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Prognostic Factors for Para-aortic Lymph Node Dissection After Neoadjuvant Chemotherapy for Gastric Cancer

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Abstract. *Background/Aim: The prognosis of gastric cancer with para-aortic or bulky lymph node metastases is poor, but the JCOG 0405 study showed relatively good outcomes of neoadjuvant chemotherapy and gastrectomy with para-aortic lymph node dissection. We investigated the prognostic factors for this treatment. Patients and Methods: Twenty patients who underwent gastrectomy and para-aortic lymph node dissection after chemotherapy were enrolled from two institutions. The prognostic factors for overall survival were retrospectively analysed using Cox's proportional hazard models. Results: The univariate analyses revealed that ypN (3/0-2, p=0.001), ypM1 (para-aortic LYM) (yes/no, p=0.03), histological response (Grade0-1b/2-3, p=0.02), and adjuvant chemotherapy (no/yes, p=0.02) were significant prognostic factors, whereas multivariate analysis revealed ypN and absence of adjuvant chemotherapy to be independent prognostic factors. Conclusion: Posttreatment nodal status may be the best surrogate marker for gastric cancer with gastrectomy and para-aortic lymph node dissection after neoadjuvant chemotherapy. Adjuvant chemotherapy seems to be essential to improve survival.*

Gastric cancer was estimated to be the fourth most common cause of cancer death worldwide in 2016, following lung, liver, and colorectal cancers (1). The prognosis of gastric cancer with extensive lymph node metastases such as para-aortic lymph node metastases or bulky lymph node metastases (≥3 cm, or at least two adjacent tumours ≥1.5 cm, along the celiac, common hepatic, splenic, or proper hepatic arteries) is still poor. To improve survival from advanced gastric cancer, neoadjuvant chemotherapy (NAC) has been developed.

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Key Words: Neoadjuvant chemotherapy, para-aortic lymph node excision, stomach neoplasms.

The Japan Clinical Oncology Group (JCOG) 0405 study (2) has reported a good prognosis for NAC with tegafur/gimeracil/oteracil (S-1) + cisplatin and gastrectomy with para-aortic lymph node dissection (PAND); the five-year overall survival (OS) rate was 53%. This strategy is now recognized as a tentative standard treatment for gastric cancer with para-aortic lymph node metastases and/or bulky lymph node metastases. However, several unresolved issues remain concerning the prognostic factors for this population. Generally, cancer stage is related with survival, but it is unclear whether the pretreatment or posttreatment cancer stage is the more appropriate prognostic factor. Research for the best surrogate marker for OS in this population seems quite important for further investigation for NAC. In addition, it is unclear whether or not adjuvant chemotherapy is needed, as postoperative treatment was not administered in the JCOG 0405 study.

In the current study, we investigated the outcomes of gastrectomy with PAND after NAC, and prognostic factors were retrospectively analysed using Cox's proportional hazard model.

Patients and Methods

The number of patients who underwent gastrectomy at Higashiosaka City Medical Center (HCMC) between 1998 and 2018 was 1,397, and that at Yao Municipal Hospital (YMH) between 2013 and 2019 was 489. Among them, 106 patients (5.6%) underwent chemotherapy before surgery. Of these 106 patients, 22 underwent dissection of the para-aortic lymph nodes (Nos. 16a2 and/or 16b1). After excluding one patient who had a macroscopic residual tumour (R2 resection) and one patient who underwent chemoradiation therapy before surgery, 20 patients were analysed. The CONSORT diagram is shown in Figure 1. The following clinical and pathological characteristics, perioperative treatment, and postoperative outcomes were collected: sex, age, histological classification, pretreatment clinical findings of gastric cancer (cT, cN, cM), NAC regimen, operative procedure, pathological findings (ypT, ypN, ypM), histological evaluation criteria of tumour response, adjuvant chemotherapy, and prognosis. The clinicopathological findings of gastric cancer were described according to the Japanese classification of gastric carcinoma, 3rd English edition (3). The histological

response of the primary tumour was evaluated as follows: Grade 0 (no effect) means no evidence of effect, Grade 1a (very slight effect) means viable tumour cells occupied more than 2/3 of the tumorous area, Grade 1b (slight effect) means viable tumour cells remained in more than 1/3 but less than 2/3 of the tumorous area, Grade 2 (considerable effect) means viable tumour cells remained in less than 1/3 of the tumorous area, and Grade 3 (complete response) means no viable tumour cells remained.

Operative procedure. In principle, all surgical procedures were performed according to the Japanese gastric cancer treatment guidelines (4). PAND indicates dissection of Nos. 16a2 and 16b1 lymph node stations according to the Japanese classification of gastric carcinoma (3), which mean para-aortic lymph nodes between the upper margin of the origin of the celiac artery and the lower border of the left renal vein, and para-aortic lymph nodes between the lower border of the left renal vein and the upper border of the origin of the inferior mesenteric artery, respectively. In the current series, incomplete dissection, including picking-up of any lymph nodes, was included. Laparoscopic surgery was not performed.

Disclosure of ethical statement. The protocol for this research project was approved by suitably-constituted Ethics Committees of the institutions, and conformed to the provisions of the Declaration of Helsinki: Committee of YMH, approval No. 020620-75; and committee of HCMC, approval No. 02-0390.

Statistical analysis. OS was defined as the interval from the date of surgery to the date of death from any cause. Univariate and multivariate analyses for OS were conducted using Cox's proportional hazards model. Survival was evaluated on Kaplan–Meier curves and compared using the log-rank test. Statistical significance was set at $p<0.05$. All analyses were performed using JMP software (version 11.0.0 for Windows; SAS Institute Inc., Cary, NC, USA).

Results

The clinical, surgical, and pathological features of participants are summarized in Table I. Clinical para-aortic lymph node metastases were recognized in 17 patients, and bulky lymph node metastases were recognized in three patients.

The neoadjuvant chemotherapy regimen varied according to the era. Between 1998 and 2004, fluorouracil + cisplatin (+ docetaxel) was selected for four patients. After 2005, S-1 + cisplatin became the major regimen, and was applied to 10 patients. After 2017, oxaliplatin-combination chemotherapy became more popular, including capecitabine + oxaliplatin (+ trastuzumab) for three patients and S-1 + oxaliplatin for one patient.

Concerning surgical complications, Clavien-Dindo (5) Grade≥III complications were encountered in six patients, including anastomosis leakage Grade IIIb (open drainage) in one patient, abdominal abscess Grade IIIa (percutaneous drainage) in two patients, ascites Grade IIIa (suturing the drain site) in two patients, and pneumothorax Grade IIIa (percutaneous drainage) in one patient. There were no surgery-related deaths.

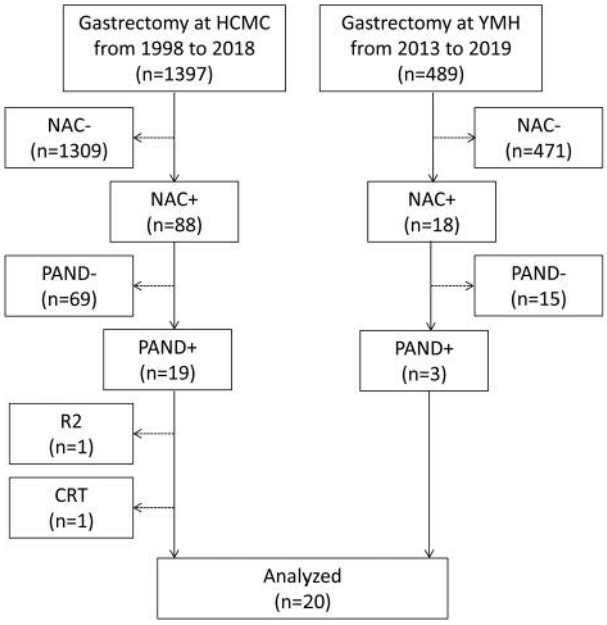

Figure 1. *CONSORT diagram of participating patients. NAC: Neoadjuvant chemotherapy; PAND: para-aortic lymph node dissection; R2: macroscopic residual tumour; CRT: chemoradiation therapy.*

Pathological metastases to para-aortic lymph nodes were recognized in seven patients. Positive peritoneal lavage cytology (CY1), peritoneum (greater omentum) metastasis (P1), left supraclavicular lymph node metastasis, and gallbladder metastasis were recognized in three, two, one, and one patient, respectively, including duplication. Accordingly, 10 patients were diagnosed as having yp Stage IV gastric cancer after NAC. Sixteen patients underwent curative resection (R0) whereas three patients with CY1 and one patient with a pathologically-positive distal margin (DM1) underwent non-curative resection (R1). Patients with distant metastases (omentum, supraclavicular lymph node, and gallbladder) underwent resection of the metastatic sites leaving no macroscopic residual tumour.

Postoperatively, adjuvant chemotherapy was administered to 13 patients. The chemotherapy regimen also varied according to the era. Before 2009, tegafur/uracil (UFT) was given to three patients, and irinotecan + cisplatin to one patient. After 2010, an S-1-based regimen was employed for six patients, and a capecitabine-based regimen for three patients.

At the time of analysis, nine patients (45%) had died, and the median follow-up period of the eleven surviving patients was 48 months. Six patients died of gastric cancer, and three of other diseases. The median survival time was 31.3 months, and the five-year OS rate was 46%.

In the univariate analyses, ypN3 compared with ypN0-2, ypM1(para-aortic LYM), histological response Grade 0-1b compared with Grade 2-3, and absence of adjuvant

Table I. *The clinical, surgical, and pathological features of the patients.*

Valuables	n=20
Gender, n (%)	
Male	15 (75)
Age, years	
Median (range)	65.5 (49-75)
Histological classification, n	
Differentiated (tub/muc)	10 (9/1)
Undifferentiated (por/sig)	10 (9/1)
cT, n	
3	5
4a	12
4b	3
cN, n	
0	1
1	7
2	5
3	7
Bulky N, n	
Yes	3
cM, n	
1(LYM)	17
cP, n	
1	0
cH, n	
1	3
cStage, n	
IIIA	1
IIIC	1
IV	18
Neoadjuvant chemotherapy regimen, n	
Fluorouracil+cisplatin	3
Fluorouracil+cisplatin+docetaxel	1
S-1+cisplatin	10
S-1 → paclitaxel	1
Capecitabine+cisplatin+trastuzumab	1
Capecitabine+oxaliplatin	2
Capecitabine+oxaliplatin+trastuzumab	1
S-1+oxaliplatin	1
Extent of gastrectomy, n	
Total	12
Distal	8
Extent of lymphadenectomy, n	
D2+	20

Valuables		n=20
Surgical complications, n		
Anastomosis leakage	Grade II	1
Anastomosis leakage	Grade IIIb	1
Abdominal abscess	Grade II	1
Abdominal abscess	Grade IIIa	2
Ascitis	Grade II	1
Ascitis	Grade IIIa	2
Pneumothorax	Grade IIIa	1
ypT, n		
0		1
1a		1
1b		2
2		1
3		10
4a		4
4b		1
ypN, n		
0		4
1		5
2		1
3a		6
3b		4
ypM, n		
1(para-aortic LYM)		7
1(neck LYM)		1
1(gallbladder)		1
ypP, n		
1		2
ypCY, n		
1		3
ypH, n		
1		0
ypStage		
IA		1
IB		2
IIA		2
IIB		3
IIIB		1
IIIC		1
IV		10
Residual tumor, n		
R0		16
R1		4
Histological response Grade, n		
0		2
1a		4
1b		5
2		8
3		1
Adjuvant chemotherapy regimen, n		
Tegafur/uracil		3
Irinotecan+cisplatin		1
S-1		5
S-1+cisplatin		1
Capecitabine		1
Capecitabine+trastuzumab		1
Capecitabine+cisplatin+trastuzumab		1
No		7

Clinicopathological findings were written according to the Japanese Classification of Gastric Carcinoma (3rd English edition).

chemotherapy compared with presence were significantly correlated with worse OS (Table II). Multivariate analysis of these four factors revealed ypN3 and absence of adjuvant chemotherapy to be independent risk factors for death.

The OS curves by ypN, ypM1(para-aortic LYM), histological response, and adjuvant chemotherapy are shown in Figures 2-5, respectively. Survivals were significantly better in ypN0-2 than in ypN3, in the absence of ypM1(para-aortic LYM) than in its presence, in histological response Grade 2-3 than in Grade 0-1b, and in the presence of adjuvant chemotherapy than in its absence.

Table II. *Univariate and multivariate analyses for overall survival.*

Valuables	n	MST (mo)	Univariate analysis			Multivariate analysis		
			HR	(95%CI)	*p*-Value	HR	(95%CI)	*p*-Value
Gender								
Female	5	14.7	Reference					
Male	15	31.3	0.57	(0.15-2.71)	0.44			
Age								
<65 Years	8	20.9	Reference					
≥65 Years	12	31.3	0.7	(0.19-2.85)	0.6			
Histological classification								
Differentiated	10	20.9	Reference					
Undifferentiated	10	31.3	1.16	(0.29-4.45)	0.82			
cT								
3	5	>216.6	Reference					
4	15	20.9	4.26	(0.77-79.4)	0.1			
cN								
0,1	8	>216.6	Reference					
2,3	12	31.3	1.12	(0.29-5.32)	0.87			
Extent of gastrectomy								
Distal	8	>209.6	Reference					
Total	12	20.9	1.62	(0.42-7.67)	0.49			
Complications								
No	11	20.9	Reference					
Yes	9	>216.6	0.58	(0.12-2.21)	0.43			
ypT								
0-3	15	>216.6	Reference					
4	5	12	3.87	(0.74-18.3)	0.1			
ypN								
0-2	10	>216.6	Reference			Reference		
3	10	14.7	16.7	(2.89-318)	0.001	26.8	(1.51-1105)	0.02
ypM1(para-aortic LYM)								
No	13	>216.6	Reference			Reference		
Yes	7	16.6	4.64	(1.19-22.6)	0.03	0.66	(0.08-5.75)	0.69
ypM(OTH) or ypP1 or ypCY1								
No	14	31.3	Reference					
Yes	6	70.7	1.26	(0.18-5.45)	0.78			
ypStage								
IA-IIIC	10	>216.6	Reference					
IV	10	16.6	2.73	(0.71-13.2)	0.15			
Histological response Grade								
2,3	9	>209.6	Reference			Reference		
0,1a,1b	11	14.7	5.86	(1.39-39.8)	0.02	1.15	(0.20-8.81)	0.88
Adjuvant chemotherapy								
Yes	13	>209.6	Reference			Reference		
No	7	12	5.35	(1.37-22.4)	0.02	5.66	(1.13-42.4)	0.04

MST: Median survival time; HR: hazard ratio; CI: confidence interval. Clinicopathological findings were written according to the Japanese Classification of Gastric Carcinoma (3rd English edition).

Discussion

We investigated the prognostic factors for gastrectomy and PAND after NAC. Posttreatment pathological findings of lymph nodes {ypN and ypM (para-aortic LYM)}, histological response grade, and adjuvant chemotherapy were significant prognostic factors, whereas pretreatment clinical findings were not. Multivariate analysis revealed ypN and adjuvant chemotherapy to be independent prognostic factors.

In Western countries, NAC has become a standard treatment for curable gastric cancer, based on the results of the MAGIC trial (6) that addition of perioperative epirubicin, cisplatin, and infused fluorouracil to surgery improved survival. In Japan, the JCOG 0405 study showed that for locally advanced gastric cancer with extensive lymph node

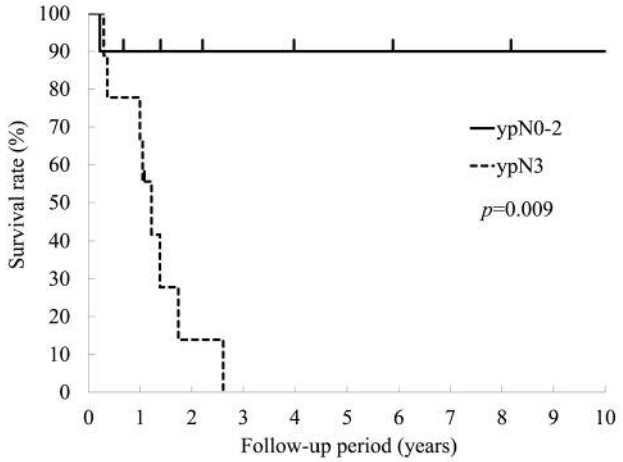

Figure 2. *Kaplan–Meier overall survival curves of ypN0-2 and ypN3 in patients who underwent gastrectomy with para-aortic lymph node dissection after neoadjuvant chemotherapy.*

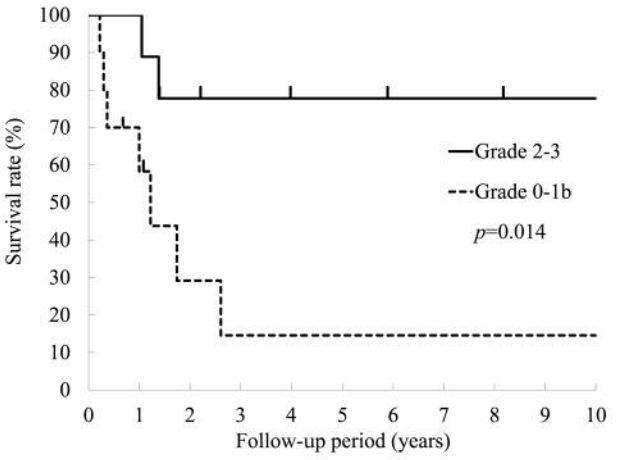

Figure 4. *Kaplan–Meier overall survival curves of histological response Grades 0-1b and 2-3 in patients who underwent gastrectomy with para-aortic lymph node dissection after neoadjuvant chemotherapy.*

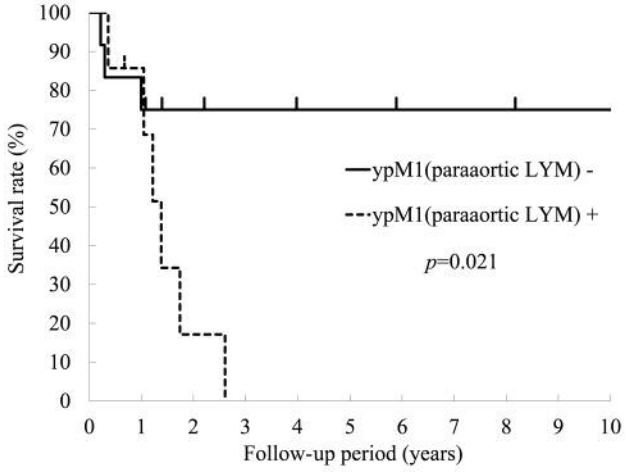

Figure 3. *Kaplan–Meier overall survival curves of the presence and the absence of ypM1(paraaortic LYM) in patients who underwent gastrectomy with para-aortic lymph node dissection after neoadjuvant chemotherapy.*

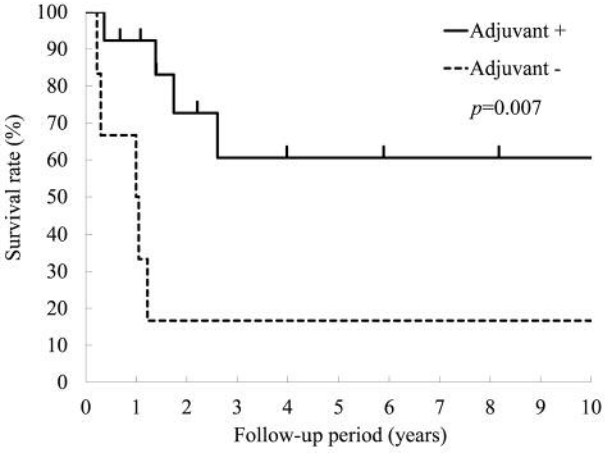

Figure 5. *Kaplan–Meier overall survival curves of the presence and the absence of adjuvant chemotherapy in patients who underwent gastrectomy with para-aortic lymph node dissection after neoadjuvant chemotherapy.*

metastasis, S-1 plus cisplatin followed by surgery including PAND was safe and effective. However, the JCOG 0501 study (7), which was a randomized phase III trial of surgery plus neoadjuvant S-1 and cisplatin compared with surgery alone for type 4 and large type 3 gastric cancers, indicated that additional NAC with S-1 plus cisplatin is not recommended for these cancers, and thus D2 surgery plus S-1 adjuvant chemotherapy remains the current standard of treatment. Accordingly, NAC with S-1 + cisplatin is now applied for clinical use in patients with para-aortic lymph node or bulky lymph node metastases. The effectiveness of adding docetaxel to S-1 + cisplatin was refuted by the JCOG 1002 study (8). Further clinical studies to improve the effects of NAC for gastric cancer with extensive lymph node metastasis are ongoing in Japan; notably a phase II study of docetaxel + oxaliplatin + S-1 (JCOG 1704) (9).

The primary endpoint of the JCOG 1704 study was the histological response rate, because Kurokawa *et al*. showed that histological response was the best surrogate endpoint for OS after NAC in a combined analysis of the JCOG 0210 and JCOG 0405 studies (10). Lowy *et al*. have also identified response to NAC as the single most important predictor of

OS after NAC for gastric cancer (11). Our study also showed histological response to be significantly correlated with OS.

However, according to the present multivariate analysis, the best surrogate marker for OS seems to be the posttreatment pathological nodal status (ypN). Fujitani *et al*. have also mentioned that posttreatment nodal status, rather than graded histologic response, predicts survival after NAC and could serve as a reliable surrogate marker for OS (12). Schmidt *et al*. have identified ypTNM stage, R category, and complications, but not histopathological tumour regression, as independent prognostic factors (13). Mansour *et al*. have found that although histologic response was associated with marked differences in OS, these associations did not persist in the multivariate analysis; only pathologic lymph node status was independently associated with OS in patients treated with NAC (14).

Postoperative treatment was not given until tumour recurrence in the JCOG 0405 study, but the results of the current multivariate analysis indicated that adjuvant chemotherapy is essential after NAC and PAND. However, the optimal chemotherapy regimen and its duration remain uncertain as various regimens were employed in this study. In the JCOG 0501, 1002, and 1704 studies, adjuvant chemotherapy with S-1 for one year was administered after NAC and gastrectomy.

Surgical complications ≥Grade II included two cases of anastomosis leakage (10%) and three cases of abdominal abscess (15%). One patient required re-operation for gastroduodenal anastomotic leakage and pan-peritonitis. NAC might have affected healing of the anastomotic site (15). In the JCOG 0405 study, the incidences of anastomotic leakage and abdominal abscess were also high, at 6.1% and 16.3%, respectively. These incidence rates may be acceptable, but careful attention should be given to avoid complications after NAC, as complications have been reported to be negative prognostic factors for OS (13).

The present study had several potential limitations. First, the number of participants was small even after collecting patients from two institutions for over 20 years. This is because the strategy with NAC and PAND was not a standard therapy in Japan. The JCOG 0405 study has proven that they are effective. Therefore, the number of cases treated with NAC and PAND will increase in the future. Second, the regimen of NAC in the current series showed great variation. The number of courses also varied, and was not considered in this analysis. In the JCOG 0405 study, the NAC regimen was two or three courses of S-1 + cisplatin. The effectiveness of other NAC regimens is still unclear. Third, the extent of PAND also varied. Some patients underwent complete dissection of 16a2 and 16b1 lymph node stations, whereas others underwent dissection of certain of these lymph nodes.

In conclusion, posttreatment nodal status (regional and para-aortic), histological response, and adjuvant chemotherapy were revealed to be prognostic factors after NAC and PAND. Posttreatment regional nodal status (ypN) may be more closely correlated with survival than histological response grade. Adjuvant chemotherapy seems to be essential to improve survival.

Conflicts of Interest

The Authors have no financial conflicts of interest to disclose concerning this study.

Authors' Contributions

S. Endo wrote the protocol. S. Endo and M. Ikenaga gathered the data. S. Endo analysed the data. All Authors were involved in the drafting, review, and approval of the manuscript and the decision to submit for publication.

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