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# Prognosis of gastric cancer patients with paraaortic lymph node metastasis versus those with distant metastases

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## ABSTRACT

**Introduction.** It has long been thought that cases of advanced gastric cancer with paraaortic lymph node (PALN) metastasis are impossible to cure. However, several recent reports on the long-term survival of patients with PALN metastasis have reported an increase in the use of gastrectomy with extended lymphadenectomy, involving the dissection of more nodes than those invaded by the tumour, as the standard surgery for advanced gastric cancer. **Material and methods.** The records of 1,015 patients with a confirmed histologic diagnosis of gastric cancer had been reviewed. Among patients with stage IV gastric cancer, 38 had PALN metastasis compared with 233 with peritoneal dissemination and 77 with hepatic metastasis.

**Results.** Based on tumour location, metastasis to the PALNs was more common in upper-third cancer ( $p < 0.01$ ); hepatic metastasis was more common in well-differentiated adenocarcinoma, and peritoneal dissemination was more common in poorly differentiated cancer ( $p < 0.001$ ). The 5-year survival in patients with metastasis to the PALNs was significantly higher (28.2%) than in patients with peritoneal dissemination (5.2%) or hepatic metastasis (12.0%) ( $p < 0.01$ ).

**Conclusions.** The results reveal a better 5-year survival associated with gastric cancer patients with PALN metastasis as compared with those with other distant metastases. Therefore, performing a more extended lymphadenectomy in patients with gastric cancer is recommended, especially those with suspected metastasis to the PALNs.

**Key words:** gastric cancer, paraaortic lymph node, survival

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## Introduction

The prognosis of gastric cancer patients with paraaortic lymph node (PALN) metastasis is very poor, even after curative resection combined with systematic PALN dissection. PALN metastasis from gastric cancer is classified as distant metastasis in both the 7<sup>th</sup> classification of the International Union against Cancer [1] and the 3<sup>rd</sup> English edition of the Japanese Gastric Cancer Classification [2].

In Korea and Japan, gastrectomy with extended lymphadenectomy, involving the dissection of more nodes than those invaded by the tumour, has recently become the standard surgery for advanced gastric cancer. It was reported that there is a need for a critical application of PALN dissection as one modality of multidisciplinary

treatment in patients with advanced gastric cancer in whom PALN metastasis is strongly suspected preoperatively [3].

This study examined the significance of PALN dissection in patients with advanced gastric cancer and evaluated the survival of patients with metastasis to the PALNs, compared with other distant metastases.

## Material and methods

This study reviewed 1,015 gastric cancer patients, who underwent gastric resection at the Division of Gastroenterological Surgery, Department of Surgery, Chonnam National University Hospital, over 5 years (2010 to 2015). There were 38 patients with metastasis

to the PALNs, 77 with hepatic metastasis, and 233 with peritoneal dissemination. The effects of age, gender, tumour size, tumour location, histologic type, Borrmann type, and survival rate were examined. This study was approved by the Institutional Review Board of the Clinical Research Institute of Chonnam National University Hospital (IRB No: CNUH-2020-379).

### Operative type

The surgical procedures used for the patients with peritoneal dissemination included gastrectomy with local excision of the peritoneum, bypass only and exploration. The hepatectomy procedure consisted of non-anatomic limited resections: segmentectomy, left hemihepatectomy, and right hemihepatectomy.

### Chemotherapy

Chemotherapy included a variety of drug combinations. The regimens used were 5-fluorouracil, oxalipl-

atin, and leucovorin (FOLFOX), taxane and cisplatin (TC), and 5-fluorouracil and cisplatin.

### Statistical analysis

The data were analysed statistically using the chi-squared test. The overall survival rates were calculated using the Kaplan-Meier method, and the differences between the curves were tested using the log-rank test. A p-value < 0.05 was considered statistically significant.

## Results

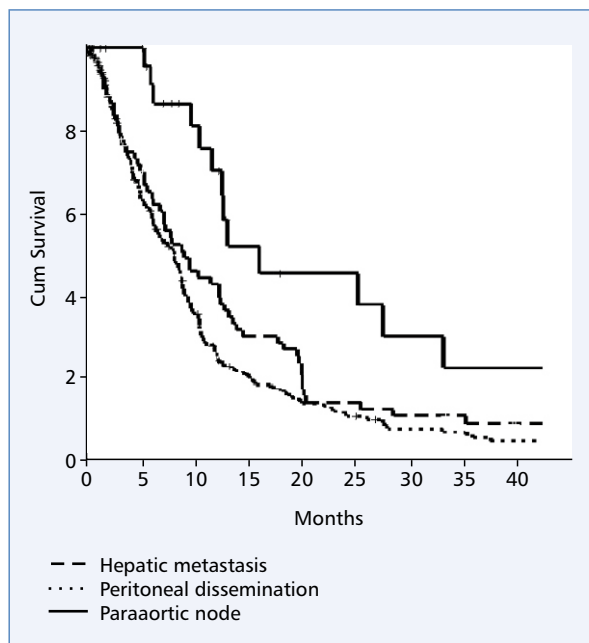
Among the 1,015 patients diagnosed with gastric cancer who underwent surgery in the hospital within the study period, 38 patients (3.7%) were diagnosed with PALN metastasis. Table 1 describes the clinicopathologic features of these 38 patients (Group I), the 233 patients with peritoneal dissemination (Group II), and the 77 patients with hepatic metastasis (Group III).

**Table 1. Clinicopathologic features of gastric cancer patients with metastasis to paraaortic lymph node, peritoneal dissemination and hepatic metastasis**

Variables	Group I (n = 38) (%)	Group II (n = 233) (%)	Group III (n = 77) (%)	p value
Age (mean, year)	54.4	53.7	58.0	NS
Gender				< 0.01
Male	24 (63.2)	157 (67.4)	67 (87.0)	
Female	14 (36.8)	76 (32.6)	10 (13.0)	
Tumor size (mean, cm)	6.2	7.0	6.1	NS
Tumor location				
Upper	<b>21 (55.3)</b>	17 (7.3)	8 (10.4)	< 0.001
Middle	12 (31.6)	58 (24.9)	13 (16.9)	
Lower	3 (7.9)	123 (52.8)	<b>52 (67.5)</b>	
Whole	2 (5.3)	<b>35 (15.0)</b>	4 (5.2)	
Histologic type				< 0.001
Well-differentiated	4 (10.5)	15 (6.4)	<b>17 (22.0)</b>	
Moderately differentiated	9 (23.7)	35 (15.0)	30 (38.9)	
Poorly differentiated	17 (44.7)	<b>138 (59.2)</b>	21 (27.3)	
Mucinous	3 (7.9)	13 (5.6)	5 (6.5)	
Signet ring cell	5 (13.2)	14 (6.0)	0 (0.0)	
Others	0 (0.0)	17 (7.3)	4 (5.2)	
Borrmann type				< 0.01
I	3 (7.9)	13 (5.6)	4 (5.2)	
II	2 (5.3)	9 (3.9)	8 (10.4)	
III	30 (78.9)	146 (62.7)	58 (75.3)	
IV	3 (7.9)	<b>65 (27.8)</b>	7 (9.1)	

NS — not significant

There was no significant difference in the mean age of the patients with PALN metastasis (54.4 years) as compared with patients with peritoneal dissemination (53.7 years) or hepatic metastasis (58.0 years). Among the 38 patients with PALN metastasis, 24 (63.2%) were male and 14 (36.8%) were female. There were more males than females in each group (I = 63.2%, II = 67.4%, III = 87.0%) ( $p < 0.01$ ). There was no significant difference in the mean tumour size (I = 6.2 cm, II = 7.0 cm, III = 6.1 cm). According to tumour location, metastasis to the PALNs was more common in upper-third cancer ( $p < 0.01$ ), peritoneal dissemination was more common in patients with cancer involving the entire stomach, and hepatic metastasis was more common in lower-third carcinoma of the stomach ( $p < 0.01$ ). According to the histologic type, there was no significant difference in patients with PALN metastasis. Peritoneal dissemination was more common in poorly differentiated adenocarcinoma and hepatic metastasis was more common in well-differentiated adenocarcinoma ( $p < 0.001$ ). Peritoneal dissemination was more common in Borrmann type IV gastric cancer (I = 7.9%, II = 27.8%, III = 9.1%) ( $p < 0.01$ ). The 5-year survival rate of Group I was significantly higher (28.2%) than that of Groups II or III (II = 5.2%, III = 12.0%) (Fig. 1)



**Figure. 1.** The Kaplan-Meier survival curves for patients with paraaortic lymph node metastasis, peritoneal dissemination, and hepatic metastasis. The 5-year survival rate for patients with metastasis to the paraaortic lymph node was significantly higher (28.2%) than with peritoneal dissemination (5.2%) and hepatic metastasis (12.0%) ( $p < 0.01$ )

( $p < 0.01$ ). The median progression-free survival was 22.7 months in Group I, and 6.5 months in Group II, and 11.8 months in Group III.

## Discussion

The prognosis of gastric cancer patients with paraaortic lymph node (PALN) metastasis is very poor, even after curative resection combined with super-extended lymph node dissection. Prophylactic PALN dissection has been the standard of care since occult metastasis had occasionally been observed in lymph nodes until a Japanese prospective randomized trial investigating the efficacy of prophylactic PALN dissection showed no survival advantage of PALN dissection for patients with locally advanced gastric cancer and no additional improvement in mortality and morbidity rates after PALN dissection [4, 5]. Since then, PALN dissection has not been routinely performed for patients with advanced gastric cancer. Thus, the significance of PALN dissection in patients with advanced gastric cancer was examined and the survival of patients with metastasis to the PALNs was evaluated, and compared with other distant metastases.

The incidence of pathological metastasis to the PALNs has been reported to vary from 1.4% to 30% [5–8]. Some authors reported that micrometastases were detected by immunohistochemical staining in 64% of patients who underwent prophylactic PALN dissection [9]. In accordance with previous reports, the incidence of pathological metastasis to the PALNs made up 3.7% of all cases in the present study.

The appropriate treatment strategy for gastric cancer patients with PALN metastasis has been a controversial one, and the Gastric Cancer Treatment Guidelines do not provide any treatment recommendations regarding chemotherapy or surgical resection in gastric cancer patients [10]. A multi-institutional prospective randomized controlled trial comparing standard D2 dissection versus D2 plus PALN dissection for serosa-positive advanced gastric cancer without gross metastasis to the PALNs was conducted in Japan. This trial demonstrated that the 5-year overall survival rates did not differ between the two groups and concluded that prophylactic PALN dissection is not effective [5].

In contrast to their result, some investigators reported that PALN dissection for advanced gastric cancer was effective, especially when it was done prophylactically [7] and when the number of paraaortic lymph node metastases were two or less [11]. It was reported that D2 lymph node dissection plus PAND may improve the overall survival for gastric cancer patients in the N3 stage [12]. Morita et al. also reported that rigorous and careful selection of patients can provide long-term survival after systemic lymph node dissection [8].

Many investigators have reported that aggressive surgery (such as extended lymph node dissection) increased operative morbidity and mortality. The Dutch trial did not recommend a routinely extended lymph node dissection because of the high operative morbidity and mortality [13]. Conversely, some authors demonstrated that the overall postoperative complications and death rates did not increase after extended lymph node dissection and they encouraged performing extended lymph node dissection in patients with advanced gastric cancer [14, 15]. De Manzoni et al. reported 2.7% postoperative morbidity with PALN dissection in patients with advanced gastric cancer [16]. It was stated that the morbidity associated with super-extended paraaortic lymphadenectomy could be minimized by very careful manipulation during dissection of the paraaortic lymph nodes, by fine and thorough ligation of the retroperitoneal tissue to prevent lymphorrhea [17]. In the current study, the postoperative mortality for gastric cancer patients with PALN dissection was acceptable. One postoperative death occurred after resection. There was a 2.6% mortality rate, which is consistent with that reported previously.

The reported postoperative 5-year survival rate of patients with pathologically-positive PALNs is 16–25% [3, 5, 6, 10, 18–20]. With several reports of long-term survival in cases with PALN metastasis, Korean and Japanese surgeons are increasingly performing extensive surgery to treat advanced gastric cancers. Several investigators reported that gastrectomy with extended lymph node dissection improves the prognosis of patients with PALN metastasis, and they recommended removing the PALNs when the surgeon detects metastasis there intraoperatively [21–23]. In the presented study, the 5-year survival rate was 28.2% for patients with PALN metastasis.

In this context, the identification of prognostic factors for patients with PALN metastasis seems important. However, it has not yet been well investigated. Previous studies have indicated prognostic factors for these patients: the macroscopic type, overall number of involved nodes [19], number of PALN metastases [10], age of patients and site of PALN metastasis [8]. However, most of these studies included few patients. In this retrospective study, prognostic factors were not investigated because of the small sample size.

In conclusion, the presented study results showed that gastric cancer patients with PALN metastasis survived longer than patients with other types of distant metastases (such as peritoneal dissemination and hepatic metastasis). Therefore, the authors recommend performing a more extended lymphadenectomy in patients with advanced gastric cancer, especially those suspected of metastasis to the PALNs.

## Conflict of interest

The researchers claim no conflict of interest.

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