Pattern of the lymph node metastasis in esophageal and gastroesophageal junction cancers undergoing surgery in tertiary care cancer in Nepal

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Abstract

Background: Esophageal carcinoma (EC) and Gastroesophageal junction carcinoma (GEJ) is characterized by a high frequency of lymph node metastasis. Metastatic lymphatic mapping is important to determine the optimal extent of the radiation field in case of chemoradiotherapy and lymphadenectomy when esophagectomy is indicated. The objective of this study is to identify the distribution pattern of metastatic lymphatic spread in relation to tumor location of esophageal and GEJ cancer.

Methods: The study group comprised of 528 patients between year 2001 and 2023 who underwent en-bloc removal of tumor with radical lymphadenectomy. Nodal stations were numbered as per Japanese classification of esophageal cancer. Location of tumor in particular segment of thoracic esophagus and GEJ has been done as per AJCC/ UICC 8th edition.

Results: Total number of lymph nodes (LN) dissected were 11566 average 22 LNS from each patient and 2268 LNs were positive. Esophageal squamous cell carcinoma (ESCC) and adenocarcinoma were found in 278 (52.6%) and 242 (45.8%) patients, respectively. Out of 528 cases, 17 cases were of upper thoracic esophageal carcinoma with highest lymph node metastasis (LNM) to lower mediastinal nodes 59 %, 149 patients were belonged to group of middle thoracic esophageal carcinoma with common LNM to middle mediastinal nodes 55 %, 159 cases siewert type I and 203 cases of siewert type II both have highest LNM to abdominal nodes 61 % and 91 %, respectively. Upper abdominal nodes were involved in 11%, 29% and 61% in upper, middle and GEJ - I tumors, respectively. Middle mediastinal nodes were involved in 2% cases of GEJ - II tumors.

Conclusion: Certain pattern of nodal metastasis exists for esophageal and GEJ cancers. For any location of thoracic esophageal cancer, upper abdominal nodes along with mediastinal need to be excised whereas for GEJ II, middle mediastinal nodal dissection may be safely omitted.

Keywords: esophageal cancer; gastric cancer; esophagectomy; lymph node

Introduction:

Esophageal cancer is the seventh most commonly diagnosed cancer and is the sixth leading cause of cancer death worldwide.[1] The numbers of cases of and deaths from esophageal cancer have

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risen rapidly in recent decades. It is one of the most malignant cancers of gastrointestinal tract, with more than 0.6 million new cases and 0.54 million deaths worldwide in 2020.[2]

The incidence of esophageal cancer varies geographically, with higher rates observed in certain regions such as Eastern Asia, parts of Africa, and Iran. Nepal had esophageal carcinoma incidence of 0.92 per 100 000 and mortality 0.88 per 100 000 among all Asian countries.[3] Overall survival of esophageal and GEJ cancer is poor. The presence and number of lymph node metastases are among the most important prognostic factors in esophageal carcinoma and are independent predictors for long-term survival.[4]

Nodal metastasis is considered as a locally advanced state of the disease. During esophagectomy, a radical lymph node dissection is recommended as it not only stages the disease properly but improves the survival as well. But there is not a unanimous agreement which stations of nodes need to be excised.[5] Japanese surgeons consider three field lymphadenectomy to be the ideal procedure as the incidence of cervical nodal metastasis is as high as 30% even for the distal esophageal cancer.[6] Studies from Japan have extensively studied the rates of nodal involvement for a particular location of tumor. NCCN and ESMO guidelines recommend at least 15 nodes to be dissected and 2-field infra-carinal dissection to be done.[7]

Our study aims at the pattern of nodal involvement for esophageal and GEJ tumors in Nepalese context which may help in formulation of a consensus for an ideal nodal dissection in Nepalese population.

Methodology

This retrospective study was conducted at B.P. Koirala Memorial Cancer Hospital (BPKMCH) following ethical approval from the Institutional Review Committee of BPKMCH. Only clinical stages I-IVa patients (UICC 8th edition) [8] with ECOG 0-1 were considered for surgery. Patients with ECOG $\geq$ 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.[9]

This study included 528 patients who underwent en-bloc removal of tumor with radical lymphadenectomy (3 -field and 2-Field during transthoracic esophagectomy and abdominal D2 + lower mediastinal during trans-hiatal esophagectomy). Nodal stations were numbered as per Japanese classification of esophageal cancer.[10, 11]

Statistical analysis was done in the Statistical Package for the Social Sciences (SPSS-26). Descriptive variables were evaluated using frequency and percentages, while continuous variables were characterized by mean and standard deviation. For inferential statistics, students-T tests were employed for analyzing continuous data, while chi-square tests were used for categorical data analysis. P-Value of <0.05 was considered as statistically significant.

Results:

This study comprised 528 patients (female: 202, male: 326). The average age of the patients was 58 years (28-81 years). Total number of LNs dissected from 528 patients were 11566 average 22 LNs from each case and out of which positive LNs were 2268. Number of cases were adenocarcinoma 242, leimyosarcoma 3, NHL 2, neuroendocrine carcinoma 1, small cell carcinoma 2 and squamous cell carcinoma were 278 (Table 1). Total of 251 patents underwent upfront surgery, 77 cases had preoperative CTRT, 80 cases received preoperative chemotherapy only, 1 case received preoperative radiotherapy, 100 cases received postoperative chemotherapy and 8 cases received postoperative radiotherapy (Table 2).

Among 528 patients, 17 cases were of upper thoracic esophageal carcinoma, 149 patients were belonged to group of middle thoracic esophageal carcinoma, 159 cases Siewert type I and 203 cases of Siewert type II (Table 3). For patients with an upper thoracic tumor (n=17) , LN metastases were frequently seen along the Posterior mediastinal LNs (94.1%) , followed by Recurrent nerve (Left) LNs (29.4%) and Subcarinal LNs (11.7%) . For patients with a middle thoracic tumor(n=149) , the prevalence of LN metastases was highest along the middle thoracic paraesophageal LNs (40.9%), subcarinal nodes LNs (32.8%) , and LNs along left gastric artery (19.5%) .

In patients with Siewert type I tumor(n=159) , the highest prevalence of LN metastases was along the common hepatic artery (45.9%) then cardinal LNs (right and left 38.9%) and lower thoracic paraesophageal LNs (38.9%) . For patients with siewert type II tumor(n=203) LN metastases was frequently seen along cardinal nodes (right and left 71.4%) , followed by LNs along left gastric artery (63.1%) and then LNs along splenic artery (29.1%) and celiac artery (26.6%)(Table 4). The LN metastasis sites of esophageal carcinomas and GEJ carcinoma are shown in (Table 5) and (Figure 1).

Table 1: Histological distribution of cases

Histology	Number of cases (n=528)
Squamous cell carcinoma	278 (52.6 %)
Adenocarcinoma	242 (45.8 %)
Leimyosarcoma	3 (0.5 %)
Non Hodgkin lymphoma	2 (0.3 %)
Small cell carcinoma	2 (0.3 %)
Neuroendocrine carcinoma	1 (0.2 %)

Table 2: Treatment Modality

Treatment modality	Number of cases (n=528)
Upfront surgery	251 (47.5%)
Surgery followed by postoperative chemotherapy	100 (18.9 %)
Preoperative chemotherapy followed by surgery	80 (15.2 %)
Preoperative CTRT followed by surgery	77 (14.5 %)
Surgery followed by postoperative radiotherapy	8 (1.5 %)
Preoperative radiotherapy followed by surgery	1 (0.2 %)

Table 3: Distribution as per location of tumor

Location of tumor	Number of cases (n=528)
Upper thoracic esophagus	17 (3.2 %)
Middle thoracic esophagus	149 (28.2 %)
Lower thoracic esophagus / Siewert type I	159 (30.1 %)
Siewert type II	203 (38.4 %)

Table 4: Showing number and percentage of cases in relation to lymph node stations and zones in upper, middle, lower (siewert I) thoracic carcinoma and siewert II carcinoma.

Lymph nodes zones	Lymph node stations	Lymph node stations name	Number of positive LNs and (/) Percentage (%) of total			
			Upper thoracic (n=17)	Middle thoracic (n=149)	Lower thoracic Siewert I (n=159)	Siewert II (n=203)
Upper Mediastinal	106 rec R	Right recurrent nerve	1 / 5.8	2 / 1.3	5 / 3.1	
	106rec L	Left recurrent nerve	5 / 29.4	8 / 5.4	6 / 3.7	
	106tb R	Right tracheobronchial		2 / 1.3	3 / 1.8	
	106tb L	Left tracheobronchial		1 / 0.7	3 / 1.8	
Middle Mediastinal	107	Subcarinal	2 / 11.7	49 / 32.8	28 / 17.6	4 / 2.0
	108	Middle thoracic paraesophageal		61 / 40.9	37 / 24.8	7 / 3.4
	109R	Right main bronchus		11 / 7.4	4 / 2.5	1 / 0.5
	109L	Left main bronchus		12 / 8.1	8 / 5.0	1 / 0.5
Lower mediastinal	110	Lower thoracic paraesophageal		17 / 11.4	62 / 38.9	37 / 18.2
	111	Subdiaphragmatic		3 / 2.0	6 / 3.7	6 / 2.9
	112	Posterior mediastinal	16 / 94.1	5 / 3.4	7 / 4.4	5 / 2.5
Abdominal	1	Right paracardial	1 / 5.8	11 / 7.4	62 / 38.9	145 / 71.4
	2	Left paracardial	1 / 5.8	11 / 7.4	62 / 38.9	145 / 71.4
	3	Lesser curvature			4 / 2.5	25 / 12.3
	7	Left gastric artery	1 / 5.8	29 / 19.5	73 / 45.9	128 / 63.1
	8	Common hepatic artery		6 / 4.0	21 / 13.2	41 / 20.2
	9	Coeliac artery		7 / 4.7	20 / 12.5	54 / 26.6
	10	Splenic hilum		1 / 0.7	8 / 5.0	36 / 17.7
	11	Splenic artery		3 / 2.0	11 / 6.9	59 / 29.1
	12	Hepatoduodenal ligament		1 / 0.7	1 / 0.6	7 / 3.4
Total number of positive lymph nodes			27	240	431	701

Upper Thoracic *Middle Thoracic* *Lower Thoracic /GEJ Siewert I* *GEJ Siewert II*

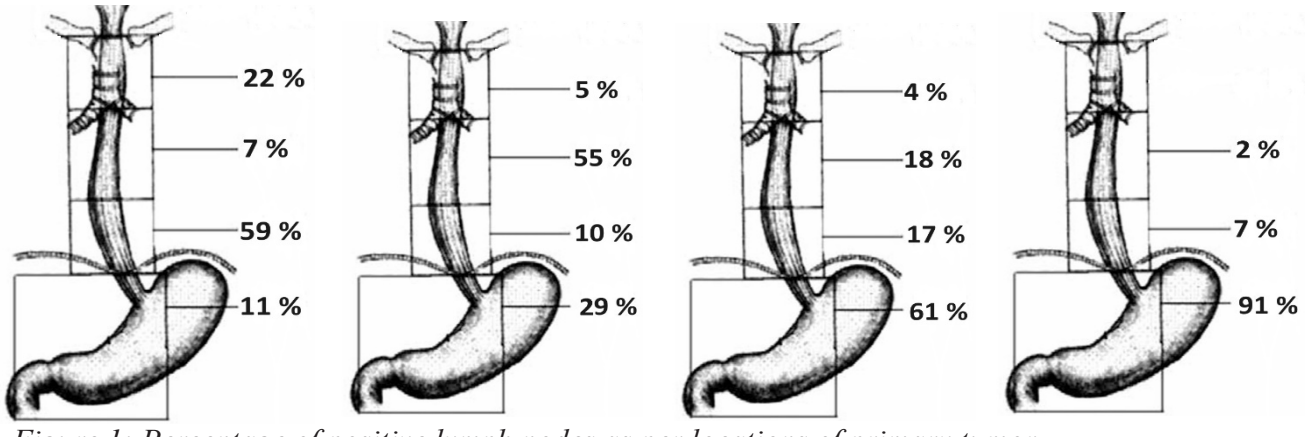

Figure 1: Percentage of positive lymph nodes as per locations of primary tumor

Table 5: Rate of positive lymph node metastasis in different regions according to location of primary tumor.

Locations	Upper	Middle	Lower / Siewert I	Siewert II
Upper Mediastinal	6/27 (22%)	13/240 (5%)	17/431 (4 %)	
Middle Mediastinal	2/27 (7%)	133/240 (55%)	77/431 (18%)	13/701 (2 %)
Lower Mediastinal	16/27 (59%)	75/240 (10%)	75/431 (17 %)	48/701 (7%)
Abdominal	3/27 (11%)	69/240 (29%)	262/431 (61 %)	640/701 (91 %)

Discussion

Surgery remains the cornerstone of the treatment of resectable and low risk esophageal carcinoma to insure optimal palliation for dysphagia, to achieve local control of the tumor and finally to provide an accurate staging of the disease.[12] Surgical treatment focusing on the completeness of the resection (R0), esophagectomy must be associated with a wide en-bloc dissection with lymphadenectomy aiming to reduce local recurrence, and thereby to improve disease free-survival.[13]

In our study, 528 patients with esophageal and GEJ tumor were treated with esophagectomy and radical lymphadenectomy. The role of three-field lymph node dissection in esophageal cancer surgery is controversial. Tachibana et al. showed that the survival rate was significantly improved in ESCC patients treated with three-field lymph node dissection compared with two field lymph node dissection.[14] In contrast, Shim et al found that there was no survival benefit from the addition of cervical nodal dissection in esophagectomy for ESCC.[15] We suggest that cervical nodal dissection can be omitted in selected cases, especially for patients who have no cervical lymph node metastasis on preoperative staging workup.

The prevalence of lymphatic metastasis varies in esophageal carcinoma of different locations. We speculate that lymph node metastasis in the upper thoracic esophageal carcinoma tends to appear upward, whereas lymph node metastasis in the lower thoracic esophageal carcinoma tends to appear downward. In the middle thoracic esophageal carcinoma, lymph node metastasis could appear both upward and downward, with the latter accounting for a higher proportion. In contrast, in the lower thoracic esophageal carcinoma siewert type I and II, the most common LNM site was the abdominal nodes.

Zheng Lin et al mentioned multistation metastases appeared to vary according to tumor locations. LN stations concurrently involved in upper thoracic carcinoma cases include cervical and upper paratracheal nodes. While for tumors located at lower thoracic esophagus, the hot area was the mid/lower mediastinum or upper abdomen nodes. However, for mid thoracic esophagus cases, obvious tendencies to develop bidirectional multi-station metastases, cervical and abdominal nodal zones were equally frequently involved.[16]

Yuji Tachimori en al had similar results to ours with the frequency of metastasis and the efficacy index (EI) of each zone were different by tumor locations. In patients with upper esophageal tumors, the EIs of the supraclavicular zone and the upper mediastinal zone were high. In patients with middle esophageal tumors, the EI of the upper mediastinal zone was the highest, followed by those of supraclavicular zone and perigastric zones. In patients with lower esophageal tumors, the EI of perigastric zone was the highest,

followed by those of upper mediastinal and lower mediastinal zones. The EIs of celiac zone were the lowest among all the zones in patients with thoracic squamous cell carcinoma.[17]

However, Hagens et al, concluded in the systemic review that both squamous cell carcinoma and adenocarcinoma metastasize to cervical, thoracic, and abdominal lymph node stations, regardless of the primary tumor location. In patients with an upper, middle, and lower thoracic squamous cell carcinoma, the lymph nodes along the right recurrent nerve are often affected (34%, 24% and 10%, respectively).[4]

To the best of our knowledge, our study is the first in its kind from Nepal looking at nodal metastatic involvement. Our study revealed the specific pattern of nodal involvement. The most common group of nodes for upper esophageal tumor was lower mediastinal, mid esophageal tumor was middle mediastinal , GEJ Siewert type I / lower esophageal tumor was abdominal and GEJ Siewert II was abdominal.

Most studies have shown, for upper esophageal tumors, upper mediastinal nodes and cervical nodes are generally involved. Whereas in our study for this particular location of tumors, lower mediastinal nodes have been found to be involved in a greater proportion of patients. A possible explanation could be the routine use of preoperative chemoradiation in these cases which might have sterilized the local nodes in upper mediastinal and neck.

There are several limitations of our study: retrospective nature, results from single center, lack of data regarding the specific mode of treatment for each location of tumor and survival results for particular location of nodal involvement.

Conclusion

Our study appears to be a bench mark study coming from Nepal. The study has clearly revealed that even for upper third and mid third lesions, abdominal nodes are involved in upto 11% and 29%, respectively. For Siewert I and II, middle mediastinal nodes were involved in 18% and 2%, respectively. Therefore, an extensive mediastinal and upper abdominal lymphadenectomy should be an optimal approach for upper, middle and GEJ I tumors. For GEJ II, upper mediastinal and middle mediastinal nodal dissection may be omitted.

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