

## Neoadjuvant chemotherapy followed by surgery in gastric cancer patients with extensive lymph node metastasis

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### Abstract

Gastric cancer with extensive lymph node metastasis (ELM) is usually considered unresectable and is associated with poor outcomes. Cases with clinical enlargement of the para-aortic lymph nodes and/or bulky lymph node enlargement around the celiac artery and its branches are generally dealt with as ELM. A standard treatment for gastric cancer with ELM has yet to be determined. Two phase II studies of neoadjuvant chemotherapy followed by surgery showed that neoadjuvant chemotherapy with S-1 plus cisplatin followed by surgical resection with extended lymph node dissection could represent a treatment option for gastric cancer with ELM. However, many clinical questions remain unresolved, including the criteria for diagnosing ELM, optimal regime, number of courses and extent of lymph node dissection.

**Key words:** Extended lymph node metastasis; Gastric cancer; Neoadjuvant chemotherapy; Gastrectomy; Lymph node dissection

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**Core tip:** Gastric cancer with extensive lymph node metastasis (ELM) is usually considered unresectable and associated with poor outcomes. Phase II studies of neoadjuvant chemotherapy followed by surgery have shown the efficacy of this multimodal therapy for this pathology, but many clinical questions remain unresolved, including the criteria for diagnosing ELM, optimal regime, number of courses and extent of lymph node dissection.

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## INTRODUCTION

Surgical resection represents the most important step in the treatment of gastric cancer and is the only approach offering complete cure. Systemic chemotherapy is administered for gastric cancer patients with liver, peritoneal, or other distant metastases, but extensive lymph node metastasis (ELM) stands on the borderline between surgical resection and systemic chemotherapy. The development of treatment for gastric cancer with ELM is a difficult and challenging task. This article reviews previous reports and looks to the future of treatment for gastric cancer with ELM.

## ELM IN GASTRIC CANCER

No widely accepted consensus has been reached regarding the definition of ELM. In most reports, cases with clinical enlargement of the para-aortic lymph nodes (PAN) but no other distant metastases have generally been dealt with as ELM<sup>[1-3]</sup>. The range of PAN that are subject to surgical resection extends from the caudal end of the celiac axis to the cranial side of the inferior mesenteric artery, and is taken to be No. 16a2-b1 in the Japanese classification of gastric cancer<sup>[4]</sup>.

Most reports consider positivity for PAN metastasis with enlargement of  $\geq 1$  cm in the long axis as ELM<sup>[1-3]</sup>. In the most recent response evaluation criteria in solid tumors (RECIST)<sup>[5]</sup>, enlargement of  $\geq 15$  mm in the short axis is considered to represent measurable and assessable lymph nodes. Using multislice computed tomography, Marrelli *et al.*<sup>[6]</sup> diagnosed clinical metastasis with enlargement of  $\geq 8$  mm in the short axis of PAN in gastric cancer, and reported positive and negative predictive values of 73% and 97%, respectively, with 93% accuracy.

Indications for surgical intervention do not always need to follow RECIST criteria, as the purpose of these criteria is to objectively evaluate treatment effect. However, further investigation of the criteria for diagnosing ELM is needed in the future.

In a series of Japan Clinical Oncology Group (JCOG) studies by Yoshikawa *et al.*<sup>[3]</sup> and Tsuburaya *et al.*<sup>[1]</sup>, bulky lymph node enlargement around the celiac artery and its branches (bulky N), in addition to clinical enlargement of PAN, is treated collectively as ELM. The reasons are that patients with such metastases are commonly considered to be inoperable and, similar to PAN-positive patients, prognosis is poor even if curative resection is possible. According to the report by Tsuburaya *et al.*<sup>[1]</sup>, survival outcomes are equivalent in PAN-only patients and bulky N-only patients. Treating PAN metastasis

and bulky N as a single disease group has thus been considered reasonable.

## STANDARD TREATMENT FOR GASTRIC CANCER WITH ELM

From the 1980s to 1990s, PAN dissection was actively performed at some institutions in Japan. As a result, PAN metastasis was seen in about 20% of patients at maximum, with long-term survival achieved in about 10%-20% of these patients<sup>[7,8]</sup>. Similar reports have recently been seen from Western countries<sup>[9]</sup>.

On the other hand, JCOG 9501 was conducted to verify the significance of prophylactic PAN dissection, but no meaningful impact was found<sup>[10]</sup>. As a result, while PAN were categorized as regional lymph nodes in past Japanese classifications<sup>[4]</sup>, the new classifications categorize them as distant lymph nodes<sup>[11]</sup> that are no longer considered a target of curative resection. PAN are also taken to be distant lymph nodes in Western guidelines<sup>[12]</sup>, and are again not considered a target of curative resection.

However, it must be noted that the results of JCOG 9501 show the ineffectiveness of prophylactic PAN dissection. In that sense, a standard treatment for gastric cancer with clinical PAN metastasis has yet to be determined.

No comprehensive investigations of gastric cancer with bulky N have been reported. In some cases, curative resection may be achieved, but many cases are judged as unresectable because of direct invasion of major blood vessels.

## TREATMENT OUTCOMES OF NEOADJUVANT CHEMOTHERAPY FOR GASTRIC CANCER WITH ELM

The JCOG 0001 was a phase II clinical study for gastric cancer patients with ELM<sup>[3]</sup>. After excluding micrometastases to the liver and peritoneum by staging laparoscopy, irinotecan plus cisplatin combination therapy (IP) was administered as neoadjuvant chemotherapy. This was followed by gastrectomy with extended lymph node dissection including PAN. As a result of three treatment-related deaths, the study was discontinued. However, a subsequent follow-up and survival analysis showed a median survival time (MST) of 14.6 mo and a 3-year survival rate of 27% (95%CI: 15.2%-38.8%), exceeding the 3-year survival rate threshold (15%) established in the initial protocol. Although careful management of adverse events and appropriate patient selection are essential, this treatment could be recommended for gastric cancer patients with ELM.

In the JCOG 0405 study<sup>[1]</sup>, S-1 plus cisplatin combination therapy (SP) was used for neoadjuvant chemotherapy in similar patients, and the primary

endpoint was the percentage of complete resections with clear margins in the primary tumor (R0 resection). Fifty-three patients were enrolled, and among the 51 who proved eligible, R0 resection was performed in 42 patients (82.4%). A subsequent survival analysis showed an unexpectedly good 3-year survival rate of 58.5% (95%CI: 44.1%-70.4%).

Some reports have shown better survival results in gastric cancer patients who had only abdominal lymph node metastases. Yoshida *et al.*<sup>[13]</sup> investigated cases of long-term survival in patients who underwent chemotherapy for advanced gastric cancer, and reported that the 2- and 5-year survival rates of patients with metastasis to the abdominal lymph nodes only were 14.3% and 10.4%, respectively. Park *et al.*<sup>[14]</sup> reported a 3-year survival rate of 13.1% in gastric cancer patients with isolated involvement of PAN.

In those reports, clinically metastases to the liver and peritoneum that were not obvious may not have been excluded, as such metastases could not be excluded with laparotomy or staging laparoscopy. In addition, the extent of abdominal lymph node involvement in those studies may have partly exceeded that of the two neoadjuvant studies. Accordingly, direct comparison of survival rates between these chemotherapy and neoadjuvant studies is inappropriate. Despite this, the 3-year survival rate seen in the JCOG 0405 study is notably high. Furthermore, Yoshida *et al.*<sup>[13]</sup> and Park *et al.*<sup>[14]</sup> reported that some kind of local therapy had been used in many cases of long-term survival in their articles. In view of these results, neoadjuvant chemotherapy followed by surgical resection could represent a useful treatment option for gastric cancer with ELM. However, Tsuburaya *et al.*<sup>[1]</sup> described a lower 5-year survival rate for patients with both bulky N and PAN. The indication of neoadjuvant chemotherapy followed by surgery for this target is controversial.

## OPTIMAL CHEMOTHERAPY REGIME FOR GASTRIC CANCER WITH ELM

From the results of the above-mentioned JCOG 0001 and JCOG 0405 studies, 2 or 3 courses of SP is currently recommended for gastric cancer patients with ELM. For unresectable or recurrent gastric cancer, on the other hand, several triplet regimes such as docetaxel/cisplatin/5-fluorouracil<sup>[15]</sup> or docetaxel/cisplatin/S-1 combination therapy (DCS)<sup>[16-19]</sup>, have been developed and are reported to provide markedly high response rates. The JCOG 1002 study was therefore undertaken with DCS as neoadjuvant chemotherapy<sup>[20]</sup>, and the results are scheduled to be published soon.

The optimal number of cycles for neoadjuvant chemotherapy has not been established, but 2 or 3 cycles of therapy have been adopted in most neoadjuvant studies. The COMPASS-D trial, a randomized phase II trial with a factorial design comparing 2 and 4 courses of SP and DCS in neoadjuvant chemotherapy,

is underway for curable gastric cancer with serosal invasion<sup>[21]</sup>. Informative results are expected in terms of optimal regime and number of courses of neoadjuvant chemotherapy for gastric cancer from that trial.

No detailed reports have been published regarding the optimal interval between neoadjuvant chemotherapy and surgery, but patients ordinarily receive surgery if they meet adequate organ functions according to laboratory testing within 14 d before surgery<sup>[20]</sup>.

## SIGNIFICANCE OF EXTENDED DISSECTION FOR GASTRIC CANCER WITH ELM

In the above-mentioned JCOG 0001 and JCOG 0405 studies, gastrectomy with D2 plus PAN dissection was performed following neoadjuvant chemotherapy. This strategy is based on the high rate of PAN metastasis seen not only in patients with clinical PAN metastasis, but also in patients with bulky N. In addition, complete elimination of cancer cells can hardly be expected with a few courses of neoadjuvant chemotherapy. Inoue *et al.*<sup>[22]</sup> evaluated the efficacy and feasibility of neoadjuvant chemotherapy with SP in initially unresectable locally advanced gastric cancer, and reported 3-year survival rates of 31.0% and 53.8% in all and curative cases, respectively. However, they also reported that the most common site for initial recurrence after R0 resection was the PAN. Wang *et al.*<sup>[2]</sup> reported an MST of 29.8 mo after performing gastrectomy with D2 dissection following capecitabine plus oxaliplatin combination therapy in patients with clinical PAN metastasis. Those results should be interpreted with caution, since selection bias for curative cases may have had an effect. The good survival outcomes in the JCOG 0405 and JCOG 0001 studies were obtained with PAN dissection as well as gastrectomy plus D2 lymph node dissection. Given these findings, gastric cancer with ELM should be treated using concurrent PAN dissection not only in patients with PAN metastasis, but also in bulky N-only patients. However, further investigation is needed regarding the optimal extent of lymph node dissection for gastric cancer patients with ELM.

## CONCLUSION

A certain level of outcome is expected with multimodal therapy combining neoadjuvant chemotherapy and extended lymph node dissection in gastric cancer patients with ELM. At the same time, many questions remain to be unresolved, including the criteria for diagnosing ELM, optimal regime, number of courses and range of lymph node dissection.

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