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Original Article

Potential benefit of adjuvant chemotherapy in T2N0 gastric cancer after radical resection without residual disease (R0)

Donghui Liu[1], Xuyao Wang[2], Xiaowei Hu[3], Jincai Wang[3], Long Li[4], Qingqin Jiang[5], Jin Wu[3]

[1]Department of Medical Oncology, The Second Hospital of Harbin, Harbin, Heilongjiang Province, China; [2]Department of Pharmacology, College of Pharmacy Harbin Medical University, Harbin, Heilongjiang Province, China; [3]Department of Medical Oncology, Harbin Medical University Cancer Hospital, Harbin, Heilongjiang Province, China; [4]Department of General Surgery, The First Affiliated Hospital of Harbin Medical University, Harbin, Heilongjiang Province, China; [5]Department of General Surgery, 242 Hospital of Harbin, Harbin, Heilongjiang Province, China

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Abstract: It is currently unclear whether chemotherapy could improve the prognosis of patients with T2N0 gastric cancer after radical resection without residual disease (R0). This study aimed to examine the impact of postoperative chemotherapy and other factors on the prognosis of patients with T2N0 gastric cancer after R0 resection. This is a retrospective study conducted in patients with T2N0 gastric cancer after R0 radical resection performed at the Tumor Hospital Affiliated to Harbin Medical University between January 2003 and January 2010. The patients had no evidence of distant metastases and were grouped according to chemotherapy. Among the 122 T2N0 patients, there were 88 males and 34 females, with a median age of 57 (range, 31-82) years. Forty-nine patients received postoperative chemotherapy, while 73 did not. The median follow-up was (75 months), and the median survival was 94.0 months. Univariate analyses showed that chemotherapy was associated with survival of patients with gastric cancer after R0 resection ($P<0.05$). Multivariate analysis showed that age and chemotherapy were independently associated with the prognosis of these patients (both $P<0.05$) after adjustment for gender, weight loss, tumor size, hemoglobin, thrombocytopenia, and albumin. This study suggests that T2N0M0 patients with gastric cancer in China could benefit from postoperative chemotherapy, but prospective studies are needed to confirmation.

Keywords: Gastric cancer, R0 resection, T2N0, overall survival, postoperative chemotherapy

Introduction

Gastric cancer arises from the gastric mucosa. The highest incidence of gastric cancer has been reported in men, older adults (60-84 years), and in eastern Asia, eastern Europe, and South America [1]. Indeed, studies have shown that 52% of patients with gastric cancer are in Asia, and 41% are in China [2]. The incidence of gastric cancer is 8.7 per 100,000 white men, compared with 17.2 per 100,000 Asian/Islander men [3]. Surgery is considered as the primary method for treatment of gastric cancer and to be the only strategy with curative possibilities. Despite the best surgical approaches, the overall prognosis has not improved significantly in recent years [4, 5].

According to the NCCN guidelines, surveillance should be considered for patients with T1 disease and chemotherapy is indicated for patients with T3-T4 or N+ disease [6], while chemotherapy could be considered for T2N0 disease. A study showed that the value of chemotherapy in patients with T2N0 gastric cancer is poorly known and there is no consensus [7]. Indeed, the NCCN guidelines recommend that T2N0M0 patients who do not receive preoperative treatment and are subjected to disease-free (R0) resection can undergo surveillance,

Table 1. Clinical characteristics of the patients with gastric cancer according to postoperative chemotherapy

	All (N=122)	Chemotherapy (N=49)	No chemotherapy (N=73)	P
Gender				0.580
Male	88 (72.1%)	34 (69.4%)	54 (84.0%)	
Female	34 (27.9%)	15 (30.6%)	19 (26.0%)	
Age				0.251
≥60	55 (45.1%)	19 (38.8%)	36 (49.3%)	
<60	67 (54.9%)	30 (61.2%)	37 (50.7%)	
Weight loss (%)				0.088
≥5	46 (37.7%)	14 (28.6%)	32 (43.8%)	
<5	76 (62.3%)	35 (71.4%)	41 (56.2%)	
Tumor location				0.363
Upper 1/3	13 (10.7%)	6 (12.2%)	7 (9.6%)	
Medium 1/3	22 (18.0%)	12 (24.5%)	10 (13.7%)	
Lower 1/3	73 (59.8%)	25 (51.1%)	48 (65.7%)	
Two or three thirds	14 (11.5%)	6 (12.2%)	8 (11.0%)	
Degree of differentiation				0.851
Low	56 (45.9%)	23 (46.9%)	33 (45.2%)	
High-medium	66 (54.1%)	26 (53.1%)	40 (54.8%)	
Tumor size				0.851
≤3 cm	56 (45.9%)	23 (46.9%)	33 (45.2%)	
>3 cm	66 (54.1%)	26 (53.1%)	40 (54.8%)	
Histological type				0.994
Adenocarcinoma	107 (87.7%)	43 (87.7%)	64 (87.7%)	
Signet-ring cell carcinoma	4 (3.3%)	2 (4.1%)	2 (2.7%)	
Others	11 (9.0%)	4(8.2%)	7 (9.6%)	
Surgical approach				0.643
Total gastrectomy	4 (3.3%)	2 (4.1%)	2 (2.7%)	
Billroth I gastrectomy	11 (9.0%)	3 (6.1%)	8 (11.0%)	
Billroth II gastrectomy	89 (72.9%)	35 (71.4%)	54 (74.0%)	
Proximal gastrectomy	18 (14.8%)	9 (18.4%)	9 (12.3%)	
Hemoglobin				0.191
Male ≥120 g/L or female ≥110 g/L	92 (75.4%)	40 (81.6%)	52 (71.2%)	
Male <120 g/L or female <110 g/L	30 (24.6%)	9 (18.4%)	21 (28.8%)	
Platelet				0.106
≥300 $\times 10^9$/L	32 (26.3%)	9 (18.4%)	23 (31.5%)	
<300 $\times 10^9$/L	90 (73.7%)	40 (81.6%)	50 (68.5%)	
Albumin				0.552
≥35 g/L	104 (85.2%)	43 (87.8%)	61 (83.6%)	
<35 g/L	18 (14.8%)	6 (12.2%)	12 (16.4%)	

according to the patient's conditions, and may receive chemotherapy using 5-FU or capecitabine in combination with leucovorin [6]. On the other hand, Japanese guidelines do not recommend chemotherapy for these patients [8]. A recent American study showed that patients with T2N0 gastric cancer that underwent suboptimal lymph node dissection benefited from chemotherapy [9].

There is no consensus on adjuvant therapy for patients with T2N0 gastric cancer [7, 9]. A retrospective study suggested a possible benefit of adjuvant therapy in these patients [9]. Fur-

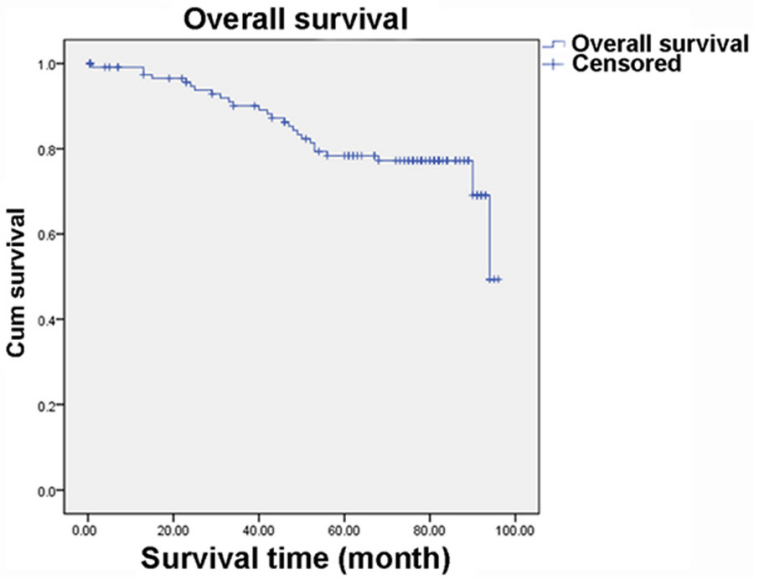

Figure 1. Survival of patients with T2N0M0 gastric cancer. The 1-, 3-, and 5-year survival rates were 99.2%, 91.0%, and 81.1%, respectively. The median survival was 94.0 months.

thermore, no study is available regarding Chinese patients with T2N0 gastric cancer. Therefore, the aim of this study was to examine the impact of postoperative chemotherapy and other factors on the prognosis of patients with T2N0 gastric cancer after R0 resection.

Patients and methods

Subjects

This is a retrospective study that was carried out in patients with T2N0 gastric cancer treated with R0 radical resection at The Tumor Hospital Affiliated to Harbin Medical University between January 2003 and January 2010. Inclusion criteria were: 1) diagnosed with gastric cancer by postoperative pathological examination; 2) no evidence of distant metastases; 3) R0 resection; 4) patients did not receive preoperative treatments; 5) pre-chemotherapy KPS scores were ≥60; and 6) no other malignant tumor or severe disease. The study was approved by The Ethic Committee of The Tumor Hospital Affiliated to Harbin Medical University. The need for informed consent was waived by the committee because of the retrospective nature of the study.

Data collection

Clinical and pathological data were collected from the preoperative laboratory examination and postoperative pathological reports. All laboratory examination results were from preoperative examinations. The data included gender (male vs. female), age (≥60 years old vs. <60 years old), weight loss (≥5% vs. <5%), tumor location (upper third, middle third, lower third, two thirds, and three thirds), tumor size (≤5 cm, 5-10 cm, ≥10 cm), tumor differentiation (low vs. medium-high), histological type (adenocarcinoma, signet ring cell carcinoma, and others), operation type (total gastrectomy, Billroth I, Billroth II, and proximal gastrectomy), and postoperative chemotherapy (yes vs. no). All cancer parameters were staged according to TNM staging (7th edition) by the American Joint Committee on Cancer (AJCC) [10]: hemoglobin (male ≥120 g/L or female ≥110 g/L), platelets (≥300 ×10^9/L, <300 ×10^9/L), and albumin (≥35 g/L, <35 g/L) [11]. The number of dissected lymph nodes was >15. The decision to undergo chemotherapy was taken after discussion between the treating oncologist and the patient.

Follow-up and outcomes

The patients were followed up every 3 months for two years, and then once a year until death or end of follow-up. Follow-up was performed by telephone, text message, and outpatient visit. The primary outcome was overall survival.

Statistical analysis

Normally distributed continuous variables are presented as mean ± SD and analyzed using the Student t test or ANOVA with the Tukey's post hoc test, as appropriate. Non-normally distributed continuous variables (age, weight, and tumor size) were presented as median (range or IQR and were analyzed with the Mann-Whitney U test or the Kruskal-Wallis test, as appropriate. Categorical variables were presented as proportions and analyzed using the Chi-square test or Fisher's exact test, as appropriate. Survival analyses were performed using the Kaplan-Meier method and the Log rank test.

Table 2. Multivariate analysis of the factors affecting survival

	Odds ratio	P	95% confidence interval
Age (≥60 vs. <60 years)	2.839	0.015	1.222-6.595
Gender (male vs. female)	1.101	0.839	0.435-2.789
Weight loss (≥5% vs. <5%)	0.920	0.845	0.398-2.124
Tumor size (≤3 cm vs. >3 cm)	0.617	0.304	0.246-1.548
Chemotherapy or not	0.228	0.004	0.122-0.678
Hemoglobin (male ≥120 g/L or female ≥110 g/L vs. male <120 g/L or female <110 g/L	0.890	0.823	0.322-2.459
Platelets (≥300 $\times 10^9$/L vs. <300 $\times 10^9$/L)	1.594	0.392	0.549-4.631
Albumin (≥35 g/L vs. <35 g/L)	6.229	0.082	0.794-49.955

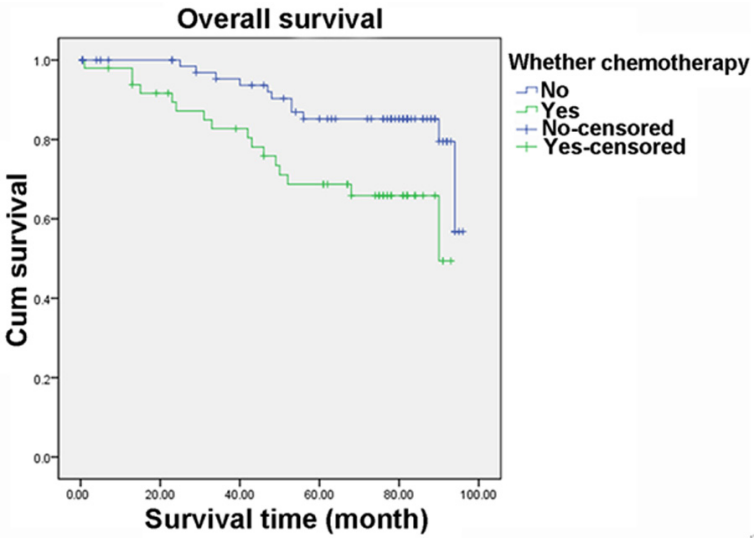

Figure 2. Survival of patients with T2N0M0 gastric cancer treated or not with chemotherapy. The mean survival time of patients without chemotherapy was 87.4 months compared with 72.6 months in the chemotherapy group (P<0.05).

Multivariate Cox regression model (enter method) was used to screen for independent factors affecting the prognosis of gastric cancer. SPSS 22.0 (IBM, Armonk, NY, USA) was used to perform statistical analysis. Two-sided *P*-values <0.05 were considered statistically different.

Results

Characteristics of patients

A total of 122 patients were included in the study. There were 88 males and 34 females, for a male-to-female proportion of 2.59:1. The median age was 57 (range, 31-82) years. D0, D1, and D2 resection rates were 4.9%, 28.7%, and 66.4%, respectively. Forty-nine patients received postoperative chemotherapy, while 73 cases did not. Chemotherapy regimens included: platinum + capecitabine (n=12), platinum + 5-FU (n=36), and others (n=1). There was no difference in survival between the patients who received XELOX and those who received FOLFOX (P=0.102). There was no significant difference between the two groups (chemotherapy vs. none) (**Table 1**).

Follow-up

The median follow-up was 75 (range, 3-96) months. The Kaplan-Meier analysis of the whole cohort showed that the one-, three-, and five-year survival rates were 99.2%, 91.0%, and 81.1%, respectively, and that the median survival was 94 months (**Figure 1**). The median follow-up of the chemotherapy group was 67 months, compared with 78 months in the no-chemotherapy group (P=0.038).

Multivariate analysis

Multivariate analysis suggested that age (OR=2.84, 95% CI: 1.22-6.60, P=0.02) and chemotherapy (OR=0.23, 95% CI: 0.12-0.68, P=0.004) were independently associated survival in these patients (**Table 2** and **Figure 2**).

Discussion

It is currently unclear whether chemotherapy could improve the prognosis of patients with T2N0 gastric cancer after R0 [6-8]. Therefore,

this study aimed to examine the impact of postoperative chemotherapy and other factors on the prognosis of patients with T2N0 gastric cancer after R0 resection. The results suggest that age and chemotherapy are independently associated with the prognosis of these patients after adjustment for gender, weight loss, tumor size, hemoglobin, thrombocytopenia, and albumin, suggesting that T2N0M0 patients with gastric cancer in China could benefit from postoperative chemotherapy.

In the present study, older age was independently associated with poorer survival in patients with T2N0M0 gastric cancer. This result is supported by previous studies. Indeed, a previous study showed that age is inversely associated with the prognosis of patients with metastatic gastric cancer [12]. Nevertheless, the influence of age on the prognosis of gastric cancer is controversial [13, 14] and that the apparent effect of age on prognosis could be in fact due to the higher prevalence of the diffuse subtype more often seen in younger patients [15, 16]. A large Japanese study showed that age was independently associated with the prognosis of gastric cancer [17]. Another study showed that age was independently associated with prognosis of gastric cancer, irrespective of tumor size [18]. In the present study, age was not associated with histological subtype (data not shown), but the sample size was small and some subtypes were under-represented. In addition, although women are at lower risk of gastric cancer than men, the age at menopause could be associated with the prognosis of gastric cancer and prevalence of the diffuse subtype [19].

Beside age, the present study suggests that adjuvant chemotherapy is an independent prognosis factor for gastric cancer. Generally speaking, patients with gastric cancer do not respond well to adjuvant chemotherapy [20-25]. In the INT-0116 trial, the benefit of adjuvant chemotherapy was uncertain because of the small number of patients with T2N0 tumors [26-28]. The recent ACTS GC trial from Japan showed that compared with surgery alone, postoperative chemotherapy showed better survival in patients with stage II (excluding T1 tumors) or stage III gastric cancer who underwent R0 resection [29, 30]. In the CLASSIC trial (from South Korea, China, and Taiwan), patients with stage II-IIIB gastric cancer that underwent complete resection with D2 lymph node dissection (at least 15 lymph nodes) showed better survival with chemotherapy compared with surgery alone [31]. A recent study suggested that chemotherapy could be beneficial only to a subset of patients with T2N0 gastric tumors [32]. Additional studies are necessary to identify patients that could benefit the most from adjuvant chemotherapy. In addition, other studies have highlighted the need for optimal lymph node dissection because the perceived benefit of chemotherapy on survival in patients with T2N0 gastric cancer could be due to overlooked invaded lymph nodes [9].

The present study is not without limitations. Because of the retrospective nature of the study, some data (like specific biochemical data, follow-up data, leukocytopenia, household income, and non-traditional risk factors) could not be analyzed because they were not recorded in the medical charts. In addition, the sample size was small, which could lead to a possible overfitting bias in the multivariate analysis. Finally, follow-up was short, affecting the survival analysis. Larger prospective studies are necessary to draw stronger conclusions about the role of chemotherapy in patients with T2N0M0 gastric cancer.

In conclusion, this study suggests that T2N0M0 patients with gastric cancer in China could benefit from postoperative chemotherapy, but prospective studies are needed to confirmation.

Disclosure of conflict of interest

None.

Address correspondence to: Jin Wu, Department of Medical Oncology, Harbin Medical University Cancer Hospital, Harbin 150040, Heilongjiang Province, China. Tel: +86-18846146540; +86-0451-82698729; Fax: +86-21-64085875; E-mail: ldhknight@163.com

References

[1] Thrumurthy SG, Chaudry MA, Hochhauser D and Mughal M. The diagnosis and management of gastric cancer. BMJ 2013; 347: f6367.

[2] Sasako M, Inoue M, Lin JT, Khor C, Yang HK and Ohtsu A. Gastric Cancer Working Group report. Jpn J Clin Oncol 2010; 40 Suppl 1: i28-37.

[3] Kohler BA, Ward E, McCarthy BJ, Schymura MJ, Ries LA, Eheman C, Jemal A, Anderson RN, Ajani UA, Edwards BK. Annual report to the nation on the status of cancer, 1975-2007, featuring tumors of the brain and other nervous system. J Natl Cancer Inst 2011; 103: 714-36.

[4] Marrelli D, Morgagni P, de Manzoni G, Coniglio A, Marchet A, Saragoni L, Tiberio G, Roviello F. Prognostic value of the 7th AJCC/UICC TNM classification of noncardia gastric cancer: analysis of a large series from specialized Western centers. Ann Surg 2012; 255: 486-91.

[5] Crane SJ, Locke GR 3rd, Harmsen WS, Zinsmeister AR, Romero Y and Talley NJ. Survival trends in patients with gastric and esophageal adenocarcinomas: a population-based study. Mayo Clin Proc 2008; 83: 1087-94.

[6] NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Gastric Cancer. Version 2.2016. National Comprehensive Cancer Netword, Fort Washington, 2016.

[7] Brar SS, Mahar AL, Helyer LK, Swallow C, Law C, Paszat L, Seevaratnam R, Cardoso R, McLeod R, Dixon M, Yohanathan L, Lourenco LG, Bocicariu A, Bekaii-Saab T, Chau I, Church N, Coit D, Crane CH, Earle C, Mansfield P, Marcon N, Miner T, Noh SH, Porter G, Posner MC, Prachand V, Sano T, van de Velde C, Wong S, Coburn NG. Processes of care in the multidisciplinary treatment of gastric cancer: results of a RAND/UCLA expert panel. JAMA Surg 2014; 149: 18-25.

[8] Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2010 (ver.3). Gastric Cancer 2011; 14: 113-23.

[9] In H, Kantor O, Sharpe SM, Baker MS, Talamonti MS and Posner MC. Adjuvant therapy improves survival for T2N0 gastric cancer patients with sub-optimal lymphadenectomy. Ann Surg Oncol 2016; 23: 1956-62.

[10] AJCC Cancer Staging Manua, 7th edition. Springer, New York, 2011.

[11] Blot WJ, Devesa SS, Kneller RW and Fraumeni JF Jr. Rising incidence of adenocarcinoma of the esophagus and gastric cardia. JAMA 1991; 265: 1287-9.

[12] Yang D, Hendifar A, Lenz C, Togawa K, Lenz F, Lurje G, Pohl A, Winder T, Ning Y, Groshen S, Lenz HJ. Survival of metastatic gastric cancer: significance of age, sex and race/ethnicity. J Gastrointest Oncol 2011; 2: 77-84.

[13] Holburt E and Freedman SI. Gastric carcinoma in patients younger than age 36 years. Cancer 1987; 60: 1395-9.

[14] Wang JY, Hsieh JS, Huang CJ, Huang YS and Huang TJ. Clinicopathologic study of advanced gastric cancer without serosal invasion in young and old patients. J Surg Oncol 1996; 63: 36-40.

[15] Lee JH, Ryu KW, Lee JS, Lee JR, Kim CG, Choi IJ, Park SR, Kook MC, Kim YW, Bae JM. Decisions for extent of gastric surgery in gastric cancer patients: younger patients require more attention than the elderly. J Surg Oncol 2007; 95: 485-90.

[16] Tso PL, Bringaze WL 3rd, Dauterive AH, Correa P and Cohn I. Gastric carcinoma in the young. Cancer 1987; 59: 1362-1365.

[17] Saito H, Osaki T, Murakami D, Sakamoto T, Kanaji S, Tatebe S, Tsujitani S, Ikeguchi M. Effect of age on prognosis in patients with gastric cancer. ANZ J Surg 2006; 76: 458-61.

[18] Im WJ, Kim MG, Ha TK and Kwon SJ. Tumor size as a prognostic factor in gastric cancer patient. J Gastric Cancer 2012; 12: 164-72.

[19] Dicken BJ, Bigam DL, Cass C, Mackey JR, Joy AA and Hamilton SM. Gastric adenocarcinoma: review and considerations for future directions. Ann Surg 2005; 241: 27-39.

[20] Nakajima T, Nashimoto A, Kitamura M, Kito T, Iwanaga T, Okabayashi K, Goto M. Adjuvant mitomycin and fluorouracil followed by oral uracil plus tegafur in serosa-negative gastric cancer: a randomised trial. Lancet 1999; 354: 273-7.

[21] Nashimoto A, Nakajima T, Furukawa H, Kitamura M, Kinoshita T, Yamamura Y, Sasako M, Kunii Y, Motohashi H, Yamamoto S. Randomized trial of adjuvant chemotherapy with mitomycin, fluorouracil, and cytosine arabinoside followed by oral fluorouracil in serosa-negative gastric cancer: Japan Clinical Oncology Group 9206-1. J Clin Oncol 2003; 21: 2282-7.

[22] Bouche O, Ychou M, Burtin P, Bedenne L, Ducreux M, Lebreton G, Baulieux J, Nordlinger B, Martin C, Seitz JF, Tigaud JM, Echinard E, Stremsdoerfer N, Milan C, Rougier P. Adjuvant chemotherapy with 5-fluorouracil and cisplatin compared with surgery alone for gastric cancer: 7-year results of the FFCD randomized phase III trial (8801). Ann Oncol 2005; 16: 1488-97.

[23] De Vita F, Giuliani F, Orditura M, Maiello E, Galizia G, Di Martino N, Montemurro F, Carteni G, Manzione L, Romito S, Gebbia V, Ciardiello F, Catalano G, Colucci G. Adjuvant chemotherapy with epirubicin, leucovorin, 5-fluorouracil and etoposide regimen in resected gastric cancer patients: a randomized phase III trial by the gruppo oncologico italia meridionale (GOIM 9602 Study). Ann Oncol 2007; 18: 1354-8.

[24] Di Costanzo F, Gasperoni S, Manzione L, Bisagni G, Labianca R, Bravi S, Cortesi E, Carlini P, Bracci R, Tomao S, Messerini L, Arcangeli A, Torri V, Bilancia D, Floriani I, Tonato M; Italian Oncology Group for Cancer Research, Dinota A, Strafiuso G, Corgna E, Porrozzi S, Boni C, Rondini E, Giunta A, Monzio Compagnoni B, Biagioni F, Cesari M, Fornarini G, Nelli F, Carboni M, Cognetti F, Enzo MR, Piga A,

Romiti A, Olivetti A, Masoni L, De Stefanis M, Dalla Mola A, Camera S, Recchia F, De Filippis S, Scipioni L, Zironi S, Luppi G, Italia M, Banducci S, Pisani Leretti A, Massidda B, Ionta MT, Nicolosi A, Canaletti R, Biscottini B, Grigniani F, Di Costanzo F, Rovei R, Croce E, Carroccio R, Gilli G, Cavalli C, Olgiati A, Pandolfi U, Rossetti R, Natalini G, Foa P, Oldani S, Bruno L, Cascinu S, Catalano G, Catalano V, Lungarotti F, Farris A, Sarobba MG, Trignano M, Muscogiuri A, Francavilla F, Figoli F, Leoni M, Papiani G, Orselli G, Antimi M, Bellini V, Cabassi A, Contu A, Pazzola A, Frignano M, Lastraioli E, Saggese M, Bianchini D, Antonuzzo L, Mela M, Camisa R. Adjuvant chemotherapy in completely resected gastric cancer: a randomized phase III trial conducted by GOIRC. J Natl Cancer Inst 2008; 100: 388-98.

[25] Kulig J, Kolodziejczyk P, Sierzega M, Bobrzynski L, Jedrys J, Popiela T, Dadan J, Drews M, Jeziorski A, Krawczyk M, Starzynska T, Wallner G. Adjuvant chemotherapy with etoposide, adriamycin and cisplatin compared with surgery alone in the treatment of gastric cancer: a phase III randomized, multicenter, clinical trial. Oncology 2010; 78: 54-61.

[26] Lee HS, Choi Y, Hur WJ, Kim HJ, Kwon HC, Kim SH, Kim JS, Lee JH, Jung GJ, Kim MC. Pilot study of postoperative adjuvant chemoradiation for advanced gastric cancer: adjuvant 5-FU/cisplatin and chemoradiation with capecitabine. World J Gastroenterol 2006; 12: 603-7.

[27] Leong T, Joon DL, Willis D, Jayamoham J, Spry N, Harvey J, Di Iulio J, Milner A, Mann GB, Michael M. Adjuvant chemoradiation for gastric cancer using epirubicin, cisplatin, and 5-fluorouracil before and after three-dimensional conformal radiotherapy with concurrent infusional 5-fluorouracil: a multicenter study of the Trans-Tasman Radiation Oncology Group. Int J Radiat Oncol Biol Phys 2011; 79: 690-5.

[28] Andre T, Quinaux E, Louvet C, Colin P, Gamelin E, Bouche O, Achille E, Piedbois P, Tubiana-Mathieu N, Boutan-Laroze A, Flesch M, Lledo G, Raoul Y, Debrix I, Buyse M, de Gramont A. Phase III study comparing a semimonthly with a monthly regimen of fluorouracil and leucovorin as adjuvant treatment for stage II and III colon cancer patients: final results of GERCOR C96.1. J Clin Oncol 2007; 25: 3732-8.

[29] Sakuramoto S, Sasako M, Yamaguchi T, Kinoshita T, Fujii M, Nashimoto A, Furukawa H, Nakajima T, Ohashi Y, Imamura H, Higashino M, Yamamura Y, Kurita A, Arai K. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. N Engl J Med 2007; 357: 1810-20.

[30] Sasako M, Sakuramoto S, Katai H, Kinoshita T, Furukawa H, Yamaguchi T, Nashimoto A, Fujii M, Nakajima T, Ohashi Y. Five-year outcomes of a randomized phase III trial comparing adjuvant chemotherapy with S-1 versus surgery alone in stage II or III gastric cancer. J Clin Oncol 2011; 29: 4387-93.

[31] Bang YJ, Kim YW, Yang HK, Chung HC, Park YK, Lee KH, Lee KW, Kim Y H, Noh SI, Cho JY, Mok YJ, Kim YH, Ji J, Yeh TS, Button P, Sirzen F, Noh SH. Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. Lancet 2012; 379: 315-21.

[32] Du C, Zhou Y, Huang K, Zhao G, Fu H and Shi Y. Defining a high-risk subgroup of pathological T2N0 gastric cancer by prognostic risk stratification for adjuvant therapy. J Gastrointest Surg 2011; 15: 2153-8.