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European Journal of Cardio-thoracic Surgery 34 (2008) 427–431

EUROPEAN JOURNAL OF CARDIO-THORACIC SURGERY

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Review

Lymph node classification of esophageal squamous cell carcinoma and adenocarcinoma

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Received 30 December 2007; received in revised form 17 April 2008; accepted 21 April 2008; Available online 23 May 2008

Summary

The lymphatic channels of the esophagus run vertically along the axis of the esophagus and some of them drain into the cervical lymph glands upwards and into the abdominal glands downwards, and the pattern of lymph node metastasis of esophageal carcinoma is widespread. In various classifications of pattern of lymphatic spread, four classifications were proposed; location, number, ratio, and size. No definite survival advantage of aggressive lymph node dissection during esophagectomy has been proved compared with less dissection. Stage migration, micrometastasis, and sentinel lymph node concept all make it possible to individualize surgical management of esophageal carcinoma as a part of various multimodal treatments. Early diagnosis, standardization of surgery including routine lymph node dissection, and perioperative management of patients have all led to better survival rates of esophageal carcinoma.

Keywords: Esophageal cancer; Lymph node metastasis; Lymphadenectomy; Lymph node dissection

1. Introduction

The worldwide incidence of esophageal carcinoma is increasing, particularly for adenocarcinoma of the distal esophagus and cardia [1,2] and esophageal carcinoma is one of the most malignant tumors in the alimentary tract. At diagnosis, most of esophageal carcinomas are in an advanced stage, thus surgery is inappropriate in 40–60% of patients mainly due to the unresectable disease status, presence of distant metastases, or high operative risk [3,4]. Neoadjuvant and/or postoperative adjuvant treatments have been widely used to improve the surgical outcomes [5,6]. The long-term survival is, however, disappointing when the disease extends through the esophageal wall or when it is diagnosed with widespread lymph node involvement [3,4,7,8].

Esophageal carcinoma has two predominant histological types; adenocarcinoma and squamous cell carcinoma. Adenocarcinoma of the distal esophagus is the main histological type in the West and squamous cell carcinoma, which is mostly located at the middle thoracic esophagus, is dominant in the East. These two predominant types might be totally different diseases with different pathogenesis, epidemiology, tumor biology including pattern of lymph node metastasis, and prognosis thereby requiring different therapeutic strategies. Therefore, in the present review, the role of lymph node dissection was separately discussed for esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC).

The presence of lymphatic ducts in the lamina propria and muscularis mucosa deep to the basement membrane distinguishes the esophagus from other gastrointestinal tract organs, where lymphatic ducts are first seen in the submucosa. In esophageal carcinoma, lymphatic metastases may develop by one of three routes; (1) longitudinally along the submucosa plexus to regional (N1) and non-regional lymph nodes (M1a and M1b), (2) perpendicularly through the muscularis propria to the N1, or (3) perpendicularly through the muscularis mucosa to the thoracic duct and the systemic venous circulation (M1b) [9]. The lymphatic channels of the esophagus run vertically along the axis of the esophagus and some of them drain into the cervical lymph glands upwards and into the abdominal glands downwards [9,10]. Therefore, it might be logical to conclude that not only the mediastinal lymph nodes but also the cervical and upper abdominal (subdiaphragmatic, celiac and hepatic artery) groups of lymph glands are part of the regional lymphatic drainage of the esophagus, and metastatic deposits in these nodes should not be considered as distant metastasis [11]. Actually, the pattern of lymph node metastasis of esophageal carcinoma is widespread [12,13].

2. Classification of lymph node metastasis

The pattern of lymphatic spread through various connections of nodes gives valuable information for tumor extent

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1010-7940/$ – see front matter
doi:10.1016/j.ejcts.2008.04.022

and prognosis. In various classifications of pattern of lymphatic spread, nodal staging seems to be artificial and it is sometimes difficult to divide certain lymph nodes into the correct tier. Therefore, the following four classifications of metastatic lymph node (LN) were proposed; (1) location of LN metastasis, (2) number of LN metastasis, (3) metastatic LN ratio (ratio of invaded to removed nodes), and (4) metastatic LN size.

The TNM classification determined by the International Union Against Cancer (UICC) [14] and American Joint Committee on Cancer Classification (AJCC) [15] is currently the most popular in North American and European countries and the Japanese staging system by the Japanese Society for Esophageal Disease [16] is popular in Japan. These two staging systems [14–16] adopted locations of the LNs as a subdivision of pN category. For example, the TNM classification defined pN1 as regional LN metastasis and pM1 as distant metastasis, and patients who have distant LN metastasis cannot be distinguished from patients with visceral metastasis. These patients can be reclassified as having N(+)M0 rather than M1 disease [17,18]. The Japanese staging system, on the contrary, divided the locations of LN metastasis into four categories in relation to the esophageal primary lesion.

In 1997, the TNM classification for gastric cancer and colorectal cancer by UICC [14] were fully revised according to the number of involved LNs, but this staging system by the number of positive nodes was not applied for esophageal cancer. The number of metastatic LNs is not an artificial classification and it also gives precise information for advancement of the disease and prognosis without the problems related to nodal staging. Among the node-positive patients, the number of metastatic LNs clearly influenced the survival after curative esophagectomy [17,19,20]. Generally, patients with a large number of diseased nodes have a worse survival than those with a few metastatic nodes (for example; 1–3 vs >4 [17], 1–4 vs >5 [19], 1–7 vs >8 [20]). This classification was significantly correlated with tumor size, macroscopic classification, histological differentiation, depth of invasion (pT), lymph node metastasis (pN), and vessel invasions [21]. Moreover, the number of diseased LNs correlated well with the Japanese nodal level and TNM stage. These findings support the fact that the number of positive LNs is useful for evaluating the tumor progression [21].

Metastatic LN ratio might be more important to evaluate prognosis rather than other categories. Metastatic ratio (>0.2 in the mediastinal LNs) was a significant predictor for survival for ESCC [22] and its ratio >0.1 was a predictor for EAC [23], respectively, and became an independent prognosticator for patients with distant LN metastasis (Mlym) [24]. These findings provide possible evidence that the extensive meticulous LN dissection i.e., a larger denominator of the LN ratio is important for long-term survival in patients both with ESCC and EAC.

Metastatic LN size might be another important factor. Metastatic LN size ≥10 mm had a significantly worse survival than those with metastatic LN size <10 mm [25]. This metastatic LN size may suggest an indicator of the balance between tumor aggressiveness and the host immune status.

3. Minimum number of retrieved lymph nodes for a proper nodal evaluation

As mentioned elsewhere [12], UICC/TNM classification [14,15] recommended at least six or more retrieved LNs for an accurate nodal classification of esophageal cancer. From the viewpoint of the number of LNs dissected in patients who underwent extensive lymph node dissection, the average number of retrieved nodes was reported as over 42 [19,26–28]. At least 12 nodes dissected were proposed as a new threshold for accurately defining pN category in patients with esophageal cancer [29,30]. Taken together, a minimum number of retrieved LNs for a proper nodal evaluation can be proposed to be at least 12 or more LNs.

4. The role of lymph node dissection

It might be important to stress that, in view of the pivotal role of LN metastasis of esophageal carcinoma, it is essential not to miss any LNs and to examine them. Lymphadenectomy is an important component of the completeness of resection aiming to reduce local recurrence and thereby improve disease-free survival, and obtain an accurate pathological staging. Opponents to extensive lymphadenectomy are proposed to reduce postoperative recovery and quality of life as a result of morbidity without improving prognosis. The role of LN dissection was separately discussed for ESCC and EAC because of different pathogenesis, epidemiology, and tumor biology including patterns of lymph node metastasis.

For ESCC, a multicenter study [31] from Japan compared three-field LN dissection (3FLND) with two-field dissection (2FLND). The 30-day operative mortality rate was 2.8% for 3FLND and 4.6% for 2FLND. Five-year survival rate was 34.3% for 3FLND and 26.7% for 2FLND ($p < 0.001$). These results probably show that the survival advantage of 3FLND is attributable to different patients' selection between 3FLND and 2FLND centers and to the advancement of perioperative management and superior surgical outcomes of the experienced institutions where 3FLND is performed. A randomized study [27] compared 3FLND with 2FLND. The average age of patients undergoing 3FLND was 4 years younger than 2FLND. The operative mortality rate after 3FLND was 2.6% compared with 12.3% after 2FLND ($p < 0.05$). The 5-year survival rate was 48.7% after 3FLND and 33.7% after 2FLND ($p < 0.01$). The result of this study, however, appears invalid because genuine randomization of the patients was not performed. A prospective randomized study with a small number of patients [32] compared 3FLND with 2FLND. Since they followed strict criteria, only 27.6% satisfied the inclusion criteria. The 5-year survival rate was 64.8% after 3FLND and 48.0% after 2FLND ($p = 0.192$). The authors intended to conclude that 3FLND might prolong survival, but it did not reach a statistical significance. Moreover, two prospective randomized trials [33,34] examined the value of intrathoracic LN dissection (transthoracic vs transhiatal esophagectomy without thoracotomy). Both reports concluded that both approaches were equally effective surgical options. Two meta-analyses [35,36] of transthoracic vs transhiatal esophagectomy showed that a transthoracic approach resulted in higher postoperative morbidity, but mortality and 5-year

survival were not different among both surgical procedures. These data may suggest that there is no survival advantage of aggressive lymphadenectomy, particularly 3FLND, compared with less dissection for ESCC.

For EAC, a large prospective randomized study compared 114 patients who underwent transthoracic esophagectomy with en-bloc 2-field lymphadenectomy with 106 patients undergoing transhiatal esophagectomy [37]. A mean (+SD) of 16 + 9 nodes was retrieved after transhiatal resection and 31 + 14 after transthoracic esophagectomy group. Transhiatal esophagectomy was associated with lower morbidity than transthoracic esophagectomy with extended lymphadenectomy. They concluded that there was a trend toward improved 5-year disease-free survival with extended transthoracic esophagectomy (38% vs 27%; $p < 0.15$). A recent meta-analysis [38] of neoadjuvant chemoradiotherapy or chemotherapy for esophageal carcinoma, moreover, showed that a significant survival benefit was evident for preoperative chemoradiotherapy in patients with EAC. These data may suggest that 2FLND is enough and the growing popularity of multimodal treatments has added to the debate of the role and optimal extent of surgery for EAC [39].

Is there any significant difference in long-term survival between ESCC vs EAC after esophagectomy? Most trials found no difference in overall survival between these two histological types [40,41], whereas others reported a survival advantage with EAC compared with ESCC [42,43] and the other was contradictory [44]. However, a large retrospective study [45] reported that a 5-year survival rate of patients with EAC was 42.3% compared to 30.3% with ESCC and that a histologic type of adenocarcinoma was an better independent prognostic parameter. Before making a final conclusion regarding the impact of histological type on patient prognosis, further information needs to be gathered.

Taken together, no statistically definite survival advantage of extensive LN dissection has been proved compared with less dissection from these results. Thus, some surgeons doubt the necessity of routine extensive lymphadenectomy during esophagectomy [1]. The importance of lymphadenectomy around the bilateral recurrent laryngeal nerves is recently recognized where the value of 3FLND may not lie with the addition of a cervical phase but with the completeness of the superior mediastinal phase [39]. In sum, for EAC, 2FLND (mediastinal and abdominal lymph node dissection) might be enough, particularly for adenocarcinoma of the distal esophagus. On the contrary, for ESCC mainly located at the middle thoracic esophagus, extended 2FLND might be justified including complete upper mediastinal lymph node dissection and 3FLND might be investigational in experienced centers at present.

5. Topics of lymph node metastasis

The number of dissected LNs increased with the proportion of patients with LN involvement. If LN examination is insufficient, the nodal stage can be erroneously assessed as an earlier stage (stage migration). Extended LN dissection and routine microscopic examination of all resected nodes, thus, can provide accurate LN information and tumor staging. In fact, extensive lymphadenectomy clearly decreases a proportion of false-negative patients as their nodal status by identifying node-negative patients and the patients with positive cervical nodes who otherwise should be considered as node-negative patients [46,47].

The presence of micrometastasis at regional LNs would suggest benefits of prophylactic lymphadenectomy and that at distant sites would nullify the benefits of clearance of locoregional disease. Such micrometastasis might be present in a certain number of patients with ESCC at the time of presentation [48]. Systemic multimodal treatment such as chemotherapy and radiochemotherapy, therefore, might be important and be the only viable solution even after radical esophagectomy with lymphadenectomy. Micrometastasis certainly occurred in up to half of patients with esophageal cancer and has been shown to be an independent prognosticator of survival [49,50]. However, recent data of lymphatic mapping of esophageal cancer indicates that the first site of micrometastasis is totally unpredictable from the location and depth of the primary tumor. Moreover, extracapsular lymph node involvement is a bad prognostic factor for esophageal adenocarcinoma, independent of the number of involved lymph nodes, and may impact on treatment strategies [51].

The sentinel node concept to identify the lymphatic drainage route from primary lesions has been extensively investigated in various types of early stage solid tumors including gastrointestinal cancer [52,53]. In ESCC, sentinel nodes should be the most important site to detect micrometastasis and it seems to be reasonable to individualize the extent of LN dissection based on the distribution and status of sentinel nodes. This concept makes it possible to individualize surgical management of ESCC as part of various multimodal treatments. Sentinel LN mapping of ESCC may properly point out the necessity of LN dissection in the near future. Skipping metastasis to regional and/or distant LNs, however, questions the clinical relevance of sentinel node concept [46].

Is it possible for surgeons to determine the necessity of three-field LN dissection (3FLND) during transthoracic esophagectomy depending on LN status? LN involvement around the bilateral recurrent laryngeal nerves seems to be significantly associated with cervical nodal metastasis [26,54]. Therefore assessment of recurrent nerve nodal metastasis may be useful in predicting cervical nodal metastasis and in selecting a possibility of 3FLND [54]. These data may indicate a selection possibility that 3FLND might be spared for a certain number of patients with lower thoracic ESCC [26,55].

Clinical significance of multimodal treatment for esophageal carcinoma has recently developed dramatically and could provide various potential therapeutic options both for ESCC and EAC. These concepts make it possible to individualize surgical management of esophageal carcinoma as a part of various multimodal treatments [38]. However, TNM classification [15] was not a good predictor of survival in patients who received neoadjuvant chemoradiotherapy [56].

In conclusion, four lymph node classifications of esophageal carcinoma were proposed; location, number, ratio, and size. No definite survival advantage of aggressive lymphadenectomy during esophagectomy has been proved compared with less dissection. Stage migration, micrometastasis,

and sentinel node concept all make it possible to individualize surgical management of esophageal carcinoma as a part of various multimodal treatments. Early diagnosis, standardization of surgery including routine lymphadenectomy, and perioperative management have all led to better survival rates after esophagectomy both for esophageal squamous cell carcinoma and esophageal adenocarcinoma.

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