Int Surg 2016;**101:**583–589
DOI: 10.9738/INTSURG-D-16-00148.1

Treatment of Gastric Cancer With Paraaortic Lymph Node Metastasis

Donghai Wang[1,2], Guojie Shen[1], Chunhui Shou[1], Kankai Zhu[1], Chao Chen[1], Jiren Yu[1]

[1]*Department of Gastrointestinal Surgery, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, China*

[2]*Department of General Surgery, Fenghua People's Hospital, Fenghua, China*

Patients with gastric cancer and paraaortic lymph node (PAN) metastasis suffered poor prognosis. The median survival time of the patients who received palliative chemotherapy was only about 12.8 months. However, the standard treatment strategy for patients with gastric cancer and PAN metastasis was controversial. This study aimed to evaluate the survival benefit of conversion chemotherapy followed by surgery in patients with gastric cancer and radiologically suspicious PAN metastasis compared with palliative chemotherapy alone. Twenty-four patients (19 males and 5 females) between January 1, 2008 and December 31, 2013 were analyzed. Fifteen patients received conversion chemotherapy followed by gastrectomy with D2 lymphadenectomy, and 9 received palliative chemotherapy. The median follow-up was 16.5 months (range: 3–50 months). The estimated median overall survival (OS) of patients who underwent the operation was longer than those who received palliative chemotherapy (44.0 versus 13.0 months; $P = 0.007$). Cox proportion hazard analysis indicated that surgery was a good prognostic factor for prolonged survival compared with that of palliative chemotherapy (hazard ratio: 0.211; 95% confidence interval, 0.061–0.732; $P = 0.014$). Moreover, the 1-year OS rate of surgical patients whose PAN shrank to <1 cm was better than those who received palliative chemotherapy (87.5 versus 55.6%; log-rank $P = 0.008$). In conclusion, patients with gastric cancer and radiologically suspicious PAN metastasis obtained a survival benefit from conversion chemotherapy followed by gastrectomy plus D2 lymphadenectomy.

Key words: Conversion chemotherapy – Gastric cancer – Paraaortic lymph node metastasis – D2 lymphadenectomy

Corresponding author: Jiren Yu, MD, Department of Gastrointestinal Surgery, The First Affiliated Hospital, College of Medicine, Zhejiang University, 79 Qingchun Road, Hangzhou 310009, China.
Tel.: +86–571–87236147; Fax: +86–571–87072577; E-mail: yujr0909@zju.edu.cn

Gastric cancer results in approximately 7 million deaths worldwide annually, and death from this disease is the second most common cancer-related fatality.[1] Lymph node metastasis is one of the most important prognostic factors for patients with gastric cancer. The standard treatment strategy in East Asia for curable gastric cancer is gastrectomy with D2 lymphadenectomy.[2,3] Paraaortic lymph node (PAN, no. 16) is the final gastric lymphatic drainage station (N3), and the incidence of PAN metastasis in advanced gastric cancer, which is distant metastasis, is 18%–40%.[4,5] Although patients with gastric cancer and PAN metastasis have more favorable prognoses than those with involvement of other organs, median overall survival (OS) of patients who have received palliative chemotherapy is only 12.8 months.[6,7] The prognosis of patients with PAN metastasis who undergo gastrectomy with D2 lymphadenectomy plus PAN dissection is also disappointing.[4,8]

The standard treatment strategy for patients with gastric cancer and PAN metastasis has not yet been determined. One study revealed that gastrectomy plus chemotherapy did not provide a survival benefit compared with palliative chemotherapy alone in gastric cancer with a single noncurable factor including PAN metastasis.[9] Conversion chemotherapy, which reduces tumor volume and makes curative resection possible, seems effective for patients with gastric cancer and PAN metastasis.[10–12] It was also reported that patients with PAN metastasis can obtain a survival benefit from neoadjuvant chemotherapy followed by surgery and radiotherapy, and the median survival time was prolonged to 29 months.[13] However, the first-line chemotherapy regimens, surgical indications and suitable surgical procedures remain controversial, particularly the extent of lymph node dissection.

In this study, we retrospectively reviewed patients with gastric cancer and isolated radiologically suspicious PAN metastasis in our hospital to investigate the survival benefit of conversion chemotherapy followed by gastrectomy plus D2 lymphadenectomy.

Methods

Patient selection

Patients diagnosed with gastric cancer and isolated radiologically suspicious PAN metastasis at the Department of Gastrointestinal Surgery, First Affiliated Hospital, College of Medicine, Zhejiang University between January 2008 and December 2013 were included in this study. Gastric cancer diagnosis was based on an endoscopic biopsy. PAN metastasis was defined as follows according to contrast-enhanced computed tomography (CT) scans:[8,14] nodes >1 cm in minimum diameter with fatty marrow. The major inclusion criteria were: newly diagnosed gastric cancer; PAN metastasis diagnosed with CT scan; underwent at least 2 conversion chemotherapy cycles; Eastern Cooperative Oncology Group performance status 0–1; no prior chemotherapy, radiotherapy, or major surgical procedures; adequate bone marrow function, normal renal function, and normal liver function. Patients with other organ metastasis, peritoneal dissemination, or other distant lymph node metastasis were excluded.

Chemotherapy and surgical procedures

The chemotherapy regimens were based on 5-fluorouracil (5-FU) and platinum, with or without taxane, as follows: SOX (S-1/oxaliplatin), mFOLFOX (5-fluorouracil/oxaliplatin/leucovorin), XELOX (capecitabine/oxaliplatin), EOX (epirubicin/oxaliplatin/capecitabine), and SPA (paclitaxel/S-1). All regimens were repeated every 3 weeks after initiation of the first cycle. Clinical responses were assessed after every 2 cycles of chemotherapy via contrast-enhanced CT scans following the Response Evaluation Criteria in Solid Tumors guidelines,[15] and were classified as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). CR, PR, and SD reflected disease control. Chemotherapy toxicity was graded using the Common Terminology Criteria of the National Cancer Institute version 3.0.[16] The surgical complication was classified according to the Clavien–Dindo Classification.

Indications for surgery: after carefully evaluating the CT scan, patients who could undergo gastrectomy for primary focus with D2 dissection were advised to receive the operation, and must make informed consent to the patients or relatives. Surgery was performed approximately 4 weeks after completion of the last course of chemotherapy. Subtotal or total gastrectomy with D2 lymphadenectomy was conducted according to the location and extent of the primary tumor. Surgical complications were recorded. According to the surgical procedures and the chemotherapy response of PAN, the patients were defined as follows: Group A, received palliative chemotherapy; group B, received surgery and PAN diameter after conversion chemo-

Table 1 Clinical characteristics of all eligible patients[a]

	Chemotherapy (N = 9)	Surgery (N = 15)	*P* value
Age[b]	62 (51–76)	62 (46–76)	0.591[c]
Gender			0.057[d]
Male	9	10	
Female	0	5	
Tumor location			0.495[d]
Upper one-third of stomach (U)	1	5	
Middle one-third of stomach (M)	2	2	
Lower one-third of stomach (L)	6	7	
Whole stomach (Multi)	0	1	
Chemotherapy Regimens			0.828[d]
SOX	3	5	
mFOLFOX	4	6	
XELOX	2	2	
EOX	0	1	
SPA	0	1	
Chemotherapy response			0.162[d]
Partial response (PR)	5	11	
Stable disease (SD)	2	4	
Progressive disease (PD)	2	0	
ECOG performance status			
0	9	15	

[a]Chemotherapy: patients received palliative chemotherapy; Surgery: patients received conversion chemotherapy followed by gastrectomy plus D2 lymphadenectomy.

[b]Values are median (range).

[c]Mann–Whitney *U* test.

[d]Chi square test.

EOX, epirubicin/oxaliplatin/capecitabine; mFOLFOX, 5-fluorouracil/oxaliplatin/leucovorin; SOX, S-1/oxaliplatin; SPA, paclitaxel/ S-1; XELOX, capecitabine/oxaliplatin.

therapy was <1 cm; group C, received surgery and PAN diameter after conversion chemotherapy was >1 cm.

Statistical analysis

Categorical variables were analyzed using the chi-square test. Median values were used to describe continuous data, which were analyzed by the Mann–Whitney *U* test or the Kruskal–Wallis test. OS was defined as the time from the start of treatment to the date of death suffered from tumor recurrence or progression. Patients who were alive on October 31, 2014 or who had died without tumor recurrence were censored from the OS analysis. OS was estimated by the Kaplan–Meier analysis, and values were compared using the log-rank test. Cox proportional model hazards regression was used for multivariate analysis, and hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. Statistical analysis was performed using SPSS version 19.0 for Windows (IBM, Armonk, New York, USA), and a two-tailed *P* value <0.05 was considered significant.

Results

Baseline characteristics, surgical findings, and pathology

A total of 24 patients (19 males and 5 females) were enrolled in this study. The median age was 62 years (range: 46–76 years). Fifteen patients received gastrectomy and D2 lymphadenectomy, and nine received palliative chemotherapy. No intergroup differences in median age, sex, tumor location, chemotherapy regimen, or chemotherapy response were detected (Table 1).

Of the 9 patients who received palliative chemotherapy, 7 patients who had a detectable response (PR = 5, SD = 2) refused to surgery, and 2 had PD during the first 2 chemotherapy cycles. The primary chemotherapy regimens included SOX (n = 3), mFOLFOX (n = 4), and XELOX (n = 2). The median total number of chemotherapy cycles was 4 (range: 3–8).

Of the 15 patients who underwent surgery, the median number of cycles of conversion chemotherapy was 4 (range: 2–6). Eleven patients had PR, and 4 had SD. The chemotherapy regimens included SOX (n = 5), mFOLFOX (n = 6), XELOX (n = 2), EOX (n = 1), and SPA (n = 1). Six patients underwent subtotal gastrectomy, and 9 underwent total gastrectomy. None of the patients underwent combined resection of other organs. The median duration of surgery was 224 minutes (range: 142–293 minutes). Three patients (3/15) developed postoperative complications (1 for grade 1, 2 for grade 2), and 2 refused postoperative chemotherapy. The remaining 13 patients received a median of 3 cycles (range: 2–7 cycles) of postoperative chemotherapy. According to pathologic examination, only 1 patient had a complete pathologic response, 10 were exposed to the serosa, and 7 were staged pathologically as pN3.

According to the response evaluation before surgery, PAN diameter decreased to <1 cm in 8 patients. Compared with other patients whose PAN remained >1 cm (n = 7), these patients more often received mFOLFOX chemotherapy and had a better chemotherapy response (Table 2). However, no intergroup differences in median age, sex, tumor location, surgical procedure, duration of surgery, tumor depth, or lymph node metastasis were observed (Table 2).

Table 2 Surgical and pathologic findings in operated patients[a]

	Group B (N = 8)	Group C (N = 7)	*P* value
Age[b]	63.5 (50–76)	60 (46–66)	0.094[a]
Gender			0.714[b]
Male	5	5	
Female	3	2	
Tumor location			0.179[b]
Upper one-third of stomach (U)	4	1	
Middle one-third of stomach (M)	0	2	
Lower one-third of stomach (L)	3	4	
Whole stomach (Multi)	1	0	
Chemotherapy regimens			0.047[b]
SOX	0	5	
mFOLFOX	4	2	
XELOX	2	0	
EOX	1	0	
SPA	1	0	
Chemotherapy response			0.013[b]
Partial response (PR)	8	3	
Stable disease (SD)	0	4	
Progressive disease (PD)	0	0	
Surgical procedures			0.833[b]
Subtotal gastrectomy	3	3	
Total gastrectomy	5	4	
Duration of surgery (min)*	232 (199–289)	198 (142–260)	0.535[a]
Tumor depth			0.517[b]
pT0	0	1	
pT1	1	0	
pT2	2	1	
pT3	0	0	
pT4	5	5	
Lymph node metastases			0.994[b]
pN0	2	2	
pN1	1	1	
pN2	1	1	
pN3	4	3	

[a]Group B: patients received surgery and the diameter of PAN after conversion chemotherapy was <1 cm; Group C: patients received surgery and the diameter of PAN after conversion chemotherapy was still >1 cm.

[b]Values are median (range).

[c]Mann–Whitney *U* test.

[d]Chi square test.

EOX, epirubicin/oxaliplatin/capecitabine; mFOLFOX, 5-fluorouracil/oxaliplatin/leucovorin; SOX, S-1/oxaliplatin; SPA, paclitaxel/ S-1; XELOX, capecitabine/oxaliplatin.

Toxicity of chemotherapy

The most common grade 1 or grade 2 toxicity during chemotherapy among all 24 patients included digestive symptoms (54.1%), leukocytopenia (41.6%), thrombocytopenia (16.7%), and hepatic dysfunction (4.2%). However, only two patients had grade 3 leukocytopenia, one patient had grade 3 nausea, and one patient had grade 3 thrombocytopenia. No patients had grade 4 toxicities.

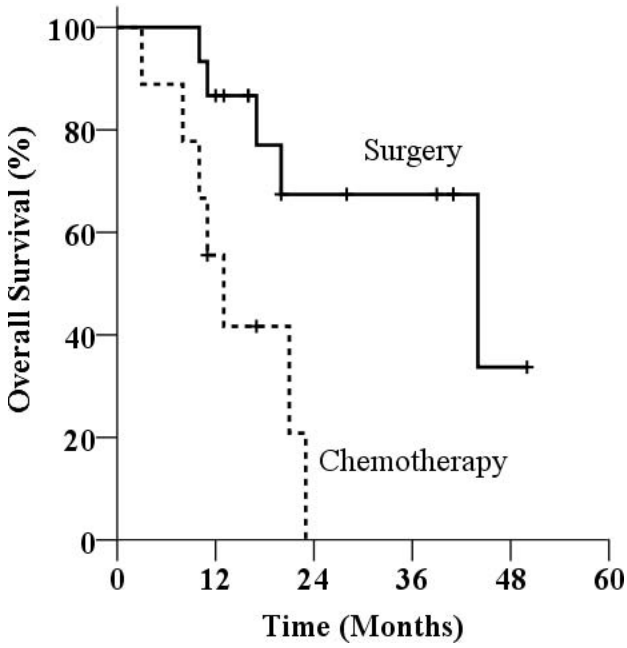

Fig. 1 Comparison of overall survival for patients with different therapeutic procedures ($P = 0.007$, log-rank test). Chemotherapy (N = 9): patients received palliative chemotherapy; surgery (N = 15): patients received conversion chemotherapy followed by gastrectomy plus D2 lymphadenectomy.

Survival analysis

No patient was lost to follow-up. The median follow-up time was 16.5 months (range: 3–50 months). At the end of the study, 8 patients who underwent surgery were alive without disease progression, 2 were alive with disease progression, and 5 patients had died from disease progression. Of the patients who received palliative chemotherapy, 2 were alive with stable disease, and 7 had died from disease progression. The estimated median overall survival of patients who received surgery was longer than those who received palliative chemotherapy alone (44.0 versus 13.0 months; $P = 0.007$; Fig. 1). Cox proportion hazard analysis revealed that surgery was a good prognostic factor for prolonged survival compared with that of palliative chemotherapy (HR: 0.211; 95% CI: 0.061–0.732; $P = 0.014$).

The 1-year OS rate of surgical patients whose PAN shrank to <1 cm was better than those who received palliative chemotherapy (87.5 versus 55.6%; log-rank $P = 0.008$). However, no survival

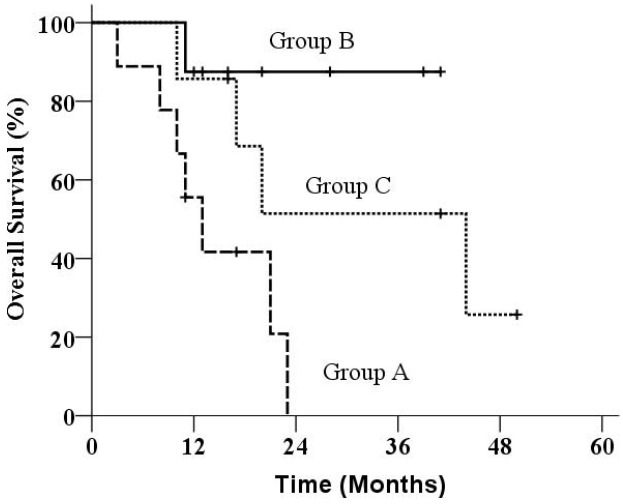

Fig. 2 Comparison of overall survival for patients with different therapeutic effect ($P = 0.019$, log-rank test). Group A (N = 9), received palliative chemotherapy; group B (N = 8), received surgery and PAN diameter after conversion chemotherapy was <1 cm; group C (N = 7), received surgery and PAN diameter after conversion chemotherapy was >1 cm.

benefit was detected compared with surgical patients whose PAN remained >1 cm (1-year OS 87.5 versus 85.7%; log-rank $P = 0.292$; Fig. 2). Meanwhile, the 1-year OS between surgical patients whose PAN remained >1 cm and those received palliative chemotherapy was not difference (1-year OS 85.7 versus 55.6%; log-rank $P = 0.083$).

Discussion

Gastric cancer with PAN metastasis is considered incurable by surgery and has a poor prognosis. The treatment strategy for these patients remains inconsistent, probably due to the small number of patients reported. In the present study, we analyzed 24 patients with gastric cancer and isolated radiologically suspicious PAN metastasis during the past 5 years, and investigated the survival benefit of conversion chemotherapy followed by gastrectomy plus D2 lymphadenectomy. OS for patients who received conversion chemotherapy and surgery was better than that of patients who received palliative chemotherapy alone (median 44.0 versus 13.0 months; $P = 0.007$). Surgery was the only significant independent prognostic factor detected in multivariate analysis (HR: 0.211; $P = 0.014$).

Because of the poor prognosis of patients with gastric cancer and PAN metastasis after palliative chemotherapy, some surgeons have attempted to find more suitable treatment strategies to improve OS. Multimodal therapy is one of the hottest topics in tumor therapy today, and some studies have proposed a survival benefit of conversion chemotherapy followed by surgery. According to existing reports, the conversion chemotherapy regimens for patients with gastric cancer and PAN metastasis are mostly fluorouracil-based regimens. The most widely used conversion chemotherapy regimens include S-1 plus cisplatin,[17] DCS (docetaxel, cisplatin, and S-1),[18] and XELOX (Xeloda and oxaliplatin).[7] The high clinical response rate (range: 65%–85%) of conversion chemotherapy makes conversion gastrectomy for these patients possible. In the present study, the clinical response rate was 66.7% (PR), which is consistent with other studies.[7,17,18] Furthermore, the most effective chemotherapy was mFOLFOX (5-fluorouracil/oxaliplatin/leucovorin), of which 80% (8/10) of the patients achieved PR. These results indicate that mFOLFOX may be a feasible and effective conversion chemotherapy regimen for patients with gastric cancer and isolated radiologically suspicious PAN metastasis.

Gastrectomy with lymphadenectomy is the mainstay treatment for gastric cancer. The standard procedure for curable gastric cancer has been gastrectomy with D2 lymphadenectomy, and prophylactic PAN dissection is not recommended.[19] However, the degree of lymph node dissection for patients with gastric cancer and PAN metastasis remains unknown. Some investigators have suggested that patients with gastric cancer and PAN metastasis might benefit from radical surgery with PAN dissection, and the favorable prognostic factors include total positive lymph nodes (< 11%), positive PAN (< 4%), and p53 expression (≤ 50%).[20] One multi-institutional phase II trial also showed that conversion chemotherapy followed by radical surgery with PAN dissection achieved a high 5-year survival rate (53%).[17] However, 1 phase II trial in China showed that patients with gastric cancer and PAN involvement whose PAN shrank to <1 cm after conversion chemotherapy (XELOX) benefitted from conversion chemotherapy and subsequent radical surgery with D2 lymphadenectomy.[7] In this study, conversion chemotherapy followed by surgery with D2 lymphadenectomy was a good prognostic factor (HR: 0.211; 95% CI: 0.061–0.732; $P = 0.014$), which is consistent with the aforementioned study.[7] Furthermore, the 1-year OS rate of surgical patients whose PAN shrank to <1 cm was 87.5%. Therefore, we speculate that PAN dissection in patients with gastric cancer and PAN involvement after effective

chemotherapy may not be necessary. The indications for PAN dissection in patients with gastric cancer and radiologically suspicious PAN involvement need further investigation.

In conclusion, patients with gastric cancer and isolated radiologically suspicious PAN metastasis obtained a survival benefit from conversion chemotherapy followed by gastrectomy with D2 lymphadenectomy. mFOLFOX was determined to be a feasible and effective conversion chemotherapy regimen for these patients. However, the limitations of this study include its retrospective design, small sample size, and false-positive rate of CT scans for PAN involvement. A multicenter randomized controlled trial with a larger sample is needed to verify our findings.

Acknowledgments

Authors Donghai Wang, Guojie Shen, Chunhui Shou, Kankai Zhu, Chao Chen, and Jiren Yu declare that they have no conflict of interest. This work was supported in part by the science and technology project of Zhejiang Province (No. 2014ZZ005).

References

1. Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. *J Clin Oncol* 2006;**24**(14): 2137–2150
2. Wu CW, Hsiung CA, Lo SS, Hsieh MC, Chen JH, Li AF *et al*. Nodal dissection for patients with gastric cancer: a randomised controlled trial. *Lancet Oncol* 2006;**7**(4):309–315
3. Wang L, Liang H, Wang X, Li F, Ding X, Deng J. Risk factors for metastasis to para-aortic lymph nodes in gastric cancer: a single institution study in China. *J Surg Res* 2013;**179**(1): 54–59
4. Isozaki H, Okajima K, Fujii K, Nomura E, Izumi N, Mabuchi H *et al*. Effectiveness of paraaortic lymph node dissection for advanced gastric cancer. *Hepatogastroenterology* 1999;**46**(25):549–554
5. Takashima S, Kosaka T. Results and controversial issues regarding a para-aortic lymph node dissection for advanced gastric cancer. *Surg Today* 2005;**35**(6):425–431
6. Park IH, Kim SY, Kim YW, Ryu KW, Lee JH, Lee JS *et al*. Clinical characteristics and treatment outcomes of gastric cancer patients with isolated para-aortic lymph node involvement. *Cancer Chemother Pharmacol* 2011;**67**(1):127–136
7. Wang Y, Yu YY, Li W, Feng Y, Hou J, Ji Y *et al*. A phase II trial of Xeloda and oxaliplatin (XELOX) neo-adjuvant chemotherapy followed by surgery for advanced gastric cancer patients with para-aortic lymph node metastasis. *Cancer Chemother Pharmacol* 2014;**73**(6):1155–1161
8. Lee JH, Paik YH, Lee JS, Song HJ, Ryu KW, Kim CG *et al*. Candidates for curative resection in advanced gastric cancer patients who had equivocal para-aortic lymph node metastasis on computed tomographic scan. *Ann Surg Oncol* 2006;**13**(9):1163–1167
9. Fujitani K, Yang HK, Mizusawa J, Kim YW, Terashima M, Han SU *et al*. Gastrectomy plus chemotherapy versus chemotherapy alone for advanced gastric cancer with a single non-curable factor (REGATTA): a phase 3, randomised controlled trial. *Lancet Oncol* 2016;**17**(3):309–318
10. Tsutsuyama M, Ito S, Ito Y, Misawa K, Kawakami J, Natsume S *et al*. A case of gastric cancer with residual tumor only in the para-aortic lymph nodes after systemic chemotherapy followed by conversion surgery. *Case Rep Oncol* 2015;**8**(2):312–322
11. Kinoshita J, Fushida S, Tsukada T, Oyama K, Okamoto K, Makino I *et al*. Efficacy of conversion gastrectomy following docetaxel, cisplatin, and S-1 therapy in potentially resectable stage IV gastric cancer. *Eur J Surg Oncol* 2015;**41**(10): 1354–1360
12. Fujiwara Y, Omori T, Demura K, Miyata H, Sugimura K, Ohue M *et al*. A multidisciplinary approach for advanced gastric cancer with paraaortic lymph node metastasis. *Anticancer Res* 2015;**35**(12):6739–6745
13. He Q, Ma L, Li Y, Li G. A pilot study of an individualized comprehensive treatment for advanced gastric cancer with para-aortic lymph node metastasis. *BMC Gastroenterol* 2016;**16**:8
14. Habermann CR, Weiss F, Riecken R, Honarpisheh H, Bohnacker S, Staedtler C *et al*. Preoperative staging of gastric adenocarcinoma: comparison of helical CT and endoscopic US. *Radiology* 2004;**230**(2):465–471
15. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R *et al*. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;**45**(2):228–247
16. Trotti A, Colevas AD, Setser A, Rusch V, Jaques D, Budach V *et al*. CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment. *Semin Radiat Oncol* 2003, 13(3):176–181
17. Tsuburaya A, Mizusawa J, Tanaka Y, Fukushima N, Nashimoto A, Sasako M *et al*. Neoadjuvant chemotherapy with S-1 and cisplatin followed by D2 gastrectomy with para-aortic lymph node dissection for gastric cancer with extensive lymph node metastasis. *Brit J Surg* 2014;**101**(6): 653–660
18. Oyama K, Fushida S, Kinoshita J, Makino I, Nakamura K, Hayashi H *et al*. Efficacy of pre-operative chemotherapy

with docetaxel, cisplatin, and S-1 (DCS therapy) and curative resection for gastric cancer with pathologically positive para-aortic lymph nodes. *J Surg Oncol* 2012;**105**(6): 535–541

19. Sasako M, Sano T, Yamamoto S, Kurokawa Y, Nashimoto A, Kurita A *et al*. D2 lymphadenectomy alone or with para-aortic nodal dissection for gastric cancer. *New Engl J Med* 2008;**359**(5):453–462
20. Kunisaki C, Shimada H, Yamaoka H, Takahashi M, Ookubo K, Akiyama H *et al*. Indications for para-aortic lymph node dissection in gastric cancer patients with paraaortic lymph node involvement. *Hepatogastroenterology* 2000;**47**(32):586–589