



Prognostic value of total retrieved lymph nodes on the survival of patients with advanced gastric cancer

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Gastric cancer (GC) is one of the most deadly cancers worldwide, because of its poor prognosis, although the incidence of GC has steadily declined over the past decades.¹ Nodal metastasis plays a key role in the recurrence and long-term survival of patients undergoing radical gastrectomy; hence, managing the lymph nodes (LN) is an essential component of the patients' outcome and prognosis.² The tumor, nodes, and metastases classification is a globally recognized standard for the staging of GC, but the minimum number of retrieved LNs has not been clearly defined yet.³ In fact, the proper extent of LN dissection and the specific number of nodes required for adequate staging and better prognosis has generated long periods of discussion with variable worldwide clinical practice.⁴

D2 lymphadenectomy is the current standard surgical procedure with reduced regional recurrence and increased long-term survival for the patients with GC undergoing radical gastrectomy.⁵ The strong association between the number of retrieved LNs with lymphadenectomy and improved survival rates of patients with GC has been demonstrated by clinical studies. Interestingly, not only the node-positive GC patients but also the node-negative patients could experience recurrences and mortal outcomes, if insufficient lymphadenectomy was performed.⁶ Hence, many researchers have proposed the ideal cutoff values of the number of LNs dissected to accurately assess the stage of GC and achieve local control. Zheng et al retrogradely evaluated 5794 patients with node-negative GC and demonstrated that there was a higher 5-year cause-specific survival rate (79.4%) in patients with ≥ 14 retrieved LNs than those with 1 to 4 retrieved LNs (64.8%) and 5 to 13 retrieved LNs (72.5%) ($p < 0.001$). These results infer that the number of the retrieved LN count was an independent prognostic factor for the node-negative GC

patients.⁷ Similarly, increased number of retrieved LNs may be associated with the long-term survival rate in the node-positive GC patients. A retrograde study analyzed 8475 node-positive GC patients undergoing gastrectomy and reported that the 5-year GC-specific survival of patients increased gradually with the number of retrieved LNs; increased GC-specific survival of patients was observed with the number of retrieved LNs < 14 .⁸ Furthermore, a recent study conducted by Lum et al divided 1314 node-positive GC patients into serosa-negative and serosa-positive groups. For the serosa-negative group, patients with number of retrieved LNs ≥ 16 had fewer tumor recurrences (30.2% vs 43.8%, $p = 0.038$), fewer distant metastases (17.8% vs 29.2%, $p = 0.048$), better 5-year overall survival (50.3% vs 32.4%, $p = 0.037$), and disease-free survival rates (46.6% vs 28.4%, $p = 0.049$) than those with number of retrieved LNs < 16 . On the contrary, number of retrieved LNs had no impact on either the recurrence or survival of GC patients in the serosa-positive group. Alternatively, adjuvant chemotherapy was the independent prognostic factor of overall survival of the serosa-positive GC patients.⁹

Two current possible hypotheses could explain the benefits of lymphadenectomy in advanced GC patients. The first is associated with stage migration. The residual tumor cells and the micro-metastasis in negative LN have potential risks of causing adverse effect on the overall survival of patients with GC. Increased retrieval of LNs could eliminate these tumor cells, prevent micro-metastasis, and reduce the possibilities of understaging, so that the survival of GC patients could increase accordingly.^{10,11} The second hypothesis is associated with the immunity of tumor-draining LNs, which includes antitumor immunity and tolerance for cancer. Resection of the regional LN could reboot the immunological balance and could reflect a host lymphocytic reaction to the tumor. The degree of lymphocytic reaction depends on the number of retrieved LNs, and higher lymphocytic reaction leads to a better prognosis of the patient with GC.¹² To date, investigators have sought to determine the optimal LN retrieval cutoff of advanced GC patients. Although heterogeneous results of these studies were presented in different researches, the investigators deduced that the optimal number of retrieved LNs could vary according to the tumor stage. However, other factors affecting the survival of patients with advanced GC, such as gastric peptide hormones (ghrelin, obestatin, and nesfatin-1), which regulate

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appetite and immune-metabolism, may be reduced by surgical removal and should be also considered. These factors should not be neglected and have not been investigated yet.¹³⁻¹⁵ In view of the association between LN retrieval and postoperative prognosis, efforts to improve the quality of clinical care could produce considerable improvements in the outcome of GC patients.

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