

Criteria for the Optimal Extent of Lymph Node Dissection for Gastric Carcinoma: Number of Harvested Lymph Nodes or Properly Dissected Relevant Lymph Node Stations? Standard or Personalized Extent?

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Received: January 08, 2021; **Accepted:** January 12, 2021; **Published:** January 19, 2021

Gastric cancer is one of the leading causes of cancer-related deaths worldwide accounting for more than 8.0% of the total deaths from all causes of malignancy. Although the prognosis for advanced gastric carcinoma has improved with the introduction of effective neoadjuvant and adjuvant chemotherapy surgical eradication of the tumor with its lymphatics remains the primary therapeutic modality for resectable tumor. With respect to surgical procedure, dissection of the regional lymph nodes is regarded an important part of radical intent surgery for gastric carcinoma. However, there are significant differences in the extent of lymph node dissection performed by surgeons in different part of the world.

Gastric carcinoma can spread early to surrounding lymph nodes. As the primary tumor invades more deeply through the wall of the stomach, the risk of lymph node metastasis increases. Comprehensive investigations have shown that the stomach has a sophisticated lymphatic flow, and gastric carcinoma follows various spreading patterns according to the tumor location and biology. Lymphatic spread occurs via the submucosal and subserosal lymphatic plexuses depending on the depth of invasion through the wall of the stomach. It means that lymphatic spread can happen at early stage and intensify at more advanced T stages.

Cancer cells fallen into lymphatic flow firstly encounter the local lymph nodes (sentinel lymph nodes) and are trapped and grow in them. From metastatic local lymph nodes cancer cells can be further carried to the regional lymph nodes located on antegrade lymph flow. The lymphatic drainage of the stomach follows its arterial supply. Although most lymphatics ultimately drain into the celiac nodal station, lymph drainage sites can include the splenic hilum, suprapancreatic nodal groups, porta hepatis, and gastroduodenal areas depending on the stage of gastric carcinoma. Studies have shown that tumors located in particular parts of the stomach rarely metastasized outside their designated drainage pattern. Lymphatic drainage tends to be centripedal toward the celiac trunk and the lymph nodes located on this route are the regional lymph nodes.

In the stomach, as in other organs, the very presence of cancer can alter the normal lymphatic drainage. Obstructed by cancer cells

lymphatic vessels can divert the lymph drainage so that metastases appear in unexpected nodes that can be named extraregional lymph nodes. With other words extraregional lymph nodes are the nodes that normally are located not on the antegrade lymphatic flow. So obturated by cancer cells normal lymphatics can form collateral lymphatics, producing a shift in the drainage pattern.

Theoretically, removal of a wide range of lymph nodes can improve the chance for cure in patients with gastric carcinoma. With other words eradication of the primary tumor without removing of lymph nodes with cancer cells cannot present a chance for cure. Extended lymph node dissection, however, could be irrelevant when no lymph nodes are affected, when the cancer has developed into systemic disease, or the dissection increases morbidity and mortality substantially. Determination of gastric cancer cases with absolutely unaffected lymph nodes and microscopically systemic disease is impossible before and during surgery. It means that probability of both absence of lymphatic spread and presence of occult hematogenous metastases cannot approve the surgery without removal of the local and regional lymph nodes.

Early in the 1960s, D2 dissection was introduced and later adopted as standard therapeutic modality in Japan for management of gastric carcinoma. Despite the first opinions of Western surgeons extracted from the results of the appropriate studies in the late 1990s about that lymphadenectomy is purely a staging rather than a therapeutic tool, after 15 year-follow up of the famous Dutch study it has been demonstrated that locoregional recurrence rate is significantly lower in patients treated with D2 lymphadenectomy in comparison with the patients who underwent D1 dissection, showing a survival benefit with the extended dissection. Therefore nowadays D2 lymph node dissection is the standard surgical procedure in the management of gastric carcinoma and is accompanied by not higher morbidity and mortality rates in the high-volume centers.

Gastric cancer can develop lymphogenic metastases at any T stage of the tumor. Even at T1 stage the frequency of lymph node metastasis accounts for up to 18%. Negative results of pathologic examination following sentinel lymph node biopsy does

not always exclude existence of lymphogenic micrometastasis (occult metastasis). Because the existence of skip metastases maybe as high as 17% and micrometastasis in local nodes may have been missed during the dissection due to complex and multi directional status of the gastric lymphatic drainage or during routine histopathologic examination. According to our data immunohistochemical staining can detect micrometastasis of gastric carcinoma in 22.2% of the lymph nodes that were tumor-free in routine histopathologic examinations performed by two pathologists who were not acquainted with the report of the another one. Moreover according to the results of the appropriate studies up to 12% of early gastric cancer cases lymph node involvement can occur in 3 of 5 gastric basins. Therefore the mentioned arguments questions absolute regional control provided by gastrectomy without extended lymph node dissection even in cases of early gastric carcinoma. As mentioned above the deeper is the extension of the carcinoma through the wall of the stomach the more the risk of lymph node metastasis is. It occurs not only due to the fact that as the primary tumor invades the gastric wall more deeply it gets greater chance to spread via subserosal lymphatic plexus along with the submucosal plexus. It takes place also because of the fact that the lymphogenic metastasis is time-dependent process like the T up staging of the primary tumor. That is why T3 gastric cancer can require more extended lymph node dissection than T1-T2 tumor at least theoretically. Some authors recognize T3-T4 depth of invasion (especially in proximal gastric cancer) as separate risk factor for lymph node involvement and define it as a criterion for D3 lymph node dissection according to the results of the study conducted by them.

It is not excluded that the correlation between the depth of invasion and the level of the risk of lymph node involvement also depends on Lauren's hystotype of the carcinoma. So unlike diffuse hystotype gastric carcinoma intestinal type adenocarcinoma in many cases develops on the background of mucosal atrophy. Dense lymphoplasmacytic infiltration of lamina propria and other pathological changes in mucosa and submucosa associating with chronic atrophic gastritis can affect negatively on lymphogenic-metastatic potential of intestinal type adenocarcinoma. Results of some studies approve D3 lymph node dissection in diffuse hystotype of gastric carcinoma that can be explained by the mentioned points along with the biology of the cancer cells.

According to the opinions of some researchers gastric upper tumor location is recognized as separate risk factor for paraaortal lymph node involment that requires extended lymph node dissection more than D2. Whether it is related to biology of the proximal cancer cells, to less frequency of accompanying atrophic gastritis or to deeper invasion at diagnostics is not fully clear. Therefore there are some tumor-related factors that can require extended lymph node dissection in greater extent.

What are the best criteria for the optimal extent of lymph node dissection – meticulous and proper dissection of regional (and extraregional) lymph node stations or greater number of harvested lymph nodes? As mentioned above lymph flow from stomach is centripedal toward the celiac trunk. So in cases of gastric cancer of the distal third of the stomach cancer cells fallen into lymphatic flow can be carried to station 9 via stations 3, 7 or 5, 8. That is why in cases with non enlarged lymph nodes in station 9 dissection of stations 7, 8a, 9 along with the perigastric lymph nodes should be the minimal extent. When lymph nodes in station 9 are clinically or radiologically large enough one can suppose that orthograde lymph channels might have been obturated by cancer cells and retrograde and bypass lymph flow might have taken place. In this

circumstance lymphatic flow can be directed toward stations 1 and 11. Therefore the cases with enlarged lymph nodes in station 9 should require dissection of stations 1 and 11 additionally. Large lymph nodes in station 8a can require dissection of stations 8p and 12, enlarged lymph nodes in station 11p – stations 11d and 10. It should be noted that we have never revealed metastasis in stations 1 and 11 without metastasis in station 9 in distal third gastric cancer. In cases of proximal-third gastric carcinoma cancer cells fallen into lymph flow are carried toward the paraceliac lymph nodes via stations 1, 7 and 2, 4sa, 11. Therefore in the proximal-third gastric carcinoma cases these lymph nodes with station 9 should be removed as a minimal extent. When the lymph nodes in station 9 are enlarged orthograde lymph vessels can be blocked by cancer cells and lymphatic flow can be diverted and be directed toward stations 3, 5, 4sb, 4d, 6, 17, 8a and 10 and 110. So in cases of proximal-third gastric carcinoma with clinically or radiologically enlarged lymph nodes in station 9 stations 8a, 10 and 110 should be removed also along with the perigastric and regional stations. Enlarged lymph nodes in station 10 can require dissection of the paraaortic lymph nodes. Therefore clinically or radiologically determined N stage of gastric carcinoma can predict the extent of lymph node dissection at least theoretically. In order to personalize the optimal extent of lymph node dissection randomized trials on a large cohort of patients taking into consideration the mentioned aspects of the question are needed.

Can the number of the harvested lymph nodes be the best criteria for the optimal extent of lymph node dissection in patients with gastric carcinoma? There is a strong and common opinion that a minimum 25 harvested lymph nodes would be better for practical and staging purposes. There are also opinions that stage-based survival is dependent on the total harvested lymph node number. How well can the number of the harvested lymph nodes determine the adequacy of the lymph node dissection in patients with gastric carcinoma? It depends on several factors – whether the lymph nodes are removed from the relevant stations considering the routes of lymphogenic spread depending on the location of the tumor, whether the specimen is properly labeled and processed prior to submission for pathologic evaluation and whether the number of the lymph nodes in the stations are individual. Moreover cases of inaccurate lymph node dissection of relevant stations with enough number of harvested lymph nodes from irrelevant stations also are not exceptional. All these factors are real and can be faced in many cases. Therefore there can arise a thought that the number of the harvested lymph nodes is not the best criterion for the optimal extent of lymph node dissection in patients with gastric carcinoma albeit it is an objective one.

Considering all the above mentioned points one can resume that scrupulous and proper lymph node dissection of relevant stations can be more reliable factor determining the adequacy of the lymph node dissection in gastric cancer. Unfortunately there are not accurate objective criteria for estimating how well the procedure was performed scrupulously and properly.

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