Minimally invasive esophagectomy/ gastroesophagectomy for cancer - Long term results from a single institution.

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Abstract

Background: Esophagectomy is a complex operation. Minimally invasive esophagectomy (MIE) may decrease the morbidity and mortality of resection. The aim of this study was to produce long term outcome of MIE from a single center in Nepal.

Methods: Patients with squamous cell carcinoma and adenocarcinoma of esophagus/ gastroesophageal junction who underwent MIE between 2001-2018 were analyzed.

Results: 215 patients were taken for MIE during 2001-2018. There was 11.2% conversion rate. Totally MIE approach was performed in 43% cases and hybrid MIE in 57% cases. Mean operative time, intra operative blood loss, anastomotic leak, pulmonary infection, recurrent laryngeal nerve injury and in-hospital mortality were 246 min, 286 ml, 13.1%, 9%, 6.8% and 3%, respectively. Final histopathology revealed most common Stages III and IV in 51.2% and 36.1%, respectively. The median survival was 34 months and 5-OS was 27%. 5-OS was 27% and o% for R0 and R+ resection (p<.001). Median survival after radical and non-radical lymphadenectomy was 36 months and 25 months (p=.003), respectively. Responders to neoadjuvant treatment had the best survival.

Conclusion: MIE has got acceptable post operative morbidities. R0 resection, early stage of disease, radical lymphadenectomy and responders to neoadjuvant treatment had got the best survival results

Keywords: Esophagectomy; Minimal invasive esophagectomy; Esophageal cancer

Introduction

Surgery remains the gold standard treatment modality for esophageal and gastroesophageal junction (GEJ) cancer usually in combination with perioperative treatment. Esophagectomy for esophageal cancer is associated with more frequent morbidity and mortality than other gastrointestinal cancer surgeries. Minimally invasive esophagectomy (MIE) is considered to be less invasive than open esophagectomy (OE) and is expected to improve postoperative short-term outcomes. The intention is to achieve a curative resection but with substantially less surgical trauma relating to operative access. Initial enthusiasm was, however, dampened when early case series reported only limited success in achieving these aims.[1] Not until the experience described by Luketich et al. did it become apparent that MIE might offer a viable alternative to traditional open surgery.[2], [3] Although the superiority of MIE in terms of short-term outcome has not been definitively

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established, MIE is being increasingly adopted.[4]

OE and moreover MIE is performed is being performed in very few centers in Nepal. This study was aimed to evaluate the postoperative complications and long term oncological outcome after MIE.

Methods

Patient:

We evaluated all patients with cancer of the thoracic esophagus and GEJ who underwent MIE at BP Koirala Memorial Cancer Hospital (BPKMCH) between 2010 and 2018. This was a retrospective analysis of prospectively maintained database. The study was approved by the Institutional Review Committee, BPKMCH. A written consent from each patient was obtained.

Staging:

The preoperative workup included physical examination, standard laboratory tests, pulmonary function test, ECG, Echocardiography and anesthesiological assessment. Esophagogastroduodenoscopy (OGD) was performed to properly locate the tumor and to obtain biopsy. CT scan of chest and abdomen was performed for staging of the disease. Clinical and final pathological staging was done as per AJCC/ UICC 8th edition.[5] Only clinical stages I-IVa patients with ECOG 0-1 were considered for surgery.

Treatment:

In initial years, patients (both SCC and adenocarcinoma) with resectable disease were subjected to upfront surgery. In adenocarcinoma of GEJ with >T2 or N+, adjuvant chemoradiation was used as per MacDonald's regimen.[6] For locally advanced SCC, neoadjuvant chemoradiation (Cisplatin + 5-FU and RT 41.4-50.4 Gy) or 2 cycles of chemotherapy alone (cisplatin + 5-FU) was used before surgery. For adenocarcinoma, MAGIC protocol was used.[7]

In recent years, for locally advanced SCC and adenocarcinoma, treatment was initiated as per CROSS protocol[8] and FLOT protocol[9], respectively.

Depending upon the location of the tumor, the following approaches were used:

1. Totally MIE
    a. 3- incision: VATS – laparoscopy – neck
    b. 2- incision: transhiatal laparoscopy – neck
    c. 1-incision- laparoscopy
2. Hybrid
    a. 3- incision – thoracotomy-laparoscopy-neck
    b. 3-incision – VATS-laparotomy-neck
    c. 2-incision-laparoscopy-thoracotomy

In years 2010-2012, a lateral approach was used during video-assisted thoracoscopic (VATS) phase. A single lung ventilation was done with the patient positioned in left lateral position. An optical 10 mm port was introduced through the 8^{th} intercostal space along the mid axillary line. A 5 mm port for lung retraction was used in 4-5 th intercostal space along anterior axillary line. A 3 cm incision for surgeon's working instruments was placed in 7^{th}-8^{th} intercostal space just posterior to the infrascapular line. Surgeon stood behind the patient. Since 2013 and onwards, a semiprone approach with 8 mm Hg pneumothorax was used. A 10 mm optical port (7^{th} intercostal space) and two 5 mm

working ports along 5th and and 9th intercostal spaces were inserted through right thorax.

During Laparoscopy phase, one 10 mm optical port and four 5 mm working ports were inserted in "V" fashion

Lymph nodal dissection was divided into radical (D2 and D2 + lower mediastinal (low med) for GEJ tumors; two-field; extended two-field; total mediastinal and three-field) and non-radical (sampling only). In two-field (2-FD), infracarinal nodal dissection along with abdominal D2 dissection was done. Nodes along right recurrent laryngeal nerve and along both recurrent laryngeal nerves were added to 2-FD in extended (ext 2-FD) and total mediastinal nodal dissection (total 2-FD), respectively. Stomach was preferably used for reconstruction. After extended total gastrectomy, jejunum was preferably used.

Follow-up:

Patients were followed up every 4 months for first 2 years then every six months for next three years.

Statistical analysis:

Pateints were analysed for presentation, staging, complications and 5 year overall (5-OS) survival using SPSS 26. Categorical variables were compared using the Chi square test, and continuous data were analyzed using the Mann–Whitney U test. Survival was estimated using Kaplan–Meier survival curves and compared using the log-rank test. P<.05 was considered significant.

Results

There were 215 patients who underwent surgery for cancer of esophagus and GEJ from 2010 till 2018.Demographic, basic clinical findings and treatment modalities are shown in table 1. In 24 patients (11.2%), conversion to open surgery was done (Fig 1.).The reasons for conversion were inability to achieve single lung ventilation or dense adhesions in thoracic cavity (18 cases) and locally advanced disease (4 cases during VATS phase and 2 cases during laparoscopy phase). Hence, proper evaluation of 191 cases, who underwent MIE was done. Full description of surgical procedures has been shown in table 2. Ninety three patients (48.7%) had VATS approach, among which 13 (6.8%) had lateral port placement and 80 (41.9%) had semi-prone port placement. Intraoperative details, final tumor histology and final staging (UICC 8th edition) has been shown in Table 3, 4 and 5, Median survival was 34 months with 5-OS of 27% (Fig.2). Survival analysis according to final stage, resection margin status, surgical approach and type of lymphadenectomy have been shown in figures 3, 4 and 5, respectively.

Table 1. Demographic, clinical presentation and treatment (n=215).

Mean Age	59 years (range: 28-81)
Sex Male Female	 122 (56.7%) 93 (43.3%)
Dysphagia	210 (98%)
Gr 0 Gr I Gr II Gr III Gr IV	6 (2.8%) 1 (0.5%) 57 (26.5%) 138 (64.2%) 13 (6%)
Duration of dysphagia	4.3 months
Co-morbidities	61 (28%)
Weight loss	8.4 kg
Treatment	
Surgery only	109 (50.7%)

Preop chemoradiation-surgery	41 (19%)
Chemotherapy-surgery-chemotherapy	27 (12.6%)
Surgery- chemoradiation	25 (11.6%)
Surgery-chemotherapy	7 (3.3%)
Chenotherapy-surgery	5 (2.3%)
Chemotherapy-surgery-chemoradiation	1 (0.5%)

5-OS for final pathological stages 0, I, II, III, and IV was 100%, 83%, 46%, 26%, and 14%, respectively. Excluding post operative mortality, 66 patients underwent neoadjuvant treatment (concurrent chemoradiation followed by surgery or perioperative chemotherapy and surgery) and 119 patients underwent upfront surgery with or without adjuvant treatment.respectively.

Table 2. Surgical procedures (n=191).

Procedure	N	%
Thoracotomy-Laparoscopy McKewon's	54	28.3
VATS-Laparoscopy McKewon's	53	27.7
VATS-laparotomy McKeown's	40	20.9
Laparoscopic Transhiatal (THE)	32	16.8
Laparoscopic extended total gastrectomy (ETG)	6	3.1
Ivor-Lewis Laparoscopy-thoracotomy	4	2.1
Laparoscopic subtotal gastroesophagectomy	2	1

In neoadjuvant group, responders and non-responders had median survival of 47 months and 19 months, respectively. Median survival in upfront surgery (+/- adjuvant treatment) was 33 months (Fig. 7).

Table 3. Surgical details and final pathological staging (n=191).

Details	N	%
Approach		
Transthoracic (TT)	151	79.1
THE	32	16.8
Abdominal only (abd)	8	4.2
Mean operative time	246 min	
Mean Intra op blood loss	286 ml	
Lymphadenectomy		
Sampling	18	9.4
2-FD	111	58.1
Abd D2	9	4.7
Ext 2-FD	7	3.7
Total 2-FD	15	7.9
Abd D2 + low med	27	14.1
Abd D1	4	2.1
Summary of lymphadenectomy		
Radical	170	89
Non-radical	21	11
Level of anastomosis		
Chest	12	6.3
Neck	179	93.7
Postop complications		
30-day mortality	4	2.1
Rec Laryngeal Nerve injury	13	6.8
Anastomotic leak	25	13.1
Pulmonary complications	18	9.4
Conduit		
Stomach	185	96.9
Jejunum	6	3.1
Margin status		
R0	182	95.3
R+	9	4.7

Table 4. Location and final tumor histology.

Location		
Upper	6	3.1
Mid	60	31.4
GEJ I	81	42.4
GEJ II	40	20.9
GEJ III	4	2.1
Final histology		
Squamous cell (SCC)	125	65.4
Adenocarcinoma	62	32.4
Leiomyosarcoma	2	1
Lymphoma	1	.5
Neuroendocrina carcinoma	1	.5

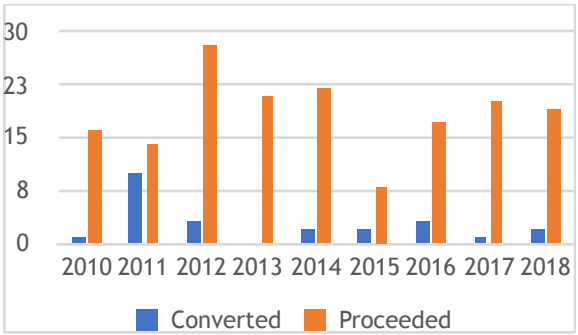

Figure 1: Surgical Procedures

Table 5. Final pUICC (8th edition)

Stage	N	%
0	1	.5
I	13	6.8
II	10	5.2
III	98	51.2
IV	69	36.1

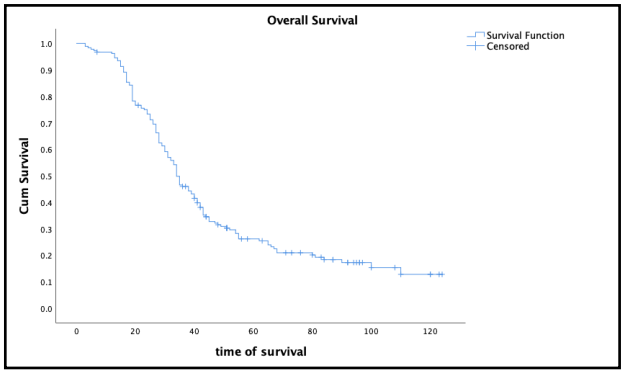

Fig. 2. Overall survival.

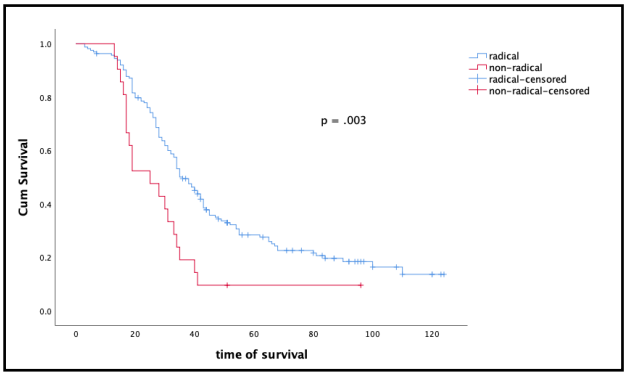

Fig.3. Final stage and survival.

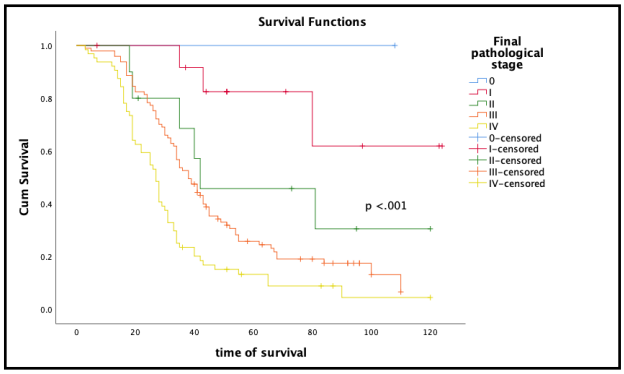

Fig 4. Resection margin and survival (5-OS: R0 – 27%; R+ - 0%

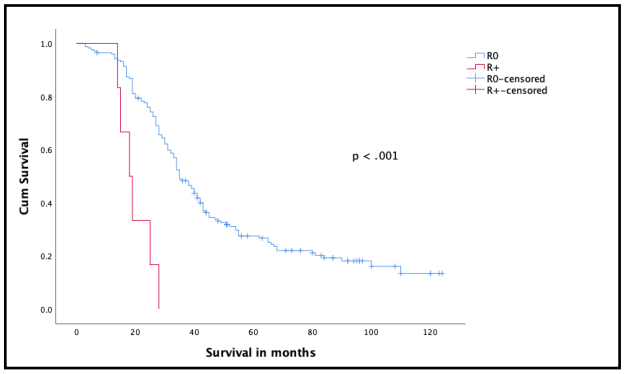

Fig. 5. Surgical approach and survival (median survival: TT – 35 months; THE – 34 months, Abd – 29 months).

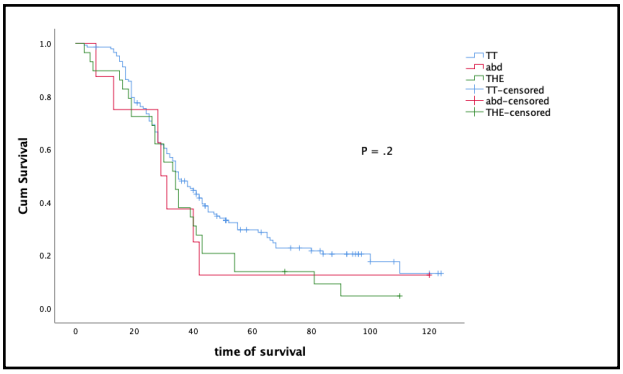

Fig. 6. Lymphadenectomy and survival (median survival: radical – 36 m; non-radical – 25 months).

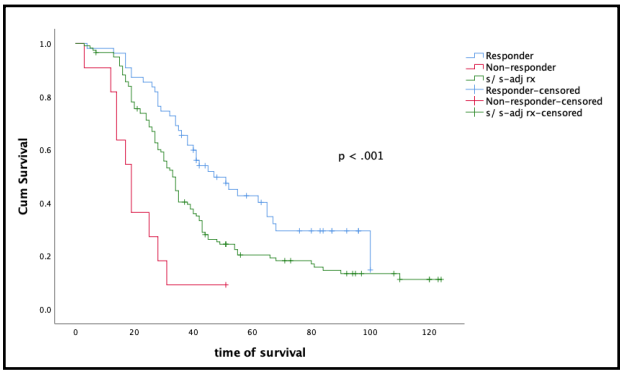

Fig. 7. Survival in neoadjuvant and upfront surgery groups.

Discussion

Management of esophageal cancer has not been well studied and reported from Nepal. The results from this study highlight the long term outcomes of MIE. We had earlier reported the feasibility, safety profile and early outcome of MIE in 34 patients.[10] So far, six RCTs have been published comparing MIE vs OE.[11, 12, 13, 14, 15, 16,] The well conducted TIME trial showed pulmonary infection was significantly less in MIE group in comparison to open group (9% vs 29%, p=.005) in first 2 weeks of surgery.[14]In a later follow up, 3–OS was 40.4% in open group vs 50.5% in MIE group (p=.207) confirming the similar oncological outcome in MIE group. [17] Similar OS and DFS (disease free survival) findings were obtained in the recently published, single-center ROBOT (Robot-Assisted Minimally Invasive Thoracolaparoscopic Esophagectomy Versus Open Transthoracic Esopha- gectomy for Resectable Esophageal Cancer) trial, which compared totally minimally invasive esophagectomy with a robotic thoracic phase vs open esophagectomy. [12]

MIRO trial compared the hybrid approach (laparoscopic abdominal phase, open thoracic phase) to OE: the. [18] Its long-term results—showing equal results for both arms—were published in 2019. Primary endpoint of the MIRO trial was the frequency of perioperative complications of grade II or higher according to the modified Clavien-Dindo classification (MCDC) . Results showed a significantly lower rate of major complications (36%), especially pulmonary complications (18%), in the hybrid group compared with the OE group (64% and 30%, respectively).

In a meta-analysis of above mentioned six RCTs (n=822), 3-OS was 56% for MIE and 52% for OE (p=.54). But overall complication rate, rate of pneumonia, pulmonary complications were significantly less in MIE group. [19]

In a review of 24233 esphagectomies (from Japanese National Clinical Dtabase) for esophageal cancer, Yoshida et al confirmed superiority of MIE over open surgery in terms of incidence of most postoperative morbidities and surgery-related mortality.[20]

In 2016, Yibulayin et al. analyzed fifty-seven studies containing 15,790 cases of resectable esophageal cancer, the highest numbered metaanalysis. It found a reduction of overall postoperative complications in patients treated with MIE (41.5%) vs. OE (48.2%).

Specifically, pulmonary complications (OR = 0.527, 95% CI = 0431~0.645, p < 0.05), cardiovascular complications (OR = 0.770, 95% CI = 0.681-0.872, p < 0.05), and surgical technology-related complications (OR = 0.639, 95% CI = 0.522-0.781, p < 0.05), as well as in-hospital mortality (OR = 0.668, 95% CI = 0.539-0.827, p < 0.05), were found to be lower in the MIE group. The number of harvested lymph nodes did not show significant differences.[21]

Currently, it is estimated that nearly 45% of patients are operated using a minimally invasive approach worldwide .[22] At BPKMCH, MIE was started in 2010 and it has become now a standard surgical modality. Since the study period was from 2010 to 2018 (8 years), treatment protocol varied from upfront surgery only or surgery/ adjuvant treatment (64.4%) to neoadjuvant treatment followed by surgery (35.6%).

In early years, during VATS phase, double lumen endotracheal tube was used to achieve single lung ventilation. A high percentage of patients needed conversion mostly due to inability to achieve single lung ventilation. From year 2012, we have adopted the policy of conventional single endotracheal tube abd making the lung collapse with CO2 pneumothorax. In later years, the conversion rate has come down to 1%.

Out of 191 patients, 82 (43%) underwent totally MIE approach; 40 patients (30%) had VATS approach for the primary tumor and only gastric mobilization was done with laparotomy approach. We believe, avoiding the major thoracotomy for the later group of patients also minimized the post operative complications. As observed in our series, SCC (65.4%) was the most common entity for which surgery was performed. Most patients had final pathological stage of III (51.2%) and a substantial percentage (36.1%) had stage IV (mostly due to T4N2-3M0 disease). The later appears to be the reason for suboptimal Median survival of 34 months and 5-OS of 27%.

If we compare with a landmark TIME trial[14] (OT time: 329 min, blood loss: 200 ml, conversion: 14%, leak: 12%, pulmonary infection: 9%, in-hospital mortality: 3%), our study has almost identical results (OT time: 246 min, blood loss: 286 ml, conversion: 11.2%, leak: 13.1%, pulmonary infection: 9%, in-hospital mortality: 3%).

Early stage, R0 resection status and radical lymphadenectomy were the most determining prognostic factors for better survival. Responders to the neoadjuvant treatment had the best survival outcome. There was no difference in survival in regards to the approach (TT/ THE/ Abdominal only) so far the oncological principles of radicality of nodal dissection and R0 resection are followed.

Though it was a prospectively maintained database, the study itself was retrospective in nature. Besides, the other limitation of the study was heterogenecity in treatment protocol during different duration of time.

Conclusion

This study highlights major benefits of MIE in Nepalese context as well with an acceptable oncological outcome.

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