J Nepal Health Res Counc 2022 Oct-Dec;20(57): 868-74

Trends in Surgical Management of Esophageal Cancer

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ABSTRACT

Background: Management of esophageal cancer has changed to a combined modality approach over the past two decades due to poor outcome. Recently, multimodal treatment has become the standard practice. The aim of this study was to evaluate the changing trends in management and outcomes of esophagectomy over 15 years from a single center in Nepal.

Methods: Patients with squamous cell carcinoma and adenocarcinoma of esophagus/ gastroesophageal junction who underwent surgery between 2001-2018 were analyzed. Patients were grouped into three successive 5-year periods.

Results: 547 patients underwent esophagectomy during 2001-2018. There was increased trend of neoadjuvant treatment from 9-13% to 52% (p<.001) and minimally invasive surgery (MIS) from 0% to 80% (p<.001). 30-day mortality decreased from 8% to 1% (p=.01). The 5-overall survival was 24% which increased from 17% to 27% (p=.003).

Conclusions: Long term outcome has improved over last 15 years with decreasing mortality which appears to be due to incorporation of MIS and neoadjuvant treatment.

Keywords: Esophagectomy; esophageal cancer; multimodality therapy

INTRODUCTION

Esophageal cancer is one of the most aggressive of gastrointestinal malignancies. At diagnosis, nearly 50% of patients have cancer extending beyond the locoregional confines of the primary.[1] The overall 5-year survival rate ranges from 15 to 25%.[2] Significant changes in the management of esophageal cancer have been introduced over the past two decades, specifically the incorporation of combined maodality approach. Esophagectomy has always remained the mainstay of treatment, usually in combination with chemoradiation.[3,4]and 84.3% patients were male. The overall morbidity rate was 41.9%. Thirty-day and operative mortality rates after esophagectomy were 1.2% and 3.4%, respectively. Overall morbidity was significantly higher in the minimally invasive esophagectomy group than in the open esophagectomy group (44.3% vs 40.8%, P = 0.016 Furthermore, surgical techniques are evolving with the introduction of endoscopic therapy and minimally invasive techniques.[5-7]the optimal treatment strategy for early-stage EAC is undefined. Endoscopic eradication therapy, consisting of endoscopic resection and mucosal ablation, has revolutionized therapy for superficial (T1a The overall impact of these changes on survival is unknown.[7]

The overall scenario of management of esophageal cancer has not been well studied and reported in Nepal. This study evaluates outcomes following esophageal resection during 15 years in a single-center in Nepal. Key changes in management strategy and their potential impact have been highlighted.

METHODS

The study was a hospital based retrospective study conducted at BP Koirala Memorial Cancer Hospital (BPKMCH) between 2001 and 2018. Three time periods were defined: 2001-2006, 2007-2012 and 2013-2018. The study was approved by the Institutional Review Committee, BPKMCH. All patients with cancer of the thoracic esophagus or gastroesophageal junction (GEJ) seeking surgical treatment at BPKMCH between 2001 and 2018 were included. Only clinical stages I-IVa patients

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with ECOG 0-1 were considered for surgery. Patients with ECOG ≥ 2 and clinical stage IVb were excluded.

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.[8]

Treatment protocol varied from surgery alone to multimodality treatment. In initial years specially during 2001-2012, 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. [9] 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.[10]

In recent years, for locally advanced SCC and adenocarcinoma, treatment was initiated as per CROSS protocol[11] and FLOT protocol[12], respectively.

Surgical management was transthoracic (Ivor-Lewis/ McKeown's/ left thoracotomy/ left throcaolaparotomy), transhiatal and extended total gastrectomy (through laparotomy alone). In three incision minimally invasive surgery (MIS), 3-4 ports were used in thorax and esophagus and nodes were excised en-block. During laparoscopy, five ports were used. In both MIS and open surgery, stomach was preferably used for reconstruction. Colon was used if stomach was not available. After extended total gastrectomy, jejunum was preferably used.

Lymph nodal dissection was divided into radical (D2 and D2 + lower mediastinal 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 and total mediastinal nodal dissection, respectively. Bilateral cervical nodal dissection was added to total mediastinal lymphadenectomy in three field dissection (3-FD).

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

SPSS version 26.0 was used for statistical analysis. A comparison of presentation, treatment modalities used and oncological outcomes were performed between 5 -year periods (2001-2006, 2007-2012 and 2013-2018). 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 547 patients who underwent surgery for cancer of esophagus and GEJ from 2001 till 2018. Demographic, basic clinical findings and treatment modalities are shown in table 1.

Table 1. Demographic, clinical presentation and treatment.

	2001- 2006 n = 111	2007-2012 n = 223	2013-2018 n = 213	p
Mean age (years)	55	58	60	<.001
Male	69 (62%)	136 (61%)	130 (61%)	.1
Female	42 (38%)	87 (39%)	83 (39%)	.1
Duration of dysphagia (months)	3.9	3.9	5	.001
Weight loss, mean	8	10	8	.6
Hb, mean	12	11.6	11.5	.06
Tumor location				
Upper	12 (11%)	12 (5%)	2 (1%)	<.001
Middle	38 (34%)	61 (27%)	62 (29%)	
GEJ I	23 (21%)	56 (25%)	77 (36%)	
GEJ II	38 (34%)	86 (39%)	71 (33.5%)	
GEJ III	0	8 (4%)	1 (.5%)	

Histopathology				
SCC	60 (54%)	113 (51%)	123 (58%)	.14
Adeno	47 (42%)	105 (47%)	87 (41%)	
Others	4 (4%)	5 (2%)	3 (1%)	
Treatment				
Surgery	65 (59%)	158 (71%)	60 (28%)	
Preop CTRT- S*	9 (8%)	24 (11%)	55 (26%)	
S-CTRT†	21 (19%)	22 (10%)	36 (17%)	
CT-S-CT‡	1 (1%)	5 (2%)	47 (22%)	
RT-S§	2 (2%)	0	0	<.001
S-CT||	6 (5%)	12 (5%)	7 (3%)	
S-RT¶	7 (6%)	2 (1%)	0	
CT-S**	0	0	5 (2.5%)	
Def CTRT-salv S††	0	0	1 (.5%)	
CT-S-CTRT‡‡	0	0	2 (1%)	
Had neoadjuvant therapy	10 (9%)	29 (13%)	110 (52%)	<.001

**Preoperative chemoradiation followed by surgery, † Surgery followed by chemoradiation, ‡Perioperative chemotherapy and surgery, §Preoperative radiation followed by surgery, ||Surgery followed by chemotherapy, ¶Surgery followed by radiation therapy, **Preoperative chemotherapy followed by surgery, ††Definitive chemoradiation followed by salvage surgery, ‡‡Chemotherapy followed by surgery and chemoradiation*

Table 2. Surgical details and post-operative complications.

	2001-2006 n = 111	2007-2012 n = 223	2013-2018 n= 213	p
Operative time (min)	297	234	205	<.001
Intraoperative blood loss (ml)	533	395	275	<.001
TTE*	103 (93%)	135 (61%)	135 (63%)	
THE†	6 (5%)	64 (28%)	49 (23%)	<.001
ETG‡	2 (2%)	24 (11%)	29 (14%)	
MIS§	0	84 (38%)	107 (80%)	<.001
Post-operative stay (days)	14	14	12	<.001
Nodal dissection				
Sampling	20 (18%)	25 (11%)	30 (14%)	
2-FD	73 (66%)	91 (41%)	99 (46.5%)	
3-FD	14 (13%)	11 (5%)	1 (.5)	
D2	4 (3%)	53 (24%)	31 (14.5%)	<.001
Ext 2-FD	0	9 (4%)	3 (1.5%)	
Total 2-FD	0	12 (5%)	10 (5%)	
D1	0	6 (3%)	2 (1%)	
D2+lower med	0	16 (7%)	37 (17%)	
Radical dissection	91 (82%)	193 (87%)	183 (82%)	.5
Reconstruction route				
Trans mediastinal	111 (100%)	218 (98%)	209 (98%)	.3
Retrosternal	0	5 (2%)	4 (2%)	
Substitute				
Stomach	103 (93%)	199 (89%)	187 (88%)	.4
Jejunum	8 (7%)	20 (9%)	24 (11%)	
Colon	0	4 (2%)	2 (1%)	

Level of anastomosis				
Chest	55 (49%)	39 (17%)	34 (16%)	<.001
Neck	56 (51%	184 (83%)	179 (84%)	
Margin status				
R0	96 (86%)	209 (94%)	196 (92%)	
R+	15 (14%)	14 (6%)	17 (8%)	.08
RLN injury	9 (8%)	13 (6%)	11 (5%)	.009
Anastomotic leak	11 (10%)	26 (12%)	31 (14%)	.008
30-day mortality	6 (5%)	13 (6%)	2 (1%)	.01

**Transthoracic esophagectomy, †Transhiatal esophagectomy, ‡Extended total gastrectomy, §Minimally invasive surgery.*

Final UICC stages are shown in table 3.

Table 3. Final UICC stage (8th edition).

	2001-2006 n = 111	2007-2012 n = 223	2013-2018 n = 213	p
0	0	0	2 (1%)	
I	11 (10%)	19 (9%)	8 (4%)	
II	15 (14%)	15 (7%)	7 (3%)	
III	41 (37%)	91 (41%)	92 (43%)	.005
IV	44 (39%)	98 (44%)	104 (49%)	
IVA	36 (32%)	80 (36%)	93 (44%)	
IVB	8 (7%)	18 (8%)	11 (5%)	

A complete data for survival analysis (excluding in-hospital mortality) was available for 485 out of 547 patients. For the whole group (n=485), median survival was 30 months and 5-OS was 24% (Fig. 1) with the poorer survival with increasing stage (Fig. 2). 5-OS was 100%, 77%, 43%, 25% and 10%, respectively in stages), I, II, III and IV (Figure 2).

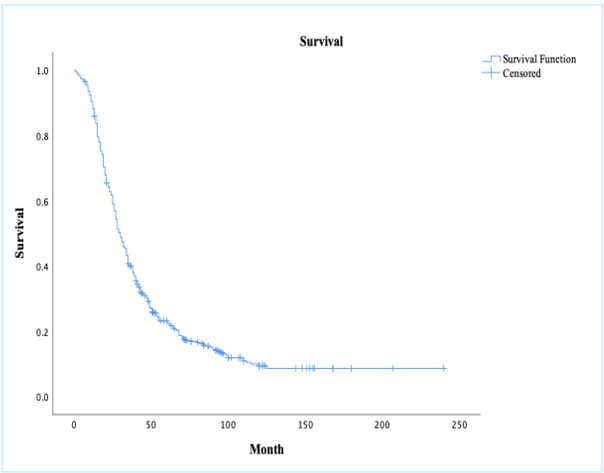

Figure 1. Kaplan-Meier survival curve for all patients.

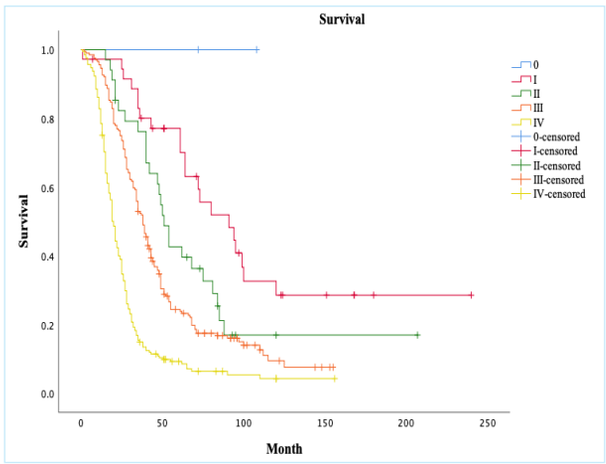

Figure 2. Kaplan-Meier survival curve for all patients according to stage.

Median survival and 5-OS were 34/ 15 months and 25%/ 10% (p<.001) for radical and non-radical nodal dissection, 32/ 15 months and 26%/ 0% (p<.001) for R0 and R+ resection, 34/ 27/ 25 months and 27%/ 18%/ 5% (p<.001) for TTE/ THE/ ETG, respectively.

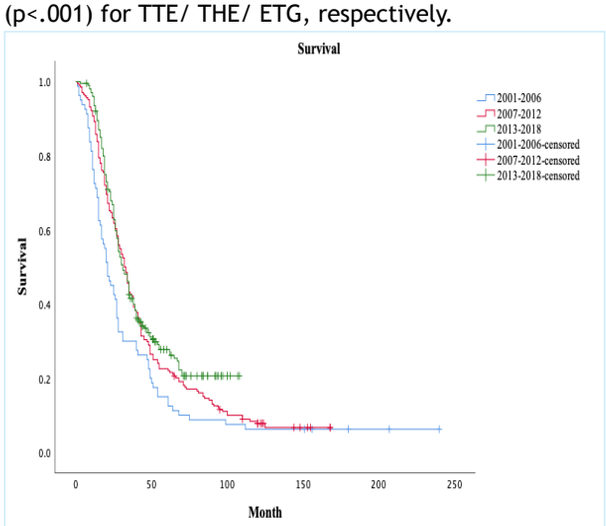

Figure 3. Kaplan-Meier survival curve by period subgroup.

DISCUSSION

Management of esophageal cancer has not been well studied and reported from Nepal. The results from this study highlight the changing trend in presentation, management, and outcomes of patients with esophageal cancer. Perhaps the most noteworthy, but not unexpected, finding is the considerable improvement in patient survival over the last 15 years. Median survival increased from 21 months in early part of the study to 31-32 months. The reasons for this are likely to be multifactorial, but the largest impact is probably due to the establishment of neoadjuvant treatment for patients with locally advanced disease. We had earlier reviewed 327 patients and 5-OS was 22% with median survival of 25 months. [13]

It is evident from the literature that the management trend of esophageal cancer is ever changing.[14] Two decades earlier, upfront surgery was the mainstay treatment which has been challenged due to poor survival outcome. In Japan, neoadjuvant chemotherapy (NACT) is the standard treatment modality for clinical stage II/III SCC.[15] But in Europe and North America, for SCC, neoadjuvant chemoradiation (NACTRT) and for adenocarcinoma of distal esophagus and GEJ, NACTRT or NACT is the standard practice. The landmark trial that has established NACTRT as the standard practice for the treatment of resectable esophageal cancer is the CROSS trial (Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study trial).[11,16] For adenocarcinoma, the alternative option of perioperative chemotherapy as per MAGIC [10] and more recently FLOT [12] protocol has been well proven.

There are few articles which have reviewed the national trend of esophagectomies. Ruol et al investigated trends in results of esophagectomies (n=3493) during past 25 years (1980-2004). The R0 resection rate increased from 74.5% to 90.1% (p <.001). In addition, an increasing proportion of patients had early-stage tumor in the resected specimen. In-hospital postoperative mortality decreased from 8.2% to 2.6% (p<.001), and the 5-year survival rate significantly improved from 18.8% to 42.3% (p<.001) for all patients who underwent resection.[14] Phillips et al conducted a similar study of evolution of esophagectomy for cancer over 30 years in a single high volume center from UK. Between 1989 and 2018, they analyzed 1486 patients. Patients were grouped into successive 5-year cohorts. An improvement in mortality from 5 to 2% (p < 0.001) was seen over the time period, and overall survival improved from 22 to 56 months (p < 0.001); however, morbidity increased from 54 to 68% (p = 0.004). The authors noted the reasons for this are multifactorial and include the use of perioperative chemo(radio)therapy, the introduction of an enhanced recovery pathway, and improved patient selection. [17]

From our study, it is evident, more patients with older age group were taken up for surgery in the last 5-year period. There was a heterogenicity in tumor location throughout the study periods (p<.001). We also had less tumors in upper esophageal region which changed from 11% in first 5 year to 1% in last group. Commonest location of tumor was mid-distal third (52-65%) which was almost consistent throughout the study period. Proportion of adenocarcinoma (41-47%) or SCC (51-58%) were not different. As treatment protocol changed globally throughout the years, we had also changing treatment protocols. Upfront surgery came down from 59-71% to 28% and proportion of neoadjuvant treatment increased from 9-13% to 52% (p<.001). The operating time decreased from 297 min to 205 min (p<.001). Intraoperative blood loss reduced as well from 533 ml to 275 ml (p<.001).

MIS got adopted around the world after confirmation of less pulmonary complications, less blood loss, less hospital stay with equivalent oncological outcomes (TIME, MIRO, ROBOT trials) [18-20]but pulmonary complications occurring in more than half of patients after open oesophagectomy are a great concern. We assessed whether minimally invasive oesophagectomy reduces morbidity compared with open oesophagectomy. METHODS We did a multicentre, open-label, randomised controlled trial at five study centres in three countries between June 1, 2009, and March 31, 2011. Patients aged 18-75 years with resectable cancer of the oesophagus or gastro-oesophageal junction were randomly assigned via a computer-generated randomisation sequence to receive either open transthoracic or minimally invasive transthoracic oesophagectomy. Randomisation was stratified by centre. Patients, and investigators undertaking interventions, assessing outcomes, and analysing data, were not masked to group assignment. The primary outcome was pulmonary infection within the first 2 weeks after surgery and during the whole stay in hospital. Analysis was by intention to treat. This trial is registered with the Netherlands Trial Register, NTR TC 2452. FINDINGS We randomly assigned 56 patients to the open oesophagectomy group and 59 to the minimally invasive oesophagectomy group. 16 (29%This study shows that in first 5-year period, there was no MIS which increased to 38% and 80% in 2nd and 3rd 5-year period, respectively (p<.001).

Major postoperative complications - RLN injury and 30-day mortality decreased from 8% to 5% (p = .009) and 5% to 1% (p=.01), respectively possibly due to better technique over the time. But anastomotic leak increased from 10% to 14% (p=.008), which may be due to older age group, more patient with stages III and IV and more use of NACT/ NACTRT in the later 5-year periods.

The 5-OS for the whole group did not improve (24%), which could be explained by a significant proportion of patients with stage IVA (32-44%). The survival analysis for all the patients confirmed better median and 5-OS for radical nodal dissection, R0 resection status and TTE.

The major limitation of this study, is that data have come from a single center with consistent reporting over time. It highlights the changes that have occurred in esophageal cancer treatment and the benefits of standardization of care.

CONCLUSIONS

This study highlights the continuous evolution in management of esophageal cancer in our center. Frequent use of MIS could be the reason for low 30-day mortality, hence it has to be used whenever feasible. Similarly, NACT/ NACTRT should become the standard practice as it has given the best 5-OS.

CONFLICT OF INTEREST

The authors declare no conflict of interest

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