Anastomotic leak after esophagectomy

Binay Thakur[1], Yang Ming[1], Nikesh Bhandari[1], Sun Zhenqing[1], Shashank Shrestha, Ashish Kharel, Deewas Neupane, Asha Thapa[2]
[1]Department of Surgical Oncology. BP Koirala Memorial Cancer Hospital, Bharatpur, Nepal.
[2]Bharatpur Hospital Nursing College, Nepal.

Abstract

Background: Esophageal anastomotic leakage (AL) remains a frequent and feared postoperative complication, associated with high mortality and impaired quality of life. The aim of this study was to assess AL rates after esophagectomy with anastomosis at neck for esophageal and gastroesophageal junction cancer (GEJ), and compare the impact of AL on oncological outcome. **Methods:** Patients with squamous cell carcinoma and adenocarcinoma of esophagus/ gastroesophageal junction who underwent surgery between 2001-2018 were analyzed for cervical anastomotic leak. **Results:** 419 patients underwent esophagectomy with anastomosis placed at neck during 2001-2018. AL rate was 16%. AL was not found to be associated with anastomotic technique, surgical approach and technique, organ of conduit and route of conduit. A subgroup of patients (n=93) who had undergone neoadjuvant chemoradiation followed by surgery had AL of 30% vs 12% in rest of the treatment modality group ($p<0.001$). Median survival was 26 months and 34 months in patients with AL and without AL, respectively ($p=0.03$). AL was managed successfully in all patients. **Conclusion:** Cervical AL after esophagectomy for cancer of esophagus and GEJ can be treated successfully without major complications.

Keywords: *Esophageal cancer; Esophagectomy; Anastomotic leakage.*

Introduction

Esophageal cancer is one of the most aggressive of gastrointestinal malignancies. Esophagectomy has always remained the mainstay of treatment, usually in combination with chemoradiation. Even when esophageal cancer is resectable, esophagectomy carries a high risk of death (3.6–4.5%) compared with most surgically treated cancers.[1] Many efforts have been made to improve the esophagectomy technique and to reduce postoperative complications, but esophageal anastomotic leakage (AL) remains a frequent and feared postoperative complication, associated with high mortality and impaired quality of life. However, improvement of surgical techniques and management of complications has led to a steady decrease in postoperative mortality over the years.[2] Some factors have been associated with AL development, such as patients' nutritional status and comorbidities, cancer stage, surgical procedure, and neoadjuvant therapy, but there are some controversies in the literature about the significant risk factors for this adverse event. [3]

Correspondence
Dr Binay Thakur , Dept. of Surgical Oncology (Thoracic Unit), BP Koirala Memorial Cancer Hospital, Bharatpur, Nepal. Email: binaythakur@hotmail.com. Phone: +977-9855055931.

The aim of this study was to assess AL rates after esophagectomy with anastomosis at neck for esophageal and gastroesophageal junction cancer (GEJ), and compare the impact of AL on oncological outcome.

Methods

Patients:

Patients with cancer of the thoracic esophagus or gastroesophageal junction (GEJ) seeking surgical treatment (Thoracic Unit) at BP Koirala Memorial Cancer Hospital (BPKMCH) between 2001 and 2018 were evaluated. This was a retrospective analysis of prospectively maintained database. The study was approved by the Institutional Review Committee, BPKMCH. Because individual patients could not be identified, the need for patients' consent was waived.

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.[4] Only clinical stages I-IVa patients with ECOG 0-1 were considered for surgery.

Treatment:

Treatment protocol varied from surgery alone to multimodality 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. 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.[5] For adenocarcinoma, MAGIC protocol was used.[6] In recent years, for locally advanced SCC and adenocarcinoma, treatment was initiated as per CROSS protocol and FLOT protocol, respectively.[7,8]

Surgical management was transthoracic (McKeown's/ left thoracotomy + neck/ left throcaolaparotomy + neck), and transhiatal. 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.

Anastomotic technique:

We have used various techniques for gastroesophageal anastomosis in the neck.

1. Single layer: anastomosis was fashioned using single layered Gambee stiches with PDS 4-0
2. Classical 2 -layer: with PDS 4-0, the full thickness inner layer was stitched. The outer layer was Lambert stiches.
3. Totally stapled: side to side stapled anastomosis with closure of anterior layers with stapler as well.
4. Orringer's technique: side to side stapled anastomosis with anterior manual stiches was used.

Definition and management of AL:

An anastomotic leak was defined as a "full thickness gastrointestinal defect involving the esophagus, anastomosis, staple line, or

conduit irrespective of presentation or method of identification" according to the Esophagectomy Complications Consensus Group definition.[9] AL has been graded as grade I, II and III. Diagnosis was made principally on clinical grounds: tenderness at neck incision site with fullness and crepitus which revealed pus, saliva or air on bed-side exploration of the wound. CT/ oral contrast study was not used. Esophago-gastroscopy was used only selectively if the leak did not show improvement after 2 weeks.

AL was managed with parenteral antibiotics, daily dressing, nil per mouth and enteral feeding through jejunostomy tube. Oral diet was gradually started once there was complete healing of neck wound. In case of development of stricture, early esophageal dilatation was done using serial Savary – Gilliard bougies at 2-3 weeks interval till a satisfactory dilatation of anastomotic lumen > 13 mm was achieved.[10]

Follow-up:

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

Statistical analysis:

A detailed analysis of anastomotic leak was done. Association of leak with anastomotic technique, preoperative chemoradiation and various surgical approaches was explored.

Categorical variables were compared using the Chi square test, and continuous data were ana- lyzed 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. SPSS version 26.0 was used for analysis.

Results

There were 419 patients who underwent esophagectomy with anastomosis in the neck 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.

Mean age	58 years
Sex	
Male	245 (58%)
Female	174 (42%)
Duration of dysphagia	4 months
Weight loss, mean	9 kg
Hb, mean	12 g/ dl
Tumor location	
Upper	26 (6.2%)
Middle	155 (37%)
GEJ I	136 (32.5%)
GEJ II	102 (24.3%)
Histopathology	
SCC	278 (66%)
Adeno	134(32%)
Others	7 (2%)
Treatment	
Surgery	207 (49%)
Preop CTRT- S*	83 (20%)
S-CTRT†	45 (11%)
CT-S-CT‡	48 (11.6%)
RT-S§	2 (0.6%)
S-CT‖	17 (4%)
S-RT¶	9 (2%)
CT-S**	5 (1%)
Def CTRT-salv S††	1 (0.2%)
CT-S-CTRT‡‡	2 (0.6%)
30-day mortality	16 (3.8%)
Anastomotic leak	67 (16%)

* 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

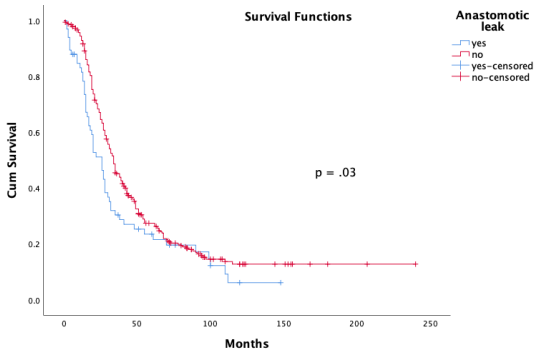
** Preoperative chemotherapy followed by surgery
†† Definitive chemoradiation followed by salvage surgery
‡‡ Chemotherapy followed by surgery and chemoradiation
Open and Minimally invasive surgery were performed in 240 (57%) and 179 (43%) cases, respectively. Two patients (0.5%) had grade I leak and 65 patients (15.5%) had grade II leak.
There was 16 (3.8%) postoperative 30-day mortality. The subsequent analysis has been done in 403 patients (excluding postoperative deaths). Association of leak with various anastomotic techniques, surgical approach, organ of conduit and route of conduit has been shown in Table 2.

Table 2. Association of leak with various factors (n = 403).

Parameters	Anastomotic leak		p
	Yes	No	
Anastomotic technique	33	201	
Single layer	9	32	
2- layers	21	79	
Totally stapled	4	24	0.3
Orringer's			
Surgical approach			
Transthoracic	51	235	
Transhiatal	16	101	0.3
Open vs MIS			
Open	43	185	
MIS	24	151	0.1
Conduit			
Stomach	67	330	
Colon	0	6	0.2
Route of conduit			
Transmediastinal	65	329	
Retrosternal	2	7	0.6

A subgroup of patients (n=93) who had undergone neoadjuvant chemoradiation followed by surgery was analyzed separately. Anastomotic leak was 28 (30%) in NACTRT-S group vs 39 (12%) in rest of the treatment modality group (p<0.001).
At different intervals after surgery, endoscopic dilatation was required in 17 patients (4.2%) due to anastomotic stricture. Dilatation was needed in 14 (21%) patients with AL and 3 (0.9%) patients without AL (p<0.001). There were no major complications after the procedure. On average, 5 sessions of dilatation were needed in AL group vs 2 sessions in no-AL group (p=.04)
Mean postoperative hospital stay was 21 days and 12 days in patients with AL and without AL, respectively (p<0.001).
Median survival was 26 months and 34 months in patients with AL and without AL, respectively (p=0.03) (Fig. 1).

Fig. 1. Kaplan-Meier survival (AL vs no AL).



Discussion

In a metanalysis of 174 studies reporting 74226 patients showed a pooled overall leak rate of 11% (range: 0-49%).[11] This study identified AL were associated with increased pulmonary and cardiac complications, in- hospital mortality, and significantly longer length of hospital stay.

This review identified that underlying cardiovascular disease such as hypertension, ischaemic heart disease, cardiac arrhythmia, vascular diseases, and underlying aortic or coeliac axis artery calcification were associated with AL. There was lesser incidence of AL in intrathoracic anastomosis in comparison to cervical anastomosis (OR = 0.48(0.36-0.64), p<0.001).

In a recently published retrospective analysis of 119 patients, AL was observed in 21.8% (cervical AL = 22%, intrathoracic AL = 25%; p=0.98). Specific emphasis has been given to endoscopic treatment (stenting/ clipping) and surgical revision, but no differentiation between the management of intrathoracic and cervical leak has been made.[12]

Most of the studies represent combined analysis of both cervical and intrathoracic AL with specific emphasis on intrathoracic AL. Literature is scarce for the management of cervical AL. We analyzed specifically cervical AL in a relatively high cohort (n=419). Incidence of AL was 16%, which is in acceptable range.

Though most of the studies do not show increased rate of AL after neoadjuvant treatment, it is important to highlight that few studies have specifically looked at leak rates when comparing anastomoses performed within and outside the radiation field. Juloori *et al*. examined the location of anastomosis in relation to the radiation field.[13] This study found that the rates of AL were significantly higher when the anastomosis was performed in the irradiated area (39% vs 2.6% for in-field vs out-of-field anastomosis, p<0.001).

A Japanese retrospective analysis of 686 esophageal cancer patients also showed that neoadjuvant chemoradiation was an independent predictor for postoperative complications with an anastomotic leak rate of 28% in patients who received neoadjuvant radiation compared to 16.5% in patients who had surgery alone (p<0.05).[14] In our study as well, there was significantly higher AL after neoadjuvant chemoradiation (30% vs 12%, p <0.001). With this knowledge, when possible, surgeons should avoid constructing the anastomosis within the radiotherapy field.

In our study, the cause of in-hospital mortality was multifactorial and in none of them, isolated AL was detected. Excluding the mortality, all the patients recovered from AL on conservative management, drainage, dressing and jejunostomy feeding. There was higher rate of anastomotic stricture requiring dilatation after AL (21% in AL group vs 0.9% in non-AL, p <0.001). AL rate was not associated with organ of conduit (stomach vs colon), anastomotic technique, surgical approach (TT vs THE), surgical technique (open vs MIS) and route of reconstruction (transmediastinl vs retrosternal). Most importantly, median OS was higher in non-AL than in AL group: 26 months vs 34 months, p=0.03).

The limitation of our study is its retrospective nature. The causes of AL were not addressed in our study, thus any specific recommendations could not be made to minimize AL. To best of our knowledge, this kind of study is first to be reported from Nepal in large number of patients.

Conclusion

Cervical AL after esophagectomy for cancer can be successfully managed conservatively with dressing, drainage and nil per mouth and jejunostomy feeding. Median OS is lesser after AL, hence further studies are needed to identify the modifiable risk factors in order to minimize AL.

References:

1. Schieman C, Wigle DA, Deschamps C, Nichols FC, Cassivi SD, Shen KR, et al. Patterns of operative mortality following esophagectomy. Dis Esophagus. 2012;25(7):645–51.
2. Lagarde SM, De Boer JD, Ten Kate FJW, Busch ORC, Obertop H, Van Lanschot JJB. Postoperative complications after esophagectomy for adenocarcinoma of the esophagus are related to timing of death due to recurrence. Ann Surg. 2008;247(1):71–6.
3. Aoyama T, Atsumi Y, Hara K, Tamagawa H, Tamagawa A, Komori K, et al. Risk factors for postoperative anastomosis leak after esophagectomy for esophageal cancer. In Vivo (Brooklyn). 2020;34(2):857–62.
4. Rice TW, Patil DT, Blackstone EH. 8th edition AJCC/UICC staging of cancers of the esophagus and esophagogastric junction: application to clinical practice. Ann Cardiothorac Surg. 2017 Mar;6(2):119–30.
5. Macdonald JS, Smalley SR, Benedetti J, Hundahl SA, Estes NC, Stemmermann GN, et al. Chemoradiotherapy after Surgery Compared with Surgery Alone for Adenocarcinoma of the Stomach or Gastroesophageal Junction. N Engl J Med. 2001 Sep 6;345(10):725–30.
6. Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJH, Nicolson M, et al. Perioperative Chemotherapy versus Surgery Alone for Resectable Gastroesophageal Cancer. N Engl J Med. 2006 Jul 6;355(1):11–20.
7. van Hagen P, Hulshof MCCM, van Lanschot JJB, Steyerberg EW, van Berge Henegouwen MI, Wijnhoven BPL, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med. 2012 May 31;366(22):2074–84.
8. Al-Batran S-E, Homann N, Pauligk C, Goetze TO, Meiler J, Kasper S, et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a ra. Lancet. 2019 May 11;393(10184):1948–57.
9. Low DE, Alderson D, Cecconello I, Chang AC, Darling GE, D'Journo XB, et al. International consensus on standardization of data collection for complications associated with esophagectomy: Esophagectomy Complications Consensus Group (ECCG). Ann Surg. 2015;262(2):286–94.
10. Badir M, Suissa A, Orlovsky M, Asbeh YA, Khamaysi I. Endoscopic dilation of benign post-esophagectomy anastomotic strictures: Long-term outcomes and risk of recurrence. Ann Gastroenterol. 2021;34(3):337–43.
11. Kamarajah SK, Lin A, Tharmaraja T, Bharwada Y, Bundred JR, Nepogodiev D, et al. Risk factors and outcomes associated with anastomotic leaks following esophagectomy: A systematic review and meta-analysis. Dis Esophagus. 2020;33(3):1–14.
12. Ortigão R, Pereira B, Silva R, Pimentel-Nunes P, Bastos P, Abreu De Sousa J, et al. Anastomotic Leaks following Esophagectomy for Esophageal and Gastroesophageal Junction Cancer: The Key Is the Multidisciplinary Management. GE Port J Gastroenterol. 2023;30(1):38–48.
13. Juloori A, Tucker SL, Komaki R, Liao Z, Correa AM, Swisher SG, et al. Influence of preoperative radiation field on postoperative leak rates in esophageal cancer patients after trimodality therapy. J Thorac Oncol. 2014;9(4):534–40.
14. Morita M, Masuda T, Okada S, Yoshinaga K, Saeki H, Tokunaga E, et al. Preoperative chemoradiotherapy for esophageal cancer: Factors associated with clinical response and postoperative complications. Anticancer Res. 2009;29(7):2555–62.