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SHORT COMMUNICATION

An integrated analysis of two phase II trials (JCOG0001 and JCOG0405) of preoperative chemotherapy followed by D3 gastrectomy for gastric cancer with extensive lymph node metastasis

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Abstract

Background Gastric cancer with extensive lymph node metastasis is commonly regarded as unresectable, while preoperative chemotherapy followed by gastrectomy has been tested since 2000 in JCOG (JCOG0001 and JCOG0405). The survivals were quite different between the trials despite the similar eligibility criteria. The aim of this study was to investigate if survival is still better in JCOG0405 after adjusting baseline factors and if there is any subset of patients who benefit more from either treatment.

Methods Eligibility criteria for both trials included histologically proven gastric adenocarcinoma; bulky nodal involvement around the celiac artery and its major branches (bulky N) and/or para-aortic lymph node (PAN); cM0 (except PAN); negative lavage cytology; not linitis plastica type; PS of 0 or 1. Patients received two or three cycles of preoperative chemotherapy of irinotecan plus cisplatin in JCOG0001, or S-1 plus cisplatin in JCOG0405, followed by D3 gastrectomy. Multivariable analysis for overall survival adjusting baseline and treatment factors was performed with the Cox regression model.

Results After adjusting baseline factors, S-1 plus cisplatin was superior to irinotecan plus cisplatin for overall survival (HR = 0.39: 95% CI 0.22–0.67). The 5-year overall survival was poor for patients with bulky N+/PAN+ (19.2%) compared with bulky N+/PAN− (50.7%) or bulky N−/PAN+ (43.5%).

Conclusions S-1 plus cisplatin was shown to be a favorable preoperative treatment for gastric cancer with extensive lymph node metastasis by multivariable analysis, while poor prognosis in patients having both bulky N+ and PAN+ may necessitate further treatment improvement.

Keywords Gastric cancer · Preoperative chemotherapy · Extensive lymph node dissection

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Introduction

Complete resection of gastric cancer with adequate lymph node dissection is necessary to achieve long-term survival [1, 2]. Generally, the prognosis is poor for patients with distant metastasis including liver, peritoneal, and para-aortic lymph node metastasis because it is already a systemic disease. In addition, the prognosis is poor for patients with locally advanced, bulky lymph nodes along the celiac, splenic, common, or proper hepatic arteries (bulky N) metastasis with or without para-aortic lymph node (PAN) metastasis, because it is difficult to perform R0 resection for them. In Western countries, these patients had been treated with chemotherapy because these tumors had been regarded as unresectable, while Japanese surgeons are still seeking to cure them and surgeons in the West also take a similar approach [3, 4].

Two phase II trials have been conducted by Japan Clinical Oncology Group (JCOG) for this population. In JCOG0001 (patient accrual: August 2000–May 2003), patients received two or three cycles of irinotecan and cisplatin therapy followed by gastrectomy with D2 plus PAN dissection. In JCOG0405 (patient accrual: February 2005–June 2007), patients satisfying the same eligibility criteria as in JCOG0001 received two or three cycles of cisplatin and S-1 therapy and then underwent the same surgery.

These trials demonstrated good 3-year survival of 27.0% in JCOG0001 and 58.8% in JCOG0405. S-1 plus cisplatin is considered to be stronger than irinotecan plus cisplatin due to the difference in the pathological response rate of primary lesion (51% in JCOG0405 and 15% in JCOG0001) [5, 6]. Based on these results, preoperative chemotherapy with JCOG0405 regimen has become de facto standard for this population in the same way as S-1 plus cisplatin has become the standard treatment for advanced and recurrent gastric cancer patients [7–9]. In addition, there was no systematic review to compare the treatment effects by the lymph node involvement status.

The aim of this study was to investigate the prognostic factors if survival is still better in JCOG0405 after adjusting baseline factors and if there is any subset of patients who benefit more from either treatment. In addition, comparing the treatment effects by the lymph node involvement status is another objective of this study.

Patients and methods

Patient data were used for this analysis among all eligible patients except patients who did not undergo surgery in JCOG0001 and JCOG0405.

Overall survival (OS) was measured from the date of registration to the date of death from any cause. OS curve was estimated using the Kaplan–Meier method. The following factors were included in this analysis as baseline factors; age (63 years old or less/64 years old or more), sex (male/female), macroscopic type of primary tumor (Type 3/Type 1, 2, and 5), histological type (differentiated/undifferentiated), primary tumor location (upper third/middle third/lower third), lymph node involvement (bulky N+/PAN− vs bulky N−/PAN+ vs bulky N+/PAN+), and type of gastrectomy (subtotal/total/others). As exploratory analyses, subgroup analyses by pathological status of lymph node metastasis (pN0/pN1/pN2/pN3) were conducted. In this study, pN0–3 meant the anatomical extent of lymph node metastasis, because tumors were staged in accordance with the 13th Japanese Classification of Gastric Carcinoma correspondent to 2nd English edition in both trials [10]. OS was compared between JCOG0001 and JCOG0405 using the multivariable Cox proportional hazard model adjusted with baseline factors, and hazard ratio (HR) and its 95% confidence interval (CI) was estimated. Subgroup analyses according to the combination of these trials and each baseline factors were performed. Interaction tests were also carried out between baseline factors and trials, and two-sided $P < 0.20$ was considered as significant.

This study protocol was approved by the JCOG Protocol Review Committee and done in accordance with the international ethical recommendations stated in the Declaration of Helsinki [11], Japanese Ethical Guidelines for Epidemiological Research [12]. All statistical analyses were done using SAS 9.1 or more.

Results

This analysis included 96 patients, 49 patients from JCOG0001 and 47 patients from JCOG0405. Baseline characteristics of this analysis are shown in Table 1. In subgroup of bulky N+/PAN+, the number of these patients was larger in JCOG0001 than in JCOG0405. Proportions of other factors were similar in both trials. Even after adjusting baseline factors, S-1 plus cisplatin was superior to irinotecan plus cisplatin for OS (HR = 0.39: 95% CI 0.22–0.67) (Table 2).

Survival curves are shown in Fig. 1a–c for the following subgroups. 5-year OS was 19.2%, 50.7%, and 43.5% by the clinical status of lymph node metastasis (bulky N+/PAN+, bulky N+/PAN−, bulky N−/PAN+) (Fig. 1a). Among 94 patients who received gastrectomy, 5-year OS by the pathological status of lymph node metastasis (pN0–N3) was 88.9%, 41.7%, 58.6% and 20.5% (Fig. 1b). In particular, 5-year OS of 30 patients having pathological N3 when they had been diagnosed with clinical PAN+ was 16.7% (Fig. 1c). Although the subgroup of bulky N+/PAN+ is not

Table 1 Baseline characteristics

	JCOG0001		JCOG0405		*P* value[a]
No. of patients	49		47		
Age					
< 63	30	61%	25	53%	0.54
> 64	19	39%	22	47%	
Sex					
Male	38	78%	39	83%	0.61
Female	11	22%	8	17%	
Macroscopic type[b]					
3	30	61%	28	60%	1.00
1, 2, 5	19	39%	19	40%	
Histological type					
Intestinal	26	53%	28	60%	0.54
Diffuse	23	47%	19	40%	
Tumor location					
U	13	26%	15	32%	0.76
M	17	35%	17	36%	
L	19	39%	15	32%	
Lymph node involvement					
Bulky N+/PAN+	16	33%	10	21%	0.31
Bulky N+/PAN−	24	49%	23	49%	
Bulky N−/PAN+	9	18%	14	30%	
Surgery					
Subtotal gastrectomy	15	31%	16	34%	0.63
Total gastrectomy	32	65%	31	66%	
Others[c]	2	4%	0	0%	

[a]Each *P* value is two-sided. Wilcoxon rank sum test was used for continuous variable, and Fisher's exact test was used for categorical data

[b]Japanese Classification of Gastric Carcinoma

[c]One is exploratory laparotomy and another is gastrojejunostomy

Table 2 Multivariable analysis for overall survival

Variable	Comparison	Hazard ratio	95% CI
Study	0405 (vs. 0001)	0.39	0.22–0.67
Age	> 64 (vs. < 63)	1.46	0.83–2.56
Sex	Male (vs. female)	0.45	0.23–0.88
Macroscopic type	3 (vs. 1, 2, 5)	0.51	0.29–0.89
Histological type	Intestinal (vs. diffuse)	0.97	0.56–1.69
Location	L (vs. U)	2.71	1.24–5.93
	M (vs. U)	2.24	1.07–4.72
Lymph node involvement	Bulky N+/PAN− (vs. Bulky N−/PAN+)	0.69	0.34–1.43
	Bulky N+/PAN+ (vs. Bulky N−/PAN+)	1.91	0.90–4.07
Surgery	Subtotal gastrectomy (vs. total gastrectomy)	0.36	0.19–0.70
	Others (vs. total gastrectomy)[a]	1.57	0.30–8.13

[a]One is exploratory laparotomy and another is gastrojejunostomy

completely the same subgroup as pN3, prognosis of both subgroups is poor.

In addition, subgroup analysis by the status of clinical lymph node metastasis in each treatment (S-1 plus cisplatin and irinotecan plus cisplatin) is shown in Fig. 2. 5-year OS by the status of lymph node metastasis (bulky N+/PAN+, bulky N+/PAN−, bulky N−/PAN+) was 18.8%, 29.2%, and 22.2% in JCOG0001, and also 20.0%, 73.4%, and 57.1% in

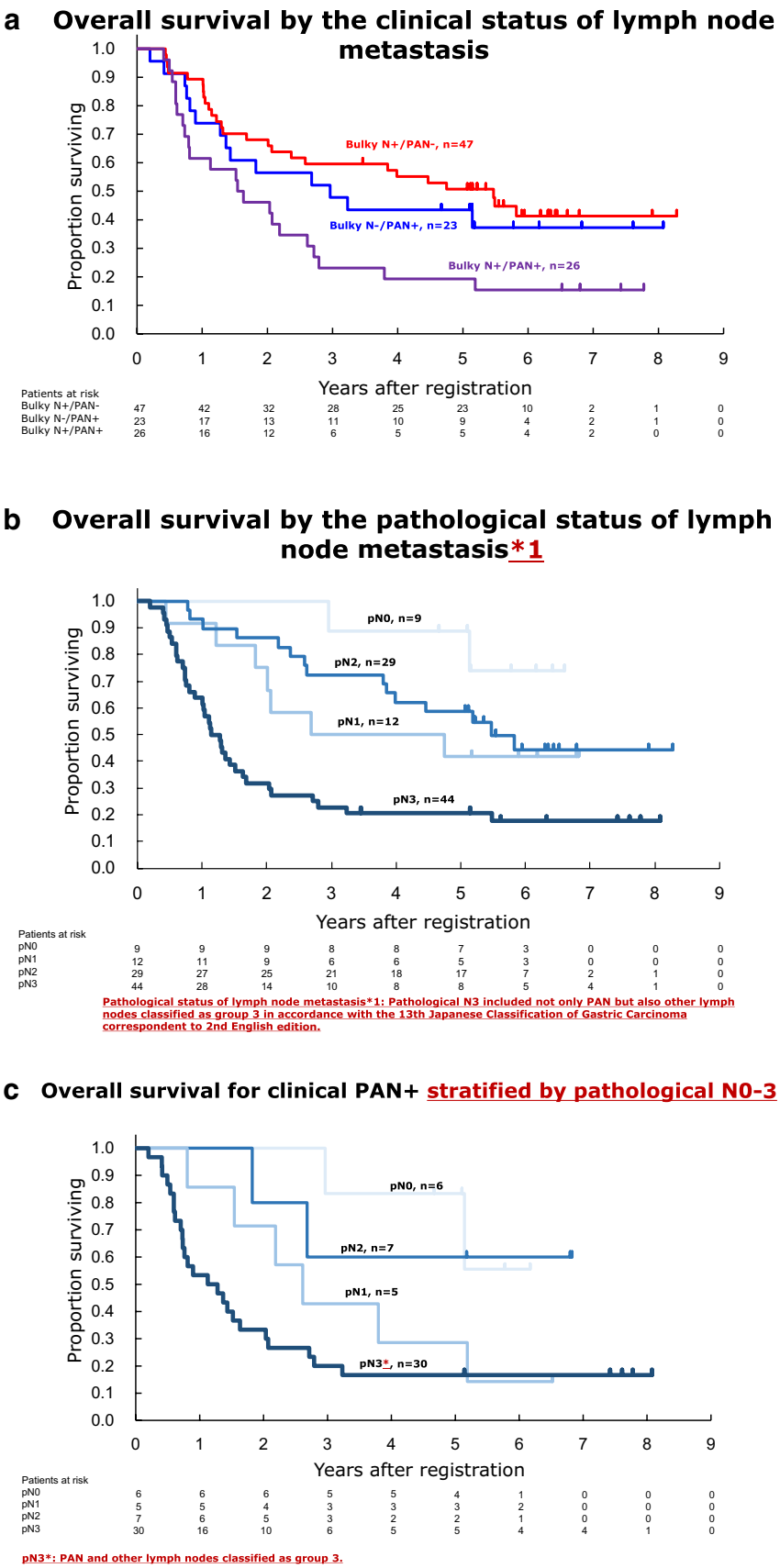

Fig. 1 **a** Overall survival by the clinical status of lymph node metastasis. **b** Overall survival by the pathological status of lymph node metastasis. **c** Overall survival for clinical PAN+ stratified by pathological N0–3

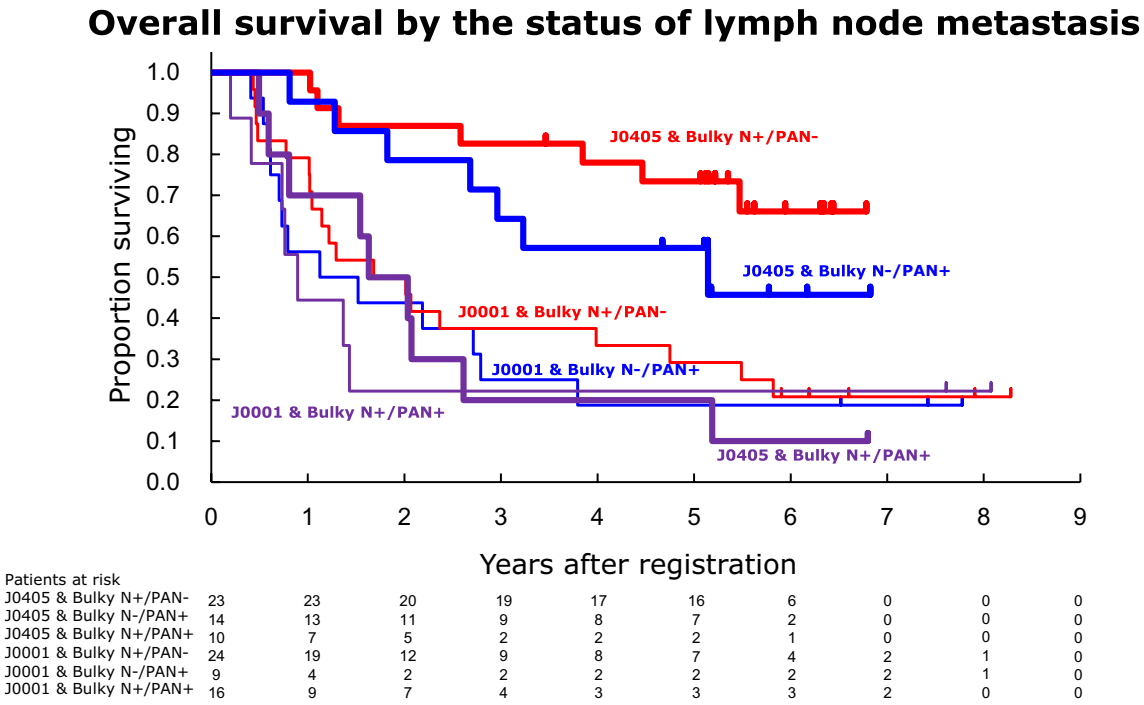

Fig. 2 Overall survival by the status of lymph node metastasis

JCOG0405 (Fig. 2). There was no interaction effect between treatment and each subgroup with significant level of 0.20.

Discussion

This integrated analysis demonstrated several findings. First, S-1 plus cisplatin combined with D3 gastrectomy was shown to be better treatment than irinotecan plus cisplatin combined with D3 gastrectomy for gastric cancer with extensive lymph node metastasis after adjusting baseline factors. Second, prognosis of patients having both bulky N+ and PAN+ was poorer than other lymph node statuses. This is an understandable result because this study population is generally considered to be a metastatic disease.

Standard treatment for the gastric cancer patients with extensive lymph node metastasis in Japan is different from that in Western countries. In the West, chemotherapy with doublet or triplet platinum/fluoropyrimidine combinations is recommended for these patients because extensive lymph node metastasis is considered to be a metastatic disease [4]. On the other hand, in Japan, preoperative chemotherapy followed by surgery with extensive lymph node dissection is the de facto standard treatment because extensive lymph node metastasis such as bulky N+ and part of para-aortic lymph nodes (No. 16a2 and No. 16b1) is historically considered to be a locoregional disease although the definition of the regional lymph nodes of the stomach is the same in Japan and in Western countries. In order to perform D3 lymph node dissection safely and effectively, this treatment should be conducted by experienced surgeons and in specialized hospitals.

Perioperative (preoperative and postoperative) chemotherapy with platinum/fluoropyrimidine combination for resectable gastric cancer patients has been developed all over the world. In European countries, perioperative chemotherapies, such as ECF (epirubicin, cisplatin, and 5-fluorouracil) based on the UK MRC MAGIC trial [13], capecitabine-containing regimen ECX, and oxaliplatin-containing regimen EOX [14], have been adopted as standard therapies. Recently, the German AIO study group demonstrated the superiority of a perioperative FLOT regimen (fluorouracil, leucovorin, oxaliplatin, and docetaxel) to ECF/X [15]. In Japan, the preoperative DCS (docetaxel, cisplatin, and S-1) did not show a sufficient response rate for patients with extensive lymph node metastasis, therefore, S-1 plus cisplatin is considered to be the current standard regimen for this population [16, 17]. Although the regimens are different in Western countries and in Japan, platinum/fluoropyrimidine/taxane triplet is considered the promising regimen and clinical trial using preoperative DOS (docetaxel, oxaliplatin, and S-1) is ongoing by Stomach Cancer Study Group of the JCOG [18].

The subgroup analysis of PAN+ patients shows extremely poor OS of patients with ypN2 or ypN3 (topographical staging), which is quite different from those with ypN0 or

ypN1. This suggests that it is still an open question if clinical PAN+ patients should undergo surgery just after a few courses of chemotherapy as bulky N+ patients or not. These patients might better undergo D2 alone surgery as conversion therapy after longer term chemotherapy.

One limitation of this study is that this is not a confirmatory study. Ideally, randomized phase III trials are needed to demonstrate the superiority of the most promising preoperative chemotherapy to the de facto standard S-1 plus cisplatin. However, this population is relatively rare, thus a standard treatment would be decided based on the single-arm study or integrated analysis like this study even though the evidence level of these studies is low. The other limitation is a progress of diagnostic devices and skills. Because these trials had not been conducted in the same era, these factors cannot be adjusted for even through multivariable analysis.

In conclusion, preoperative S-1 plus cisplatin combined with D3 gastrectomy was shown to be favorable treatment for gastric cancer with extensive lymph node metastasis and prognosis in patients having both bulky N+ and PAN+ tended to be poor. Therefore, S-1 plus cisplatin is considered the de facto standard treatment for patients with gastric cancer with extensive lymph node metastasis.

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Compliance with ethical standards

Disclosure of potential conflicts of interest Hiroshi Katayama reports grants from Ministry of Health, Labour and Welfare, Japan, during the conduct of the study; personal fees from Johnson & Johnson, outside the submitted work. Akira Tsuburaya reports grants from Ministry of Health, Labour and Welfare, Japan, during the conduct of the study. Junki Mizusawa reports grants from Ministry of Health, Labour and Welfare, Japan, during the conduct of the study. Kenichi Nakamura reports grants from Ministry of Health, Labour and Welfare, Japan, during the conduct of the study; personal fees from Merck, personal fees from Chugai, personal fees from Bayer, outside the submitted work. Hitoshi Katai reports grants from Ministry of Health, Labour and Welfare, Japan, during the conduct of the study; personal fees from Covidien, personal fees from Taiho, outside the submitted work. Hiroshi Imamura reports grants from Ministry of Health, Labour and Welfare, Japan, during the conduct of the study. Atsushi Nashimoto reports grants from Ministry of Health, Labour and Welfare, Japan, during the conduct of the study. Norimasa Fukushima reports grants from Ministry of Health, Labour and Welfare, Japan, during the conduct of the study. Takeshi Sano reports grants from Ministry of Health, Labour and Welfare, Japan, during the conduct of the study; personal fees from Taiho Pharma, personal fees from Chugai Pharma, personal fees from Ono Pharma, personal fees from Eli Lilly, personal fees from MSD, personal fees from Yakult, personal fees from Daiichi-Sankyo, outside the submitted work. Mitsuru Sasako reports grants from Ministry of Health, Labour and Welfare, Japan, during the conduct of the study; personal fees from Lilly, personal fees from Ono, personal fees from Taiho, personal fees from Chugai, personal fees from Yakult, outside the submitted work.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of Helsinki declaration and its later amendments and with Japanese Ethical Guidelines for Epidemiological Research.

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