Total Oesophagectomy for Squamous Cell Carcinoma With or Without Standard Two Field Node Dissection - A Prospective Study

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Abstract Cancer of the esophagus and gastroesophageal junction (GEJ) is notorious for its advanced stage at the time of diagnosis with transmural invasion and early lymphatic spread in the majority of the patients. R0 resection is the aim of surgery with curative intent. Regarding the role of lymphadenectomy, as in any other solid organ cancer, there are opposing views. Some surgeons argue that the presence of lymph node involvement equals systemic disease and that survival remains unchanged despite removal of these lymph nodes. For others the presence of lymph node involvement, even at a distance from the primary tumor, justifies an aggressive approach with radical esophagectomy combined with lymphadenectomy. The purpose of this article is to compare standard two field lymph node dissection versus non formal lymph node dissection in carcinoma esophagus. The conclusions are based on the experience with 60 cases of carcinoma esophagus over 2 years. In our opinion total esophagectomy with 2-field lymphadenectomy is the standard surgery for resectable squamous cell carcinoma of esophagus. It improves the lymphnode yield thereby ensuring adequate staging of the disease. It can be performed with acceptable morbidity and mortality as the nonformal lymphadenectomy procedure. Locoregional recurrence following 2 field lymphadenectomy is significantly low as compared to nonformal lymphadenectomy procedure though the distant recurrence rate is same. 2 year disease free survival in this study shows advantage of 2 field lymphadenectomy compared to non formal lymphadenectomy procedure.

Keywords Nonformal lymphadenectomy ·
2 field lymphadenectomy · Cancer esophagus

Introduction

Cancer of the esophagus and gastroesophageal junction (GEJ) is notorious for its advanced stage at the time of diagnosis with transmural invasion and early lymphatic spread in the majority of the patients. R0 resection is the aim of surgery with curative intent. Regarding the role of lymphadenectomy, as in any other solid organ cancer, there are opposing views. Some surgeons [1] argue that the presence of lymph node involvement equals systemic disease and that survival remains unchanged despite removal of these lymph nodes. For others [2] the presence of lymph node involvement, even at a distance from the primary tumor, justifies an aggressive approach with radical esophagectomy combined with lymphadenectomy. Extended lymphadenectomy became widely practiced in Japan as evidenced by a nationwide study reporting the results of 3-field lymphadenectomy [3]. Surgeons in the West, in part influenced by a more minimalistic attitude, have been sceptical and reluctant to adopt the procedure because in North America and Europe most cancers occur in the distal esophagus and GEJ and because of fear for increased mortality and morbidity when adding a bilateral cervical lymphadenectomy. Data from Western experience with 3-field lymphadenectomy are therefore scarce and dealing with relatively small numbers [4]. Hence standard 2 field lymphadenectomy is the surgical treatment of choice for localised squamous cell carcinoma of mid and lower esophagus.

Materials and Methods

A prospective non-randomized comparative study of 60 patients who were surgically treated for SCC mid and lower esophagus without receiving any form of neoadjuvant therapy in the year 2009 and 2010 in our department was undertaken.

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Initial oncologic evaluation included routine history and physical examination, upper GI endoscopy, barium swallow, computerized tomography of the chest and upper abdomen. All patients underwent further workup to assess the pre op medical fitness.

Out of the total of 60 patients included in the study, 36 patients underwent standard lymph node (2-field) dissection via trans thoracic approach while remaining 24 patients underwent trans hiatal esophagectomy without formal lymph node dissection (Table 1). A wide peritumoral resection was performed with standard lymphadenectomy of the upper abdominal compartment combined with a lymphadenectomy in the posterior mediastinum in case of 2-field lymph node clearance. Great care was taken not to damage the recurrent laryngeal nerves. Non formal lymphadenectomy arm patients only had abdominal lymph node dissection performed with few peritumoral nodes removed along with the main specimen. Routine histopathologic examination was performed. All patients were classified according to the AJCC TNM staging system 2002. No adjuvant therapy was given to both arms.

Complete follow up of each patient was carried out for 2 years or till the patient's death whichever was earlier. Patients were seen at regular interval of 3 months. Oncologic follow-up consisted of history and physical examination, Upper GIscopy, chest radiograph, and ultrasound of the abdomen. CT scan thorax and abdomen and PET scan was done as clinically indicated.

Locoregional recurrence was defined as recurrence within the surgical field. Distant recurrence included hematogenous metastasis in form of lung/liver/bone metastasis. In case of any doubt concerning this definition, the recurrence was classified as locoregional.

The aim of this study is to determine the impact of primary Total esophagectomy with or without standard 2 field lymphadenectomy on:

1. Lymph node yield.
2. Staging.
3. Anastomotic leak rate.
4. Locoregional recurrence.
5. Distant recurrence.
6. 2 year Disease-Free Survival. Tables 2 and Fig. 1

The total number of nodes retrieved from formal two field lymphadenectomy was 25 as compared to 17 in non formal lymphadenectomy group. The chest infection rate in both the group was 8 %. The anastomotic leak in formal lymphadenectomy group was 11 %, similar figure for non formal group was 12.5 %, which is statistically non significant. The rate of distant metastasis in two field and non formal lymphadenectomy group was 25 and 29 % respectively, statistically non significant. The locoregional recurrences after two field lymphadenectomy was 5.5 % which was statistically significant than 33 % in non formal lymphadenectomy group of patients (Fig. 2). The 2 year disease free survival was 75 % in two field group

Table 1 Demographic and clinical variables

	Non formal lymphadenectomy	Formal 2- field lymphadenectomy
1) Sex		
Male	15 (62.5 %)	25 (69.44 %)
Female	9 (37.5 %)	11 (30.55 %)
2) Age group		
<40 years	2 (8.33 %)	4 (11.11 %)
40-50 years	09 (37.5 %)	11 (30.55 %)
50-60 years	10 (41.66 %)	15 (41.66 %)
>60 years	3 (12.5 %)	6 (16.66 %)
3) Location of tumor		
Middle 1/3 esophagus	14 (58.33 %)	20 (55.55 %)
Lower 1/3 esophagus	10 (41.66 %)	16 (44.44 %)
4) Stage of disease		
Stage 1	4	8
Stage 2	20	28

and 37.5 % in non formal lymphadenectomy group (Fig. 3). This is statistically significant.

There was no mortality in our study.

Discussion

Esophageal cancer is unique among the gastrointestinal tract malignancies because it embodies two distinct histopathologic types, squamous cell carcinoma and adenocarcinoma. Which type of cancer occurs in a given patient or predominates in a given geographic area depends on many variables, including individual lifestyle, socioeconomic pressures, and environmental factors. The United States, along with many other Western countries, has witnessed in recent decades a profound increase in incidence rates of adenocarcinoma, whereas squamous cell carcinoma continues to predominate worldwide. Present-day therapeutic interventions have had limited impact on survival, as evidenced by the case fatality rate of 90 %.

The epidemiology of esophageal cancer is defined by its substantial variability as a function of histologic type, geographic area, gender, race, and ethnic background [5]. Incidence rates of squamous cell carcinoma may vary 200-fold between different populations in the same geographic area because of unique cultural practices. The highest incidence rate for males (more than 15 per 100,000 person-years) reported from population-based tumor registries were in Calvados, France; Hong Kong; and Miyagi, Japan; and the highest rates for females (more than 5 per 100,000 person-years) were in Bombay, India; Shanghai, China; and Scotland. Tata Memorial Hospital, Mumbai has 800–1000 newly diagnosed cases of esophageal cancer every year. Incidence, mortality, and survival patterns vary greatly depending on race, gender,

Table 2 Summary of results

	Non formal lymphadenectomy	Formal 2- field lymphadenectomy
Average no. of lymph nodes retrieved from thoracic field	8	15
Average no: of lymph nodes retrived from abdominal field	9	10
Total no; of lymph node retrived	17	25
Nodal positivity in thoracic group of lymph node	5.5 (68.75 %)	10.2 (68 %)
Nodal positivity in abdominal group of lymph node	5.6 (62 %)	6.2 (62 %)
Overall node positivity rate	11.1 (65.3 %)	16.4 (65.6 %)
Chest infection	2/24 (8 %)	3/36 (8 %) $p>0.05$ (non significant)
Anastomotic leak	3/24 (12.5 %)	4/36 (11 %) $p>0.05$ (non significant).
Locoregional	8/24 (33.3 %)	2/36 (5.5 %) $p<0.01$ (highly significant)
Distant	7/24 (29 %)	7/36 (25 %) $p>0.05$ (non significant)
2 year DFS	9/24 (37.5 %)	27/36 (75 %) $p<0.05$ (significant)
Stage 1	2/4 (50 %)	6/8 (75 %)
Stage 2	7/20 (35 %)	21/28 (75 %)

and histologic type. Interestingly, the death rate per 100,000 for esophageal cancer has increased in men yet decreased in women during the past decade. Although survival rates for all esophageal cancer patients are uniformly dismal, regardless of race or gender, 5-year relative survival rates have significantly improved since the 1970s based on Surveillance, Epidemiology, and End Results population-based tumor registry reporting [6].

Tumors of the middle third of the esophagus drain both cephalad and caudad with lymph nodes at risk in the paratracheal, hilar, subcarinal, periesophageal, and pericardial nodal basins. Lesions in the distal esophagus primarily drain to lymph nodes in the lower mediastinum and celiac axis region. Because of the extensive lymphatic network and rich mucosal and submucosallymphatics within the wall of the esophagus, skip metastases for upper third lesions have been noted in celiac axis nodal basins, and likewise, cervical lymph node metastases have been noted in as many as 30 % of patients with distal esophageal lesions. This forms the basis for some surgeons recommendation of a more thorough oncologic procedure, a combined transthoracic and abdominal approach for lesions of the middle and distal esophagus [7, 8], and for others

recommendation of a three-field (cervical,mediastinal, and abdominal) lymphadenectomy for all tumors of the middle through distal esophagus [2, 4]. However, lymphatic spread correlates with pathologic T category of the primary esophageal tumor, and lymph node metastases are initially limited in an overwhelming majority of patients to regional lymph nodes. Lymph node involvement in lymphatic basins distant from the primary tumor are rarely identified unless metastases to regional lymph nodes have already occurred [9, 10]. These data challenge the validity of extensive lymphadenectomy and also suggest the potential value of sentinel lymph node sampling to direct surgical dissection.

Squamous cell carcinomas account for approximately 40 % of esophageal malignancies diagnosed in the United States and most cancers arising in high-incidence areas throughout the world [11]. Approximately 60 % of these neoplasms are located in the middle third of the esophagus, whereas 30 % and 10 % arise in the distal and proximal third of the intrathoracic esophagus, respectively. Typically, these tumors are associated with contiguous or noncontiguous carcinoma in situ as well as widespread submucosal lymphatic dissemination.

Fig. 1 Morbidity **Fig. 2** Recurrence

Fig. 3 2 years disease free survival

The largest experience with transhiatalesophagectomy was reported by Orringer et al [12], and included 800 patients with esophageal cancer, 69 % of whom had adenocarcinoma and 28 % of whom had squamous cell carcinoma. Tumors were located in the lower third of the esophagus in 74.5 %, in the middle third in 22 %, and in the upper third in 4.5 %. In-hospital mortality was 4.5 %. The most common complications were anastomotic leak (13 %) and recurrent laryngeal nerve palsy (7 %).

Transhiatal Versus Transthoracic Esophagectomy

Four phase III trials have prospectively examined the outcomes for patients randomly assigned to undergo either trans-hiatal or transthoracic esophagectomy [13–16]. No definitive conclusions can be drawn from three of these trials because of the extremely small sample size. The trial in the Netherlands, however, deserves special attention. Hulscher et al [16], randomly assigned 220 patients with middle or distal esophageal carcinoma to undergo either transhiatalesophagectomy or transthoracic esophagectomy. The transthoracic group underwent a systematic mediastinal and upper abdominal lymph node dissection. Although the number of lymph nodes retrieved was significantly higher in the transthoracic group (31 vs. 16; $P < .001$), there was no difference in the radicality of the two procedures with equivalent R0, R1, and R2 resections. Postoperative pulmonary complications, ventilatory time, intensive care unit stay, and hospital stay were significantly higher in those patients assigned to the transthoracic group. Despite the higher perioperative morbidity, there was no statistically significant increase in in-hospital mortality (4 % vs. 2 % for transthoracic vs. transhiatalesophagectomy, respectively; $P = .45$). At a median follow-up of 4.7 years, there were no significant differences between the transhiatal and transthoracic esophagectomy groups with respect to median disease-free interval (1.4 vs. 1.7 years, respectively) and median overall survival time (1.8 vs. 2.0 years, respectively). Likewise, no significant

differences were noted in locoregional recurrence, distant recurrence, and combined locoregional and distant recurrence for patients randomly allocated to the transthoracic or transhiatalesophagectomy arm. The investigators point out that a trend toward improved disease-free survival (39 % vs. 27 %) and overall survival (39 % vs. 29 %) at 5 years favoured the transthoracic approach group.

The presence of lymph node (LN) metastases in patients with esophageal cancer has important prognostic implications. The current American Joint Committee on Cancer (AJCC) System 2010 classifies patients into 3 groups according to the LN (N) status: N0 disease for patients without involvement of regional LNs versus N1 disease for those with 1–2 lymph node metastases to regional LNs, N2 with 3–6 lymph node metastases and N3 with 7 or more lymph node metastases. As with other cancer types, LN status remains one of the most important prognostic factors for resected cases [17, 18]. Fewer than 10 % of patients with LN involvement survive 5 years from diagnosis compared with >50 % of patients with LN-negative disease [17, 19, 20]. Adjuvant treatment regimens for SCC esophagus also depend on the extent of LN clearance (R0 resection), with standard concurrent chemoradiotherapy recommendation for R1 or R2 resection and observation preferred for the R0 resection group as per the recent 2011 NCCN guidelines.

Lymph node status is a critical determinant of the prognosis and management of esophageal carcinoma. Adequate LN staging is very important for both patients and clinicians because the extent of LN involvement is the most significant prognostic factors for patients with resected esophageal cancer. Although current guidelines do not consistently recommend adjuvant therapy for patients with R0 resected adequately staged squamous cell esophageal carcinoma; R1 and R2 resection with inadequately staged disease (inadequate retrieval of lymph nodes i.e. less than 15 nodes) merit adjuvant chemoradiotherapy regardless of LN status. Thus, the status of regional LNs is critical when selecting the most appropriate postoperative management of these patients. Rizk et al [21], found that 18 LNs should be removed for adequate staging purposes based on data from a single institution study of 336 cases of stage I to stage IV esophageal carcinoma. In a study of 198 cases (also including all tumor and LN stages), Bollschweiler et al [22], suggested that 15 LNs be sampled to minimize misclassification of LN-positive patients. It is also possible that some patients in the study may have had pathologically negative LNs after receiving neoadjuvant chemotherapy.

In our study the number of lymph node retrieved from thoracic field in standard 2 field lymphadenectomy group was more as compared to the non formal lymphadenectomy arm (average 15 vs. 8). However the difference in abdominal field of nodal retrieval was not statistically significant (average 10 vs 9). Thus the total no of retrieved from standard 2 field lymphadenectomy and non formal lymphadenectomy were 25 and 17 respectively.

The node positivity rate in either of group is almost same. However the total no of lymphnode retrieved in formal 2 field lymphadenectomy in thoracic group (15) is statistically significant as compared to non formal lymphadenectomy group(8). This difference is reflected in the disease free survival at the end of 2 years [23].

The complication rate in form of morbidity (chest infection, anastomotic leak) were comparable between the two arms and standard 2 field lymphadenectomy arm did not show any added morbidity.

Overall 2 year disease free survival was 60 % (36/60) including both arms. Locoregional recurrence was more common in non formal lymphadenectomy arm compared to formal lymphadenectomy arm while distant recurrence was comparable in both arms. Further follow up at 3 and 5 year is required to extrapolate this data in terms of survival advantage in standard lymphadenectomy group.

Conclusion

Total esophagectomy with 2-field lymphadenectomy is associated with significantly better DFS as compared to non formal lymphadenectomy for resectable carcinoma of esophagus. It improves the lymphnode yield thereby ensuring adequate staging of the disease. It can be performed with acceptable morbidity and mortality as the nonformal lymphadenectomy procedure. Locoregional recurrence following 2 field lymphadenectomy is significantly low as compared to nonformal lymphadenectomy procedure though the distant recurrence rate is same. Two year disease free survival in this study shows advantage of 2 field lymphadenectomy compared to non formal lymphadenectomy procedure. More follow up at 3 and 5 years is required to extrapolate this data to establish the survival advantage of 2 field lymphadenectomy.

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