compare categorical variables. All statistical tests were two-sided and an α (type I) error <0.05 was considered statistically significant.

Neoadjuvant chemoradiation therapy

Patients were discussed in a weekly multi-disciplinary tumor board conference and pathology was reviewed at our institution. Pre-operative staging including endoscopic ultrasound, CT chest, abdomen and pelvis and PET scan as per NCCN guidelines (17). Patients who had locally advanced disease ($\geq T2$ and/or $\geq N1$) were treated with neoadjuvant chemoradiation. The choice of chemotherapy

Table 1 Pre-operative patient and tumor

Characteristics	Neoadjuvant chemoradiation		P value
	Yes (n=67)	No (n=22)	
Mean patient age (years)	64±11	69±9	0.05
Gender			
Male	54 (80.6%)	18 (81.8%)	≤0.0001
Female	13 (19.4%)	4 (18.2%)	
Mean BMI (kg/m ²)	31±5	27±5	≤0.001
Pre-operative stage by EUS			
Stage 0	0	2 (9.1%)	0.059
Stage 1	5 (7.5%)	18 (81.8%)	≤0.0001
Stage 2	24 (35.8%)	2 (9.1%)	≤0.0001
Stage 3	38 (56.7%)	0	≤0.001

was left to the discretion of the treatment medical oncologist.

Patients treated at our institution receive infusional 5-fluorouracil (5-FU) and cisplatin, with concurrent external beam radiation for a total dose of 50.4 Gy over the course of 5-6 weeks. Six weeks after the conclusion of therapy, patients restaging PET-CT scans were performed. Patients without evidence of metastatic disease and good performance status were then offered esophagectomy. Esophagectomy was performed during the 6-12 week window after conclusion of chemoradiation. Patients are referred to cardiac and pulmonary specialists for pre-operative risk assessment and optimization prior to surgery.

Surgical technique

Our surgical technique for RAIL has been previously described (22,23) using the DaVinci Surgical System (Intuitive Surgical, Sunnyvale, CA, USA). Of note, no patients underwent pyloric emptying procedure. Rather, in lieu of a pyloromyotomy, three-hundred units of botulinum toxin (Botox[®]) were injected into the pylorus. A feeding jejunostomy tube was placed routinely in all the patients.

The thoracic portion of the procedure was done entirely with the robot using three incisions. Mediastinal lymph node dissection of levels 7, 8, and 9 was routinely performed. Intra-operative frozen section was used to confirm negative margins. The anastomosis was performed either via a circular stapling technique, or handsewn.

Post-operative care

Patients were extubated in the operating or recovery room and admitted to the ICU overnight for observation. On post-operative day 4 or 5, an esophagram is obtained to identify leaks and delayed gastric emptying. If the esophagram is normal, the nasogastric tube was removed and clear liquid diet started. The chest tube was removed once patients were tolerating a regular diet and there was no evidence of chyle leak.

Results

Patient demographics

Eighty-nine patients underwent RAIL during the study period. Seventy-seven patients (87%) had NCR and 22 patients did not (13%). The median age was 66 (range, 44-83), there were 69 men (80%). The median age of the patients treated with NCR was younger than the patients in the non NCR group {69 [44-83] *vs.* 64 [46-81] years respectively, P=0.05}. The patients who underwent NCR had a higher BMI than those who went straight to esophagectomy. The median overall BMI was 28 kg/m². The mean BMI for those receiving NCR was 31±5 and 27±5 for those who did not (P=0.001). Seventy-seven patients had adenocarcinomas (86%), 8 (9%) patients had SCC, 3 (3%) patients had neuroendocrine tumors and two patients (2%) had high-grade dysplasia (HGD). Patients treated with NCR had a higher pre-operative BMI compared with patients treated with RAIL alone (P=0.001) (*Table 1*).

Perioperative outcome

There were no conversions to open laparotomy or thoracotomy in either group. There were no statistically significant differences in the mean operative times and EBL between both groups. The mean operative time in the group treated with NCR was 434±89 and 427±82 minutes in the cohort of treated with surgery alone (P=0.74). The mean EBL was 149±98 mL in the NCR and 153±78 mL in the group treated with surgery alone (P=0.52).

Post-operative complications

Complications occurred in 17 (19.1%) patients. There were no statistically significant differences in the rates of any

Table 2 Perioperative morbidity and mortality

Variables	Yes	No	P value
Mean operative time (min)	434±89	427±82	0.74
Mean EBL (mL)	149±98	153±78	0.52
Conversion to open	0	0	1
Median ICU (days)	2 [1-30]	2 [1-21]	0.25
Median length of hospitalization (days)	9 [6-30]	10 [6-28]	0.09
Morbidity	10 (15%)	7 (32%)	0.11
Atrial fibrillation	4 (6%)	2 (9%)	0.63
Pneumonia	4 (6%)	3 (13.6%)	0.36
Wound infection	0	0	1
Leaks	–	–	0.12
Anastomotic	0	2	1
Conduit	1	0	1
90-day mortality	0	0	1

EBL, estimated blood loss; ICU, intensive care unit.

Table 3 Pathologic characteristics

Characteristics	Neoadjuvant chemoradiation		P value
	Yes, n=67	No, n=22	
Histology			
Adenocarcinoma	58 (86.6%)	19 (86.4%)	1
Squamous cell carcinoma	7 (10.4%)	1 (4.5%)	0.67
High grade dysplasia	0	2 (9.1%)	0.06
Other	2 (3%)	0	1
Resection status			
R0	67	22	1
Pathologic response			
Complete	22 (32.8%)		
Partial	32 (47.8%)		
None	13 (19.4%)		
Lymph nodes harvested (mean)	20.2±8.4	21.7±11	0.5

complications between patients receiving NCR n=10 (15%) and those that did not receive NCR n=7 (32%) (P=0.11). The post-operative complications included Afib 6 (6.7%), pneumonia 7 (7.9%), anastomotic leak n=2 (2.2%), conduit staple line leak n=1 (1.1%) and chyle leak n=1 (1.1%). A-fib occurred in 4 (6%) of the NCR patients and 2 (9%)

of the non NCR patients (P=0.63). Of the 7 patients who developed pneumonias, 4 (6%) were in the NCR cohort and 3 (13.6%) in the non NCR group (P=0.36). The two anastomotic leaks occurred in the patients in the patients treated without NCR and one gastric conduit leak in the patient treated with NCR (P=0.12). There were no deaths in either group (Table 2).

The total number of days in hospital and total number of ICU days were also similar in both groups (Table 2). The NCR patients spent a median of 9 [6-30] days in the hospital compared to the non NCR group who spent a median of 10 [6-28] days hospitalized (P=0.09). The median ICU stay for both groups was 2 [2-30] days (P=0.25). Those patients who developed a complication had a median LOH of 15 days [7-30] compared to 9 [6-21] days in those who did not experience a complication (P<0.0001).

Pathology

The tumor was located in the mid esophagus in 7 (7.8%), and in the lower third or gastro-esophageal junction in 82 (92.2%) of patients. All patients underwent an R0 resection. Of the 67 patients receiving NCR, there were 22 (32.8%) who exhibited a pathological complete response (pCR), 32 (47.8%) with a partial response, and 13 (19.4%) who exhibited no response. There was no statistically significant difference in the mean number of lymph nodes harvested in the patients treated with NCR compared with those treated without NCR. The mean number of LN's harvested in the NCR group was 20.2±8.4 compared to 21.7±11 in the non NCR cohort (P=0.5) (Table 3).

Discussion

We report our series of 89 patients who underwent RILE with or without receiving neoadjuvant therapy. We demonstrated that there was no increase in operative time or EBL in patients receiving NCR compared to those who did not. Additionally, incidences of post-operative complications including anastomotic leak, Afib, wound infection, chylous thorax, and pneumonia did not differ between cohorts. No mortalities were noted in either group. Length of ICU stay and hospitalization was similar between groups and not found to be statistically significant. As to be expected, patients in either cohort who developed a complication exhibited an increase in LOH.

Esophageal cancer was the seventh leading cause of death

in the United States in 2012 (24). For tumors invading beyond the muscularis propria or involving locoregional lymph nodes, surgery alone is associated with dismal survival thereby necessitating a multimodality approach employing chemoradiation (3,4,7,16). The response to neoadjuvant chemoradiation continues to be one of the most important factors in predicting OS in patients undergoing NCR (18,25). The CROSS trial randomized patients with the resectable esophageal cancer to receive surgery alone or chemotherapy followed by surgery. The median OS was 49.4 months in the chemoradiotherapy-surgery group *vs.* 24 months in the surgery group (HR, 0.657; 95% CI, 0.495-0.871; P=0.003) (16). In patients who underwent NCR, the pCR rate was 29%.

Esophagectomy alone remains the cornerstone treatment for early-stage esophageal carcinoma. Compared with surgery for other gastrointestinal malignancies, esophagectomy has higher morbidity and mortality rates. Data does suggest that performing esophagectomy in a high volume reduces the post-operative complication rate and mortality (26). Pulmonary and wound complications contribute to the majority of the morbidity following a transthoracic esophagectomy. The minimally invasive approach to esophagectomy offers the potential to reduce pulmonary complications, wound infections, post-operative pain, improve recovery times, and shorter lengths of hospitalization (27).

The initial trials of MIE involved the mobilization of the gastric conduit laparoscopically with completion of the thoracic portion of the procedure done either thoracoscopically or through a small thoracotomy (22); however this approach still has the potential for increased wound and pulmonary complications. A retrospective review of 530 patients treated with minimally invasive total minimally invasive ILE treated at the University of Pittsburgh, demonstrated an operative mortality rate of 1% with a median length of stay of 7 days (28).

A multicenter, open-label, controlled trial of 115 patients randomized to open or minimally invasive transthoracic esophagectomy, demonstrated significantly lower rates of pulmonary infections in patients undergoing MIE (24% *vs.* 12%, P=0.005). The length of stay was also shorter in those patients undergoing less invasive techniques (11 *vs.* 14 days, P=0.044) (27). Retrospective data and case series have also demonstrated that minimally invasive approaches are safe and have comparable oncologic outcomes (29).

Robotic esophageal surgery has the ability to overcome some of the limitations of laparoscopic and thoracoscopic

approaches to esophagectomy. Specifically, it allows for a broader view of the operative field in the mediastinum and greater range of instrument motion. The data regarding the safety and oncologic outcomes in patients undergoing robotic-assisted esophagogastrectomies is limited, with fewer than a hundred patients published in the surgical literature.

The utility of the robotic esophagectomy in patients undergoing treatment with NCR is unknown however it may allow improved visualization of the operative field and more precise dissection and manipulation of friable tissues. We have demonstrated that in patients who were treated with NCR and underwent robotic approaches to esophageal resection, there was no increase in AEs compared to those who did not receive NCR. Additionally, there were no differences in adverse outcomes when comparing to historical minimally invasive approaches (data not shown).

Due to its retrospective nature, there are potential for selection bias. We currently offer the robotic approach to all patients regardless of their treatment characteristics, age, or BMI. Additionally patients must be able to tolerate the operation from a cardiopulmonary standpoint. There were no differences in age amongst groups and the NCR group actually had higher BMI's then the non NCR cohort. Also we report all consecutive patients undergoing the approach thereby limiting patient selection bias in our data.

Conclusions

We have demonstrated that RILE is a safe and feasible option for patients with esophageal cancer. The administration of neoadjuvant chemotherapy to RAIL did not result in an increase in perioperative morbidity and mortality. Operative time, and EBL was not impacted by patients undergoing NCR. The number of lymph nodes harvested and the completeness of resection was also similar between patients who received neoadjuvant chemoradiation and those who did not. Longer follow-up is required in order to determine long term oncologic outcome.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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