Total Lymphadenectomy and Nodes-Based Prognostic Factors in Surgical Intervention for Esophageal Adenocarcinoma

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Background. To evaluate prognostic factors based on the number of resected lymph nodes, we considered 202 patients who underwent radical resection and "total lymphadenectomy" for esophageal adenocarcinoma according to a prospective protocol.

Methods. Fifty-eight tumors surrounded by Barrett's epithelium underwent esophagectomy and esophagogastrostomy, and 144 tumors without Barrett's epithelium underwent esophageal resection at the azygos vein level, total gastrectomy, and Roux-en-Y esophagojejunostomy. All nodes and fat tissue were resected at the following stations: chest 4L and R3, R4, R7, R8, and R9 (TNM seventh edition) and abdomen 1–12 according to the Japanese Classification of Gastric Carcinoma (1998). The nodes were counted, excluding fragments. The correlations between the number of nodes yielded and the ratio of the metastatic lymph nodes/lymph nodes yielded with pT stage, grading measurements, and cancer-specific survival (CSS) were calculated.

Results. A total of 6,270 nodes were yielded (interquartile range per patient, 22–38; minimum, 4 nodes; maximum, 61 nodes). In 3 of 21 (14%) stage pT1 cases, less than 10 nodes were counted, in 2 of 27 (8%) stage pT2 cases, less than 20 were counted, and in 73 of 154 (47%) stage pT3-4 cases, less than 30 nodes were counted. The lymph node yield (LNY) and T stage were not correlated ($r = 0.048$; $p = 0.5$). The metastatic lymph nodes to lymph nodes yielded ratio was correlated with pT stage ($r = 0.272$; $p = 0.0001$), and G ($r = 0.385$; $p = 0.0001$). CSS positively correlated with pT stage ($p = 0.02$), G ($p = 0.001$), and metastatic lymph nodes/lymph nodes yielded ratio ($p = 0.01$) (multivariate analysis).

Conclusions. The total number of lymph nodes to be removed in total and within each T stage indicated as thresholds could not be reached in up to 38.6% of patients. The metastatic lymph nodes/lymph nodes yield ratio not the total LNY, did correlate with cancer-specific survival.

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In esophageal cancer operations, population-based studies indicate thresholds for the number of lymph nodes to remove in total [1–3] or according to the T stage [3] to improve survival. Lymph node yield (LNY) has been considered a benchmark of surgical quality assessment [2, 4]. LNY and the ratio of metastatic lymph nodes to the total number of nodes yielded (LNR) have been correlated with survival [1–5]. In fact, LNR has been proposed as an alternative staging method [6].

Yet there is no standard of care regarding the minimum LNY to remove [3, 6]. Retrospective population-based studies have methodologic limitations [7], such as a lack of specific details on the extension and technique of lymphadenectomy [1], absence of uniform protocols for a pathologic review of a resection specimen [3, 8] and differences in inclusion criteria, follow-up [2], and characteristics and volumes of hospitals and surgical groups participating in the surveys [2, 9]. The prognostic role of the extent of lymphadenectomy during surgical procedures for esophageal cancer is uncertain and requires clarification [7]. It is unclear if the survival improvement statistically linked with the extent of a lymphadenectomy results from stage migration phenomena or therapeutic effects [1, 3, 8]. Using a prospective protocol established in the 1990s, our tertiary center operated on a series of patients with adenocarcinomas of the esophagus and cardia who were not given neoadjuvant therapy [10, 11]. The protocol defined the resection area, the resection of all visible lymph nodes with the surrounding cellular tissue of defined lymph node thoracic and abdominal stations, a research-dedicated pathologic study of the specimen, and the follow-up. On the assumption that in

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our case series, all lymph nodes of the resection area had been removed and counted by the surgeon and pathologist, end points of the study were to verify the validity of the number of lymph nodes to remove (given as benchmarks of an efficient lymphadenectomy in the literature) and to clarify the relationship between cancer-specific survival (CSS), LNY, and LNR. The secondary aim was to provide further data on modalities, extension, and effectiveness of lymphadenectomy.

Patients and Methods

We considered patients with adenocarcinoma of the esophagus who were operated on between 2001 and 2013. The majority of the considered cases had been included in a previous study in which diagnosis, surgical procedure, pathologic workup, and follow-up were extensively described [11].

The preoperative workup included medical history and symptoms, upper gastrointestinal tract endoscopy with multiple biopsies of the tumor and surrounding mucosa and fundic and antral mucosa, and thoracoabdominal computed tomography (CT), positron emission tomography (PET), or CT-PET. Patients clinically defined as stage T1-3N0-1 were not given neoadjuvant therapy [11]. Cases were staged pathologically according to the sixth edition of the American Joint Committee on Cancer/Union for International Cancer Control TNM classification system [12] and restaged according to the seventh edition [13] for the present study. We tailored the surgical technique according to the presence or absence of Barrett's intestinal metaplasia (BIM) in the mucosa surrounding the tumor. Patients with BIM underwent subtotal esophagectomy and proximal gastrectomy with intrathoracic esophagogastric anastomosis. Patients without BIM underwent total gastrectomy and esophageal resection at the level of the azygos vein and Roux-en-Y esophagojejunostomy [10, 11, 14]. A right anterolateral thoracotomy and an upper midline laparotomy were performed. Lymphadenectomy included chest stations classified according to the AJCC TNM seventh edition (L/R 3, 4, and 7 and R 2, 8, and 9) [13] and abdominal stations classified according to the Japanese Classification of Gastric Carcinoma (1998) [15] (stations 1–12). For each lymph node station, all nodes and the surrounding cellular tissue were removed. A surgical team labeled each lymph node when it was removed from the peripheral stations and excluded or grouped fragments of lymph nodes. Surgical pathologists performed or controlled the isolation and counted and labeled the lymph nodes from the surgical resection block. Surgical specimens were fixed with 10% buffered formalin. Staging, grading (G1-4), and vascular invasion were classified according to the aforementioned AJCC TNM seventh edition classification [13]. After operation, patients were followed twice a year according to a structured protocol (serum tumor markers, chest roentgenography, abdominal ultrasonography, and CT-PET). Dates and causes of late death were assessed by telephone or by the Health Information System of the Italian National Health Service. CSS was calculated (in months) from the date of operation to the time of death from recurrent disease. Adjuvant multimodality therapy was mainly administered in case of disease recurrence. The local institutional review board approved using the database from the division of thoracic surgery for research purposes.

Statistical Analysis

Data are expressed as median and interquartile range. The χ^2 test or Fisher's test were used when appropriate to evaluate the association between nominal variables. Spearman's rho was calculated to indicate the correlations of the number of harvested nodes and LNR with pT stage and grade. CSS analysis was performed using the Kaplan-Meier method and log-rank test. In the CSS calculation, individuals who died of causes other than those specified were considered to be censored [16]. Cox regression was used for multivariate analysis. A probability value less than 0.05 was considered significant. Statistical analyses were performed using SPSS, version 13.0, software package (SPPS Inc, Chicago, IL).

Survival regression trees were used to assess the effect of LNR on CSS (R software package; R Project for Statistical Computing, Vienna, Austria). This statistical tool estimates a survival function by binary recursive partitioning in a conditional inference framework. Briefly, the algorithm looks for the best split in the predictor variable. Therefore the survival functions on observations with smaller or larger values of the predictor cutoff are maximally separated, ie, the log-rank test of the 2 curves is the most significant among all possible splits. Patients were recursively split according to LNR. Resulting subgroups were homogeneous within groups, but CSS functions were the most different between groups on the basis of the log-rank test.

Results

Two hundred two patients entered the study. The median age was 66 years (IQR, 58–71 years; male to female ratio, 4.9:1; $p = 0.27$). Fifty-eight BIM$^+$ tumors were treated using a subtotal esophagectomy and esophagogastrostomy at the thoracic dome. One hundred forty-four patients without BIM underwent total gastrectomy and esophageal resection at the azygos vein level and Roux-en-Y esophagojejunostomy. The postoperative mortality (within 30 days) was 4% (9 of 202 patients).

The R0 resection rate was 98% (198 of 202 patients). In 4 patients, submucosal microscopic involvement of the esophageal margin (R1) was diagnosed. Two of these 4 patients were younger than 40 years with a G4 tumor. The distribution of cases according to pT stage, grade, and vascular invasion is presented in Table 1. In total, 6,270 lymph nodes were resected (LNY), with a median of 30 (22–38) nodes harvested per case. No differences in the median number of harvested nodes were calculated ($p = 0.892$) between the BIM$^+$ group (gastric pull-up: median, 30; range, 19–38.5) and the BIM$^-$ group (esophagogastrectomy: median, 30; range, 22–38); lymph nodes positive for metastases (N$^+$) were detected in 67%