

# Gastric cancer lymph node resection—the more the merrier?

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Provenance: This is a Guest Editorial commissioned by Section Editor Rulin Miao, MD [Key laboratory of Carcinogenesis and Translational Research (Ministry of education/Beijing), Gastrointestinal Tumor Center, Peking University Cancer Hospital & Institute, Beijing, China].

Comment on: Deng J, Yamashita H, Seto Y, *et al.* Increasing the number of examined lymph nodes is a prerequisite for improvement in the accurate evaluation of overall survival of node-negative gastric cancer patients. *Ann Surg Oncol* 2017;24:745-53.

Received: 07 December 2017; Accepted: 12 December 2017; Published: 05 January 2018.

doi: 10.21037/tgh.2017.12.08

View this article at: <http://dx.doi.org/10.21037/tgh.2017.12.08>

The minimum number of examined lymph nodes for an accurate staging in gastric cancer patients is controversial. Since 1997 the UICC and AJCC define a minimum number of 15 examined lymph nodes for the pN0 status but over the last twenty years this has been challenged by several studies. Especially in advanced tumor stages a minimum number of 22–25 lymph nodes seem to provide better prognostic information and is reported to be significantly associated with prolonged survival and therefore for example examination of at least 25 lymph nodes is suggested in the German S3 guidelines (1-3).

In a recent article in *Annals of Surgical Oncology*, Deng *et al.* present a retrospective study on the question if increasing the number of examined lymph nodes is mandatory to accurately predict overall survival of node-negative gastric cancer patients (4). By performing an analysis of 2,455 gastric cancer patients curatively operated at two high-volume hospitals in Japan and China the authors conclude that the number of examined lymph nodes is significantly associated with survival rates in node-negative patients. In comparison the cohort of Japanese patients included significantly more patients with early stage gastric cancer, while the Chinese patient cohort was mostly diagnosed with advanced stage tumors. Node-negative patients in Japan presented more examined lymph nodes compared to the Chinese patient group.

By performing multivariate and cut-point survival analyses the authors define a minimum number of 15 examined lymph-nodes as a prerequisite for an accurate pN0-staging in pT1pN0pM0 patients. For patients with

advanced tumors and negative lymph nodes (pT4pN0pM0) a cut-off value of 35 examined lymph nodes is suggested for an accurate pN0-staging and to prevent stage migration.

These findings are quite important and clinically relevant for treatment and staging of gastric cancer patients but before transferring this results to western gastric cancer patients some limitations have to be discussed and further studied. Importantly surgical and perioperative treatment differ between Asia, Europe and the US in several ways. The benefit of a D2-lymphadenectomy has been proven in several prospective trials (5-7) and is regarded as the standard therapy for gastric cancer beyond pT1-tumors. The quality of this lymphadenectomy, indeed, is varying and leads to differences in the number of harvested lymph nodes. In a US trial, even if a D2-lymphadenectomy was seen as a standard, the proportion of patients with more than 15 lymph nodes removed was lower than 40% (8). In the current study the quality seems to differ between the two hospitals as well. The 5-year-survival of pT1apN0-patients was 100% in the Japanese and only 76.5% in the Chinese patient cohort. This relatively low survival rate for early gastric cancer patients lead to a relevant heterogeneity in the pooled patient cohort and raises the question if this data is generally transferable into the clinical practice.

In addition, the influence of a potential neoadjuvant chemotherapy has to be discussed at this point. Lymph node harvest is significantly decreased after preoperative therapy (9) even when surgery and pathological examination was performed adequately. In rectal cancer similar effects have been shown with a reduced number of lymph nodes

after preoperative therapy without any effect on the overall survival (10). If pN- and ypN-category in gastric cancer are comparable in terms of prognostic value is controversial and needs to be further investigated. Currently, based on anatomical studies a number of 25 examined lymph nodes correlates with an appropriate D2-lymphadenectomy (11). This number has been adapted by European guidelines and is seen as a quality index marker for surgery and has been shown to be a reliable cut-off value in western gastric cancer patients (2).

While not only the number of removed but the number of pathological examined number is more important, pathologist in Japan seem to be excellently trained in the detection of gastric cancer lymph node metastasis. Regarding this topic the authors claim that the lower number of examined lymph nodes in the Chinese hospital was caused by the lack of experience by the pathologist compared to respective Japanese pathologists. As the study is only authored by surgeons without any pathologist as a co-author this potential bias might be difficult to control. So even if surgical quality of lymphadenectomy did not differ, various quality of pathological examination has to be controlled as detection of lymph node metastasis is challenging and can vary among different techniques (12).

In addition to the challenge of correct identification of macrometastasis the detection of micrometastasis is affecting the staging and prognosis in gastric cancer patients as well. Micrometastasis is defined as islets of tumor cells with a diameter between 0.2 mm and 2.0 mm and were shown to be present in almost 50% of patients with negative lymph nodes in the standard HE-staining (13). Especially after neoadjuvant treatment the detection of these micrometastasis is challenging and requires pathological experience. While preoperative therapy is generally not applied to Asian patients with advanced tumors it is the standard of care in Europe. The ypN-category has been shown to predict outcome (14) and an exact lymph node staging after preoperative chemotherapy is therefore essential for evaluating prognosis. This topic remains unaddressed in the current study and is thereby limiting the results. In this context it is questionable if the number of 35 examined lymph nodes proposed by Deng *et al.* for pT4-tumors is reasonable. The more important question is whether the pathological examination is performed thoroughly enough to detect macro- and micrometastasis in a reliable pattern. This can only be achieved by a continuous communication between surgeon and pathologist and if the result are 25 or 35 lymph nodes seems to not as important

as the sufficient detection of metastasis. The ideal setting to clarify the exact number of lymph nodes needed for a perfect staging of gastric cancer patients would be a study performed together by surgeons and pathologists with standardized lymph node dissection as well as a standardized pathological work-up.

## Acknowledgements

None.

## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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doi: 10.21037/tgh.2017.12.08

**Cite this article as:** Nienhüser H, Schmidt T. Gastric cancer lymph node resection—the more the merrier? *Transl Gastroenterol Hepatol* 2018;3:1.