Extent of lymphadenectomy for esophageal squamous cell cancer: Interpreting the post-hoc analysis of a randomized trial

Vaibhav Gupta, MD

From the Division of General Surgery, Department of Surgery and Institute of Health Policy, Management, and Evaluation, University of Toronto, Toronto, Canada.

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Address for reprints: Vaibhav Gupta, MD, Sunnybrook Health Sciences Centre, K3W-15, 2075 Bayview Ave, Toronto, Ontario M4N 3M5 Canada (E-mail: Vaibhav.Gupta@mail.utoronto.ca).

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Dr Vaibhav Gupta, University of Toronto, Canada

Central Message

There are important considerations to note in the interpretation of post-hoc analyses of randomized trials, as highlighted with a study published in this issue of the *Journal*.

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Although esophageal adenocarcinoma is more common in North America and Europe, squamous cell cancer (SCC) remains the most common type of esophageal cancer worldwide. Li and colleagues from Fudan University in Shanghai, China, performed a single-center surgical randomized trial to determine the value of extended lymphadenectomy for SCC. In 2015, they showed extended lymphadenectomy via a right thoracic approach (Ivor Lewis esophagectomy) had lower rates of postoperative complications and greater lymph node retrieval than limited lymphadenectomy via a left thoracic approach (Sweet esophagectomy).¹ Then, in May 2018, they showed improved 3-year disease-free and overall survival in the extended lymphadenectomy group.² Subgroup analysis showed the benefit was driven by patients with positive nodes or positive margins.

In this issue of the *Journal*, Li and colleagues³ present a post-hoc, subgroup analysis to look further into the benefit of extended versus limited lymphadenectomy in patients with node-positive esophageal SCC (129 of the 300 randomized patients). With 5-year follow-up data, they found that extended lymphadenectomy has a significant survival benefit, which appears to be driven by improved locoregional control.

One important message for readers of this paper is that a subgroup analysis of a randomized trial removes the balanced nature which allows us to draw causal inferences between the 2 groups in randomized trials. For example, the extended lymphadenectomy group has lower body mass index, more American Society of Anesthesiologists class 2 and 3 patients, and more middle thoracic cancers; these differences may not be due to chance alone. In other words, by studying patients with node-positive disease, this is essentially a prospective cohort study. Hence, the authors use multivariable Cox regression to control for confounders in their analysis.

Second, post-hoc exclusions introduce selection bias and make the study less generalizable. For example, this study excludes patients with negative nodes on postoperative pathology. When deciding between extended versus limited lymphadenectomy preoperatively, we do not know which patients will have positive nodes. This makes direct clinical translation of the study more challenging. Results can be applied to patients who have clinically detected node positive disease preoperatively, but we are still unclear what to do with clinically-node-negative patients who may have undetected nodal disease.

Third, all patients in this subgroup were recommended adjuvant chemotherapy per practice patterns in China, but not all patients received it because of low performance status or financial reasons. Patients in the extended lymphadenectomy group had more nodes examined and therefore were more likely to have positive nodes and receive adjuvant therapy. Differential use of adjuvant therapy in the extended versus limited arms (80% vs 75%, see Table 2 in their paper) can account for some of the survival difference. Of note, patients in this study did not receive neoadjuvant therapy.

Keeping these methodologic features in mind can aid readers in understanding the study and considering whether the results are applicable to their practice.

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