Prognostic Value of Lymph Node Yield on Overall Survival in Esophageal Cancer Patients

A Systematic Review and Meta-analysis

Els Visser, MD, Sheraz R. Markar, MRCS, MSc, MA, PhD,† Jelle P. Ruurda, MD, PhD,* George B. Hanna, FRCS, PhD,† and Richard van Hillegersberg, MD, PhD**

Objective: This meta-analysis determines whether increased lymph node yield improves survival in patients with esophageal cancer undergoing esophagectomy with or without neoadjuvant therapy.

Background: Esophagectomy involves resection of the esophagus and surrounding lymph nodes, which are commonly the first stations of cancer spread. The extent of lymphadenectomy during esophagectomy remains controversial, with several studies publishing conflicting results, especially in the era of neoadjuvant therapy.

Methods: An electronic literature search was undertaken using Embase, Medline, and the Cochrane library databases (2000 to 2017). Articles with esophageal cancer patients undergoing esophagectomy with lymphadenectomy and investigating the effects of low and high lymph node yield on overall survival and disease-free survival were included. Meta-analysis of data was conducted using a random effects model. If the study divided the cohort into multiple groups based on lymph node yield, survival was compared between the lowest and highest lymph node yield groups. In addition to analysis of the entire cohort, subset analysis of only those patients receiving neoadjuvant therapy was also performed.

Results: A total of 26 studies were included in this meta-analysis with a follow-up ranging from 15 to 94 months. For the analysis of overall survival, 23 studies were included. A meta-analysis showed that overall survival significantly improved in the high lymph node yield group [hazard ratio (HR) = 0.81; 95% confidence interval (95% CI) = 0.74–0.87; $P < 0.01$]. In the 10 studies describing disease-free survival, this was significantly improved in the high lymph node yield group (HR = 0.72; 95% CI = 0.62–0.84; $P < 0.01$). Subset analysis of neoadjuvant-treated patients demonstrated a survival benefit of high lymph node yield on overall survival (HR = 0.82; 95% CI = 0.73–0.92; $P < 0.01$).

Conclusion: This meta-analysis demonstrates the benefit of an increased lymph node yield from esophagectomy on overall and disease-free survival. In addition, a survival benefit of a high lymph node yield was demonstrated in patients receiving neoadjuvant therapy followed by esophagectomy.

Keywords: esophageal cancer, esophagectomy, lymphadenectomy, meta-analysis, neoadjuvant therapy, prognosis, survival

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From the *Department of Surgery, University Medical Center Utrecht, Utrecht, The Netherlands; and †Department of Surgery and Cancer, Imperial College London, London, UK.

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Reprints: Richard van Hillegersberg, MD, PhD, Department of Surgery, Division Cancer Center, University Medical Center Utrecht, Heidelberglaan 100, Utrecht 3508 GA, The Netherlands.

E-mail: R.vanHillegersberg@umcutrecht.nl.

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Esophageal cancer affects more than 450,000 people globally and ranks sixth among cancer-related mortality.[1] Esophagectomy is the mainstay of therapy in patients with locoregional esophageal cancer in the absence of systemic disease. The addition of neoadjuvant therapy has been shown to improve long-term survival for more advanced stages.[2–6]

Presently, tumor-node-metastases (TNM) classification separates patients with lymph node metastases into those with N1 disease: 1 to 2 regional nodes involved, N2: 3 to 6 regional nodes, and N3 disease: 7 or more regional nodes.[7] Lymph node status is one of the strongest prognostic factors for resected cases.[8–10] Despite the clear prognostic implications and recommendation by clinical guidelines, there is still no consensus regarding the therapeutic implications of an extensive lymphadenectomy, especially after neoadjuvant therapy.

This meta-analysis examines the existing evidence to determine whether increased lymph node yield (LNY) improves overall survival (OS) and disease-free survival in patients with esophageal cancer undergoing esophagectomy, with specific attention to those patients receiving neoadjuvant therapy.

METHODS

Literature Search Strategy

A systematic literature search was undertaken using Embase, Medline (via Pubmed), and the Cochrane library databases up to September 2017. The search terms "(o)esophageal," "(o)esophagus," "cancer," "carcinoma," "lymph," "lymphadenectomy," "survival," "prognosis," and "recurrence" and Medical Subject Headings (MeSH), were used in combination with the Boolean operators "AND" or "OR." A full description of the search strategy is presented in Supplementary Table 1, http://links.lww.com/SLA/B430. Two authors (EV and SRM) performed the electronic search independently in May 2017.

Study Selection

After eliminating duplicates, titles and abstracts were scrutinized by 2 of the authors (EV and SRM) to determine their suitability for inclusion in the pooled analysis. The full text of potentially relevant articles was retrieved and independently assessed for inclusion. Primary articles with esophageal cancer patients undergoing esophagectomy with lymphadenectomy were eligible for inclusion. Only comparative studies investigating the effects of low and high LNY on OS or disease-free survival were included. In the situation in which authors from the same institution had published a primary paper and then an updated analysis with a larger patient cohort, the most recent publication was included. Case reports, studies with fewer than 10 patients, reviews, posters abstracts, animal studies, studies published before 2000, and studies in a language other than English were excluded. In addition, noncomparative studies or studies not concerning lymphadenectomy and esophageal cancer were excluded. The reference lists of articles obtained were searched