Table 6 Inter-factor correlations among symptom subscales of the PGSAS-45

Subscale	I	II	III	IV	V	VI	VII
I. Esophageal reflux	1.000						
II. Abdominal pain	**0.590**	1.000					
III. Meal-related distress	**0.598**	**0.608**	1.000				
IV. Indigestion	**0.545**	**0.549**	**0.584**	1.000			
V. Diarrhea	0.276	*0.374*	*0.364*	*0.450*	1.000		
VI. Constipation	*0.391*	*0.445*	*0.447*	*0.454*	0.274	1.000	
VII. Dumping	**0.514**	**0.607**	**0.640**	**0.575**	*0.467*	*0.391*	1.000
Interpretation of effect size	*r*						
Small	≥0.100						
Medium	*≥0.300*						
Large	**≥0.500**						

The fonts of values of *r* were varied according to their effect size; 'Small' as normal fonts, 'Medium' as italic fonts and 'Large' as bold fonts

PGS [1–6]. Although the primary objective of gastrectomy is to cure cancer, the second most important goal is to minimize PGS-related adverse events and to preserve the patients' QOL. This goal is particularly important in the Far East where gastric cancer is often found at early clinical stages so that more patients manage to survive their cancer and consequently need to face the PGS in the long term [9]. It is known that the type of gastrectomy affects the incidence and severity of PGS [10–21], and various procedures to preserve or reconstruct gastric function have been proposed to confront these problems [7, 8]. To gain deeper understanding of the PGS, a group of iatrogenic disorders, and treat them appropriately, it is important to grasp the impact of various symptoms, along with feeding problems and body weight loss, to the living status and QOL of the patients. In addition, identifying the problems and their correlations with various types of surgical procedures may lead to evolution of a novel surgical technique as well as more adequate selection of conventional technique to circumvent the problems. However, instruments designed to focus on the evaluation of PGS have not been established to date.

Patient-reported outcome directly reflects the symptoms and complaints of patients. This type of report is particularly valuable as an endpoint when evaluating QOL after surgery because PGS often is detected only through complaints from the patients [22]. Several studies made comparisons between different surgical procedures to find which procedure is beneficial for the patients from the point of view of PGS, but these comparisons often looked only at specific outcomes that particularly aroused the interest of the investigators [17, 19] and were not necessarily comprehensive and convincing. Moreover, using arbitrary endpoints renders comparisons between different studies impossible. More recently, investigators turned to the established and authorized questionnaires for comparisons between gastric surgery procedures [10–15, 18, 20], because there are several combinations of core questionnaires and disease-specific modules that are considered appropriate and have been approved for evaluation of QOL [23, 24]. A combination of SF-36, a core questionnaire, and GSRS, a symptom-specific QOL, has been one of the examples [11, 14], but the GSRS may have a tendency to overlook some of the symptoms that are peculiar to the patients who have undergone gastrectomy and are unusual for other disorders of the gastrointestinal tract. EORTC QLQ-C30 [25], a cancer-specific core questionnaire, and STO-22 [26] is another combination that has been used to evaluate postgastrectomy patients [12, 13]. However, these questionnaires have been developed to evaluate QOL of the patients who are burdened with cancer and are receiving treatments rather than those who became cancer free through surgery but are suffering from PGS.

The investigators who wish to evaluate PGS had thus been obliged to turn to modules designed for other purposes because of the lack of an optimally constructed questionnaire. Therefore, there are possibilities that a large proportion of these studies have overlooked several important postgastrectomy symptoms that actually affect the living status of the patients but cannot be evaluated by conventional scales. More recently, Nakamura et al. reported on DAUGS, a questionnaire designed to measure symptoms after upper gastrointestinal surgery, and the actual attempt to use this in the clinical setting [16, 21]. However, items concerning living status or QOL of the patients rather than the symptoms were lacking in the DAUGS.

PGSAS-45 was constructed through contribution of several expert surgeons with abundant experience coping with postgastrectomy patients as the only comprehensive questionnaire that is suitable for evaluating patients who have undergone various types of gastrectomy and reconstruction. PGSAS-45 is a package with complex structures

and includes items from multiple dimensions. Its core stems from internationally acclaimed questionnaires in that it contains items from SF-8 [27] and GSRS under the permission of each copyright owner for this study. GSRS has five subscales that are in common with the PGSAS-45 and has been extensively used to evaluate patients with various disorders of the gastrointestinal tract [28, 29]. However, it does not cover some symptoms that are peculiar to postgastrectomy patients such as postprandial satiation and symptoms related to the dumping syndrome. PGSAS-45 was constructed through contributions of several expert surgeons during the comprehensive item generation phase. Inclusion of the 8 additional symptom-related items that were proposed and selected by the surgeons to evaluate postgastrectomy patients is expected to increase sensitivity to more meticulously detect and evaluate the PGS. Multivariate regression analysis has shown through larger β coefficients that the 8 items actually correlated more significantly with most of the subscales looking at the living status and QOL of the patients when compared with the 15 items derived from GSRS. Moreover, the R^2 values of the JPGSWP items as calculated by the bivariate regression analysis were almost equivalent to R^2 values of all symptom items calculated by the multivariate analysis, indicating that the 8 items had a decisive role in evaluating the effect of surgery on the living status and QOL of the patients. The relatively large effect size of the total symptoms in the R^2 value, which was calculated by multivariate analysis, indicates that the symptom has a certain impact on living status and QOL in the postgastrectomy patients (Table 4).

Factor analysis resulted in construction of five subscales that are in common with the GSRS. Two of these subscales actually contained items that are different from the GSRS. In addition, two novel subscales, meal-related distress and dumping, were generated that would apparently result in extra sensitivity to detect symptoms. Two further subscales showing dissatisfaction for daily life and quality of ingestion were added to augment QOL and living status domains. Cronbach's α is a coefficient of internal consistency and is commonly used as an estimate of the reliability. The interpretation of Cronbach's α is shown in Table 5. Acceptable internal consistency was observed in all nine subscales, including the four new subscales.

Conclusions

In conclusion, we have developed a useful multidimensional integrated quality of life measure, PGSAS-45. This questionnaire benefited from addition of the eight symptom-related items derived from comprehensive item generation process contributed by expert surgeons, and led to generation of two additional subscales: meal-related distress subscale and dumping subscale. It is expected to serve as a gold standard in the evaluation of PGS and provide a meticulous profile of symptoms in postgastrectomy patients. Furthermore, the PGSAS study generated a prospective multi-institutional database of HRQOL assessed by PGSAS-45 among patients who were treated by the six most frequent types of gastrectomy. Several comparative analyses using these data and main outcome measures as defined in the current study are ongoing, and results are awaited.

Acknowledgments This study was supported by a grant from Jikei University and the Japanese Society for Gastro-surgical Pathophysiology. This study was conducted by JPGSWP and registered to UMIN-CTR #000002116 entitled as "A study to observe correlation between resection and reconstruction procedures employed for gastric neoplasms and development of postgastrectomy syndrome." The results of this study were presented at Digestive Disease Week 2013, Orland, FL, USA [30]. The authors thank all the physicians who participated in this study and the patients whose cooperation made this study possible.

References

1. Bolton JS, Conway WC 2nd. Postgastrectomy syndromes. Surg Clin N Am. 2011;91(5):1105–22.
2. Carvajal SH, Mulvihill SJ. Postgastrectomy syndromes: dumping and diarrhea. Gastroenterol Clin N Am. 1994;23(2):261–79.
3. Cooperman AM. Postgastrectomy syndromes. Surg Annu. 1981;13:139–61.
4. Eagon JC, Miedema BW, Kelly KA. Postgastrectomy syndromes. Surg Clin N Am. 1992;72(2):445–65.
5. Harju E. Metabolic problems after gastric surgery. Int Surg. 1990;75(1):27–35.
6. Jay BS, Burrell M. Iatrogenic problems following gastric surgery. Gastrointest Radiol. 1977;2(3):239–57.
7. Katai H. Function-preserving surgery for gastric cancer. Int J Clin Oncol. 2006;11(5):357–66.
8. Lehnert T, Buhl K. Techniques of reconstruction after total gastrectomy for cancer. Br J Surg. 2004;91(5):528–39.
9. Maruyama K, Kaminishi M, Hayashi K, Isobe Y, Honda I, Katai H, et al. Gastric cancer treated in 1991 in Japan: data analysis of nationwide registry. Gastric Cancer. 2006;9(2):51–66.
10. Endo S, Nishida T, Nishikawa K, Yumiba T, Nakajima K, Yasumasa K, et al. Motility of the pouch correlates with quality of life after total gastrectomy. Surgery (St. Louis). 2006;139(4):493–500.
11. Hayami M, Seshimo A, Miyake K, Shimizu S, Kameoka S. Effects of emptying function of remaining stomach on QOL in postgastrectomy patients. World J Surg. 2012;36(2):373–8.
12. Huang CC, Lien HH, Wang PC, Yang JC, Cheng CY, Huang CS. Quality of life in disease-free gastric adenocarcinoma survivors: impacts of clinical stages and reconstructive surgical procedures. Dig Surg. 2007;24(1):59–65.
13. Kobayashi D, Kodera Y, Fujiwara M, Koike M, Nakayama G, Nakao A. Assessment of quality of life after gastrectomy using EORTC QLQ-C30 and STO22. World J Surg. 2011;35(2):357–64.
14. Kono K, Iizuka H, Sekikawa T, Sugai H, Takahashi A, Fujii H, et al. Improved quality of life with jejunal pouch reconstruction after total gastrectomy. Am J Surg. 2003;185(2):150–4.

15. Lee MS, Ahn SH, Lee JH, Park do J, Lee HJ, Kim HH, et al. What is the best reconstruction method after distal gastrectomy for gastric cancer? Surg Endosc. 2012;26(6):1539–47.
16. Nakamura M, Kido Y, Yano M, Hosoya Y. Reliability and validity of a new scale to assess postoperative dysfunction after resection of upper gastrointestinal carcinoma. Surg Today. 2005;35(7):535–42.
17. Nakane Y, Michiura T, Inoue K, Iiyama H, Okumura S, Yamamichi K, et al. A randomized clinical trial of pouch reconstruction after total gastrectomy for cancer: which is the better technique, Roux-en-Y or interposition? Hepatogastroenterology. 2001;48(39):903–7.
18. Namikawa T, Kitagawa H, Okabayashi T, Sugimoto T, Kobayashi M, Hanazaki K. Roux-en-Y reconstruction is superior to Billroth I reconstruction in reducing reflux esophagitis after distal gastrectomy: special relationship with the angle of His. World J Surg. 2010;34(5):1022–7.
19. Nunobe S, Okaro A, Sasako M, Saka M, Fukagawa T, Katai H, et al. Billroth 1 versus Roux-en-Y reconstructions: a quality-of-life survey at 5 years. Int J Clin Oncol. 2007;12(6):433–9.
20. Svedlund J, Sullivan M, Liedman B, Lundell L, Sjodin I. Quality of life after gastrectomy for gastric carcinoma: controlled study of reconstructive procedures. World J Surg. 1997;21(4):422–33.
21. Takiguchi S, Yamamoto K, Hirao M, Imamura H, Fujita J, Yano M, et al. A comparison of postoperative quality of life and dysfunction after Billroth I and Roux-en-Y reconstruction following distal gastrectomy for gastric cancer: results from a multi-institutional RCT. Gastric Cancer. 2012;15(2):198–205.
22. Karanicolas PJ, Bickenbach K, Jayaraman S, Pusic AL, Coit DG, Guyatt GH, et al. Measurement and interpretation of patient-reported outcomes in surgery: an opportunity for improvement. J Gastrointest Surg. 2011;15(4):682–9.
23. Borgaonkar MR, Irvine EJ. Quality of life measurement in gastrointestinal and liver disorders. Gut. 2000;47(3):444–54.
24. Moyer CA, Fendrick AM. Measuring health-related quality of life in patients with upper gastrointestinal disease. Dig Dis. 1998;16(5):315–24.
25. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993;85(5):365–76.
26. Vickery CW, Blazeby JM, Conroy T, Arraras J, Sezer O, Koller M, et al. Development of an EORTC disease-specific quality of life module for use in patients with gastric cancer. Eur J Cancer. 2001;37(8):966–71.
27. Turner-Bowker DM, Bayliss MS, Ware JE Jr, Kosinski M. Usefulness of the SF-8 Health Survey for comparing the impact of migraine and other conditions. Qual Life Res. 2003;12(8):1003–12.
28. Svedlund J, Sjodin I, Dotevall G. GSRS—a clinical rating scale for gastrointestinal symptoms in patients with irritable bowel syndrome and peptic ulcer disease. Dig Dis Sci. 1988;33(2):129–34.
29. Revicki DA, Wood M, Wiklund I, Crawley J. Reliability and validity of the Gastrointestinal Symptom Rating Scale in patients with gastroesophageal reflux disease. Qual Life Res. 1998;7(1):75–83.
30. Nakada K, Ikeda M, Takahashi M, Kinami S, Yoshida M, Uenosono Y, et al. Development and validation of PGSAS-45, an integrated questionnaire to assess postgastrectomy syndrome. Gastroenterology. 2013;144(5 suppl 1):S-1111.

Ann Surg Oncol (2015) 22:787–792
DOI 10.1245/s10434-014-4084-9

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – GASTROINTESTINAL ONCOLOGY

Long-term Survival Outcomes of Advanced Gastric Cancer Patients Who Achieved a Pathological Complete Response with Neoadjuvant Chemotherapy: A Systematic Review of the Literature

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ABSTRACT

Background. A pathologic complete response (pCR) can sometimes be induced by intensive or long-term neoadjuvant chemotherapy (NAC). This prognostic research study based on a systematic review of the literature evaluated the impact of a pCR on the long-term survival of gastric cancer (GC) patients.

Methods. Articles were extracted from PubMed and the Japanese medical search engine "Ichu-shi," using the terms "GC," "NAC," and "pCR." Articles were selected based on the following criteria: (1) full-text case report, (2) R0 resection following NAC for locally advanced GC, and (3) pathological complete response in both the primary stomach and in the lymph nodes. A questionnaire regarding the patients' prognoses was sent to the corresponding authors of the articles selected in July 2013.

Results. Twenty-four articles met the criteria. Twenty authors responded to the questionnaire. Finally, 22 patients from 20 articles were entered into the present study. The median follow-up time (range) of the survivors was 76 (range 13–161) months. Tumors that were stage III/IV (86 %: 19/22) and of an undifferentiated histology (61.9 %: 13/21) were dominant. An S1-based regimen was frequently selected for the NAC. All patients underwent R0 resection and D2/D3 lymphadenectomy. The overall survival and recurrence-free survival rates at 3 and 5 years were 96 % and 85 % and 91 % and 75 %, respectively.

Conclusions. Although a pCR was a relatively rare event, a high pCR rate would be helpful to select the regimen and courses of NAC, especially when the pathological response rates are similar.

Electronic supplementary material The online version of this article (doi:10.1245/s10434-014-4084-9) contains supplementary material, which is available to authorized users.

First Received: 10 June 2014;
Published Online: 16 September 2014

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Gastric cancer (GC) is the second leading cause of cancer-related death worldwide.[1] Although surgical resection remains a mainstay of treatment for localized/regional GC, the R0 resection rate with surgery alone is unsatisfactory when the tumor is already in an advanced stage. Adjuvant chemotherapy with S-1[2] or capecitabine/oxaliplatin[3] after D2 gastrectomy improved the survival of patients with stage II/III GC. However, the survival remains unsatisfactory in stage III patients, at approximately 50 % at 5 years. Theoretically, neoadjuvant chemotherapy (NAC) represents a promising strategy, because it is associated with a high R0 resection rate, downstaging, high compliance for an intensive regimen, low toxicities, a high rate to initiate chemotherapy, and avoidance of unnecessary surgery compared with adjuvant chemotherapy.[4]

To develop NAC in the phase III setting, the identification of optimal surrogate endpoints representing the survival is essential in phase II studies. Previous phase II studies had selected the R0 resection rate, clinical response rate by The Response Evaluation Criteria in Solid Tumors (RECIST) or the pathological response rate as a primary endpoint. However, the pathological response was shown to have higher response assessment validity than the RECIST, thus suggesting that a pathological response would be a better surrogate endpoint than the RECIST.[5]

Recently, more intensive regimens have been developed to improve the survival in metastatic GC.[6–8] Intensive chemotherapy induced a high response rate, but also some sporadic pathological complete responses (pCR) in locally advanced GC.[9–11] More recently, we clarified that long-term chemotherapy induced a high pathological complete response rate but did not affect the overall pathological response rate itself in a randomized phase II study.[12] To select the most promising regimen and courses, it should be clarified whether a pathological complete response induces long-term survival. So far, only a few sporadic case reports showed a certain survival benefit of a pCR, but the follow-up period in those reports was short.[13–33]

Because NAC is an investigational treatment in Japan and the pCR rate is still low, we conducted a prognostic research study based on a systematic review of the literature to evaluate the impact of a pCR on the long-term survival in GC patients.

PATIENTS AND METHODS

Literature Search Strategy

A comprehensive literature search was performed to evaluate the prognosis of the patients who achieved a pCR following NAC for GC. The MEDLINE database was searched using the terms "gastric cancer," "neoadjuvant chemotherapy," and "pathological complete response (or histological complete response)" using PubMed for reports published from 2002 to 2011. An extended search with the Japanese medical search engine "Ichu-shi" also was performed to include corresponding cases which were reported in Japanese journals.

Inclusion Criteria

Articles were selected for inclusion if they met the following criteria: (1) full-text case report, (2) R0 resection following NAC for locally advanced GC, and (3) pathological complete response not only in the primary stomach, but also in the lymph nodes. Surgical interventions for GC with distant metastasis were distinguished from neoadjuvant treatment and excluded from eligibility, even when the metastatic site was completely resected and was proven to be a pCR. Clinically detected para-aortic nodal metastases close to the celiac artery were eligible in cases where these nodes were proven to have disappeared following NAC, either by imaging studies after NAC or based on the resected specimen. Cases with positive peritoneal cytology were also eligible in cases where the intraoperative lavage cytology was confirmed to be negative. Patients who received other treatment modalities than chemotherapy, such as chemoradiotherapy or radiotherapy, were excluded.

Prognostic Data

A questionnaire (Supplemental Fig. 1) regarding the patients' prognoses was sent to the authors of the articles selected by the above criteria in July 2013.

Statistical Analysis

The overall survival (OS) was defined as the period from the initiation of NAC to any cause of death, and the recurrence-free survival (RFS) as the period from the initiation of NAC to the occurrence of an event, recurrence or death, whichever came first. The data for patients who had not experienced an event were censored as of the date of the final observation. The Kaplan–Meier method and the log-rank test were used to estimate the RFS and OS. The software program used for this analysis was IBM SPSS Statistics, version 21 (IBM corporation, North Castle Drive, Armonk, NY). The tumor stage was expressed by 7th edition of the TNM classification (TNM 7th).[34]

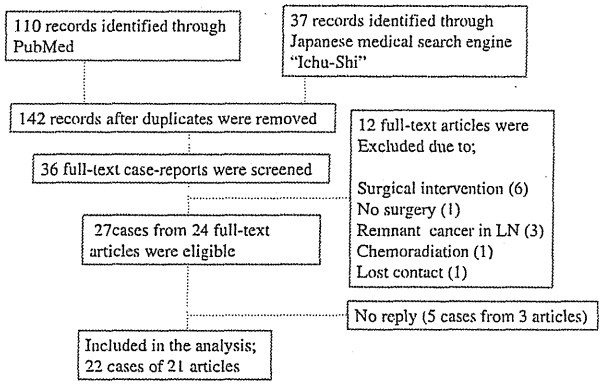

FIG. 1 CONSORT diagram of the literature search

RESULTS

Patient Selection and Compliance

Twenty-four articles met the criteria for this study (Fig. 1). These 24 articles were all reported from Japan. A questionnaire was retrieved from the authors of 21 articles. Thus, the response rate for the questionnaire was 87.5 %. Finally, 22 patients from the 21 articles were entered into the present study.

Patient Characteristics

The baseline characteristics of these 22 patients are shown in Table 1. The clinical stages had been determined by the Japanese classification of gastric carcinoma 13th edition (JCGC 13th) in all articles.[35] Because the clinical N status was defined not by the number of lymph nodes, but by the lymphatic location in the JCGC 13th, we could not translate the clinical N from the JCGC 13th into the TNM 7th in 11 patients. Among them, five patients had metastasis to the para-aortic lymph nodes (expressed as N3 in JCGC 13th) which corresponded to stage IV in the TNM 7th. The other six patients could not be precisely classified into a TNM clinical stage due to unknown nodal status; however, all six patients had clinical T4 N+ disease and could be classified to stage III-unspecified (Table 1). Three patients underwent staging laparoscopy (SL). Among them, two were diagnosed to be positive for peritoneal cytology. A total of 86 % (19 of 22) of the patients had either stage III or IV disease based on the TNM 7th.

The pathological details of the changes in the primary tumor after NAC had been described for 11 patients. The relationship between the clinical stage and fibrotic scar also are demonstrated in Table 1. A fibrotic scar was observed at the same or deeper depth as determined before NAC in 10 patients. Pathological examination was done by serial section of the whole portion where the primary tumor was considered to be located in five cases but was not done or not described in detail in 17 cases.

TABLE 1 The characteristics of the patients and the tumors

Age, median (range)	67.5 years (54–78)
Male/Female	13/9
Primary tumor	
Macroscopic type	
Type I/II	1/7
Type III/IV/V	9/3/2
Histology	
Differentiated/undifferentiated	9/13
Clinical stage (TNM 7th)	
T	
T1(M/SM)	0/0
T2 (MP)	3
T3 (SS)	1
T4a/T4b (SE/SI)	13/4
N	
N0/N1	1/6
N2/N3	4/0
N+ (number unassessed)	11
M	
M0	15
M1 (PAN/CY)	7 (5/2)
Stage	
IB	1
IIB	2
IIIA/IIIB/III-unspecified	4/2/6
IV	7
Pathological findings	
Extent of fibrotic scar	
MP	3 (cT2:2, cT3:1)
SS	5 (cT2:1, cT4a:4)
SE	2 (cT4a:1, cT4b:1)
SI	1 (cT4b:1)
NA	11 (cT4a:9, cT4b:2)

PAN para-arortic node, *CY* peritoneal cytology, *NA* not available

Most regimens (21/22, 95 %) of NAC included a fluoropyrimidine; with 86 % (19/22) of the NAC regimens containing S-1 (Table 2). The surgical procedures and postoperative treatments also are summarized in Table 2. All patients underwent D2 or D3 lymphadenectomy. Seventeen patients (77 %) required combined resection of adjacent organs. After surgery, ten patients (45 %) received S-1-based adjuvant chemotherapy.

OS and RFS

The median follow-up period (range) of the survivors was 76 (range 13–161) months. Two patients died of

TABLE 2 Pre-surgical/surgical/post-surgical treatments

Regimen of NAC	
Non FU-based	
PTX/CDDP	1
FU-based	
S1/CDDP	14
S1/PTX	3
S1/CPT11	1
S1	1
FLP	1
FP	1
Median total course of NAC (range)	2 (1–4)
Surgical procedure	
Gastrectomy	
Total	17
Distal	5
Lymphadenectomy	
D2	20
D3	2
Combined resection	
None	5
Left upper abdominal exenteration	1
Spleen	6
Spleen, gall bladder	6
Lower esophagus, spleen	1
Transverse colon	1
Left adrenal gland, pancreas tail, spleen	1
Left adrenal gland, spleen	1
Postoperative adjuvant chemotherapy	
None	12
S1	9
S1/PTX	1

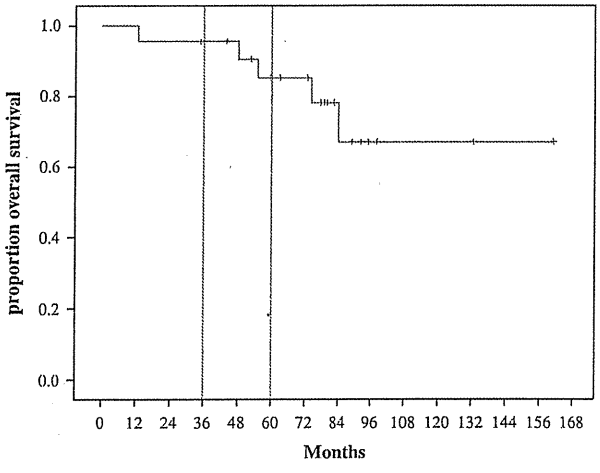

FIG. 2 Kaplan–Meier overall survival

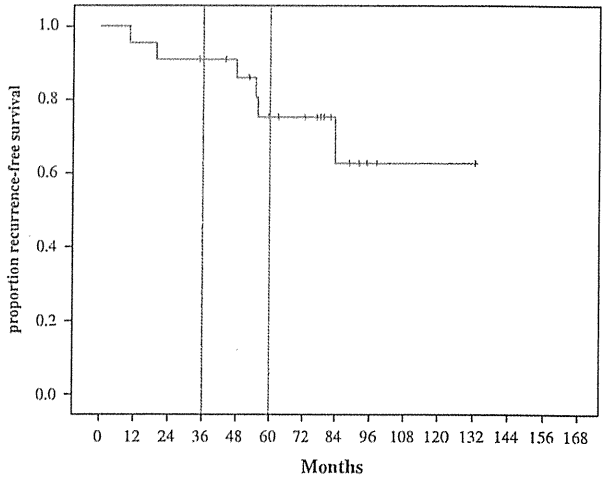

FIG. 3 Kaplan–Meier recurrence-free survival

gastric cancer while three died of other diseases. Only three patients developed recurrence: to the brain in one patient, liver in one, and para-aortic lymph nodes in one. As a whole, the OS rates at 3 and 5 years were 96 % (95 % confidence interval [CI] 100–87) and 85 % (95 % CI 100–70; Fig. 2), and the RFS rates at 3 and 5 years were 91 % (95 % CI 100–79) and 75 % (95 % CI 94-56; Fig. 3). When limited to the 19 patients with clinical stage III/IV disease, the OS rates at 3 and 5 years were 94 % (95 % CI 100–85) and 83 % (95 % CI 100–66), and the RFS rates at 3 and 5 years were 89 % (95 % CI 100–76) and 72 % (95 % CI 93–51).

DISCUSSION

The present study first clarified that the GC patients who showed a pCR to NAC had an excellent RFS and OS. According to the Japanese nationwide survey, the 5-year survival rates for GC were reported to be approximately 90 % in stage I, 70 % in stage II, 50 % in stage III, and 15 % in stage IV.[36] Although the number of patients was very small and the clinical staging was not fully validated in our study, the 5-year survival rate of the patients showing a pCR, even when the patients were limited to those with clinically confirmed stage III/IV disease, was similar to that of the stage I/II patients who did not receive NAC.

In the patients with a pCR, NAC eradicated the primary tumor. If NAC also eradicates micrometastasis, NAC can cure cancer. In our study, 12 of 22 patients (54 %) lived longer than 5 years without recurrence. In two patients with positive peritoneal cytology, the disseminated cancer cells disappeared after NAC. These data suggest that NAC is effective for micrometastasis, as well as the primary

tumor. The survival benefit of NAC has also been proven in randomized, controlled trials. As shown in two phase III studies, the MAGIC trial and the FNCLCC/FFCD trial, perioperative chemotherapy significantly improved the progression-free and OS rates compared with surgery alone.[37,38] Furthermore, two Japanese phase II studies evaluating NAC, the JCOG 0001 and JCOG 0405, also demonstrated excellent three-year survival rates (27 and 59 %, respectively), despite the fact that those studies targeted the patients with bulky nodal metastasis of the celiac axis or major branched arteries or para-aortic nodal metastasis, which were considered to be non-curable disease.[39,40]

There is a possibility that the longer survival can be explained by several factors other than the effects of NAC. First, there is a possibility that there was contamination by patient in an earlier stage due to an overdiagnosis of the clinical staging. We previously examined the accuracy of clinical staging and showed that the staging accuracy was approximately 75 % when the decision was made by CT alone according to the evidence-based criteria.[41] In all 21 articles cited in this study, the tumor progression was evaluated by CT, endoscopy, and/or barium gastrography, but none of the articles commented on the decision criteria used for the clinical staging. Although the accuracy of the staging could not be evaluated in this study, the present results demonstrated that a fibrotic scar was seen at the same or deeper depth, as determined clinically, in 10 of 11 patients. Considering that chemotherapy induced fibrotic changes through necrosis of the primary tumor, the clinical stage was not overdiagnosed, at least in these 10 patients. The remaining one patient with a clinical T3 had fibrotic changes to the depth of proper muscle layer. Although this case showed an overdiagnosis, the differential diagnosis of T2 and T3 is very difficult, in contrast to that of T1 and T2. Thus, the contamination of earlier stage cases was limited.

Next, there was a possibility of selection bias. The biological characteristics of NAC super-responders were not sufficiently examined. These patients may have had a good prognosis irrespective of tumor progression or treatment selection. Another possible bias is publication bias. It has been found that statistically significant results are three times more likely to be published than papers affirming a negative result.[42] It therefore cannot be denied that doctors may have submitted the reports of pCR patients just because the survival outcomes of these patients were excellent. Furthermore, a responding bias may exist. Of the 24 doctors to whom we sent the questionnaire, 3 did not respond. They might have hesitated to respond, because the postpublication outcomes of the patients were poor.

In conclusion, the present study demonstrated that a pCR induced by NAC was associated with the long-term survival of patients with locally advanced gastric cancer. Although a pCR was a relatively rare event, a high pCR rate would be helpful to select the regimen and courses of NAC, especially when the pathological response rates are similar.

DISCLOSURE There are no conflicts of interest associated with this study.

REFERENCES

1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer.* 2010;127:2893–917.
2. Sakuramoto S, Sasako M, Yamaguchi T, Kinoshita T, Fujii M, Nashimoto A, et al. Adjuvant chemotherapy for GC with S-1, an oral fluoropyrimidine. *N Engl J Med.* 2007;357:1810–20.
3. Bang YJ, Kim YW, Yang HK, Chung HC, Park YK, Lee KH, et al. Adjuvant capecitabine and oxaliplatin for GC after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomized controlled trial. *Lancet.* 2012;379(9813):315–21.
4. Yoshikawa T, Rino Y, Yukawa N, Tsuburaya A, Masuda M. Neoadjuvant chemotherapy for gastric cancer in Japan: a standing position by comparing with adjuvant chemotherapy. *Surg Today.* 2014;44:11-21.
5. Kurokawa Y, Shibata T, Sasako M, Sano T, Tsuburaya A, Iwasaki Y, et al. Validity of response assessment criteria in neoadjuvant chemotherapy for gastric cancer (JCOG0507-A). *Gastric Cancer.* DOI 10.1007/s10120-013-0294-2
6. Koizumi W, Nakayama N, Tanabe S, Sasaki T, Higuchi K, Nishimura K, et al. A multicenter phase II study of combined chemotherapy with docetaxel, cisplatin, and S-1 in patients with unresectable or recurrent gastric cancer (KDOG 0601). *Cancer Chemother Pharmacol.* 2012;69:407-13.
7. Koizumi W, Narahara H, Hara T, Takagane A, Akiya T, Takagi M, et al. S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. *Lancet Oncol.* 2008;9:215-21.
8. Bang YJ, Cutsem EV, Feyereislova A, Chung HC, Shen L, Sawaki A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet* 2010;376:687–97.
9. Stahl M, Walz MK, Stuschke M, Lehmann N, Meyer HJ, Riera-Knorrenschild J, et al. Phase III comparison of preoperative chemotherapy compared with chemoradiotherapy in patients with locally advanced adenocarcinoma of the esphagogastric junction. *J Clin Oncol.* 2009;27:851–56.
10. Fields RC, Strong VE, Gonen M, Goodman KA, Rizk NP, Kelsen DP, et al. Recurrence and survival after pathologic complete response to preoperative therapy followed by surgery for gastric or gastrooesophageal adenocarcinoma. *Br J Cancer.* 2011;104:1840–47.
11. Lorenzen S, Thuss-Patience P, Al-Batran SE, Lordick F, Haller B, Schuster T, et al. Impact of pathologic complete response on disease-free survival in patients with esophagogastric adenocarcinoma receiving preoperative docetaxel-based chemotherapy. *Ann Oncol.* 2013;24:2068–73.
12. Yoshikawa T, Tanabe K, Nishikawa K, Ito Y, Matsui T, Kimura Y, et al. Induction of a pathological complete response by four courses of neoadjuvant chemotherapy for gastric cancer: early results of the randomized phase II COMPASS trial. *Ann Surg Oncol.* 2014;21:213–9.

13. Tanaka K, Kobayashi S, Fujita Y, Nakamura J, Kanneko K, Nakagawa K, et al. Histological complete response in a case of advanced GC treated by neoadjuvant TS-1 combined with CDDP therapy. *Jpn J Cancer Chemother.* 2011;38:101–4.
14. Asaumi Y, Miyanaga T, Ito H, Sawada K, Fujita M, Miyazaki M, et al. Type 4 advanced GC responding to histological complete response after neoadjuvant S-1 combined with CDDP therapy-report of a case. *Jpn J Cancer Chemother.* 2011;38:1325–28.
15. Tsuchiya Y, Nashimoto A, Nakagawa S, Yabusaki H, Takii Y, Tsuchiya Y, et al. Advanced GC responding to pathological CR after neoadjuvant TS-1 combined with CDDP therapy-report of a case. *Jpn J Cancer Chemother.* 2006;33:807–9.
16. Yabusaki h, Nashimoto A, Tanaka O. A complete response after neoadjuvant chemotherapy for advanced GC with esophageal invasion. *Jpn J Cancer Chemother.* 2002;29:119–23.
17. Sakon M, Sekino Y, Okita K, Kusama K, Seki H, Munakata Y, et al. A case of advanced GC responding to paclitaxel/CDDP neoadjuvant chemotherapy leading to pathologically complete response. *Jpn J Cancer Chemother.* 2008;35:1383–6.
18. Takasu N, Nomura T, Fukumoto T, Shibata K, Kamio Y, Hachiya O, et al. Advanced GC showing complete response to neoadjuvant chemotherapy with CPT-11 and S-1: a case report. *Jpn J Cancer Chemother.* 2009;36:111–3.
19. Kobayashi T, Kubota Y, Ueyama S, Satomoto K, Ogino T. A case of advanced GC showing a complete histological response after S-1/CDDP neoadjuvant chemotherapy. *Jpn J Cancer Chemother.* 2011;38:1329–32.
20. Aoki T, Tanida T, Tsukao Y, Igarashi Y, Komori T, Matsumoto T, et al. A case of GC responding to S-1/paclitaxel was pathologically complete response. *Jpn J Cancer Chemother.* 2008;35:2045–7.
21. Shiraishi O, Hatabe S, Ishikawa S, Kitano Y, Kawasaki M, Sakai K, et al. A case of advanced GC responding to TS-1/CDDP therapy was pathological complete response. *Jpn J Gastroenterol Surg.* 2007;40:1769–74.
22. Mori S, Kishimoto H, Tauchi K, Higuchi K. Histological complete response in advanced GC after 2 weeks of S-1 administration as neoadjuvant chemotherapy. Gastric Cancer. 2006;9:136–9.
23. Tokunaga M, Ohyama S, Nunobe S, Hiki N, Fukunaga T, Seto Y, et al. A case of advanced GC—histological CR was attained by one course of neoadjuvant chemotherapy with S-1/CDDP. *Jpn J Gastroenterol Surg.* 2007;40:1479–84.
24. Yanagisawa S, Takayanagi H, Tsuchiya S, Kaiho T, Takeuchi O, Togawa A. Histological complete response in a case of advanced GC treated with TS-1/CDDP, a neoadjuvant chemotherapy. *J Jpn Surg Assoc.* 2008;69:1065–9.
25. Kobayashi N, Mizuta M, Otani H, Kubo M, Udaka T, Shirakawa K. A case of locally advanced GC responding to pathological CR treated with S-1/CDDP neoadjuvant chemotherapy. *Jpn J Cancer Chemother.* 2010;37:1965–9.
26. Suda T, Takagi Y, Katayanagi S, Hoshino S, Serizawa H, Tsuchida A, et al. A case of far advanced GC of type 4 treated with TS-1/CDDP resulting in chemotherapy efficacy of grade 3. *J Jpn Surg Assoc.* 2007;68:1142–7.
27. Yamakawa T, Onoda Y, Tokuno M, Oka T, Ohashi R, Shiota K. Two cases of advanced GC treated with S-1/paclitaxel showing a complete response on pathology. *J Jpn Surg Assoc.* 2009;70:3571–7.
28. Hiraoka K, Mizutani S, Oyama T, Uchikoshi F, Yoshidome K, Tori M, et al. A case of stage IV advanced GC responding to TS-1/CDDP neoadjuvant chemotherapy which leads to a pathological complete response. *Jpn J Cancer Chemother.* 2007;34:93–5.
29. Fujisawa T, Sano W, Ouchi S, Ueyama S, Mori T, Tsuchihashi D, et al. Complete histological response in GC stage IV after neoadjuvant chemotherapy including S-1 combined with CDDP—report of a case. *Jpn J Cancer Chemother.* 2007;34:2297–300.
30. Matono S, Horiuchi H, Kishimoto Y, Fukumitsu T, Yoshimura F, Shirouzu K. a case of advanced GC with para-aortic lymph node metastasis responding to neoadjuvant chemotherapy which leads to a pathological complete response. *J Jpn Surg Assoc.* 2008;69:815–9.
31. Horikawa M, Nakatsuji N, Sugihara S, Takayama T, Nomi T, Maruyama H. A case of dramatically improved GC responding to TS-1/CDDP as neoadjuvant chemotherapy. *J Jpn Surg Assoc.* 2004;65:375–9.
32. Seya T, Tanaka N, Yokoi K, Ishikawa N, Horiba K, Kanazawa Y, et al. Complete response of a patient with advanced GC, showing Epstein-Barr virus infection, to preoperative chemotherapy with S-1 and cisplatin. *Int J Clin Oncol.* 2007;12:472–7.
33. Oshima N, Tanizawa Y, Bando E, kawamura T, Tokunaga M, Sugisawa N, et al. histological complete response in a case of advanced GC treated by neo-adjuvant chemotherapy with S-1/CDDP. Jpn J Cancer Chemother. 2010;37:697-701.
34. The TNM classification of malignant tumors, 7th edn. New York: Wiley; 2009.
35. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma: 2nd English edition. Gastric Cancer. 1998;1:10-24.
36. Nashimoto A, Akazawa K, Isobe Y, Miyashiro I, Katai H, Kodera Y, et al. Gastric cancer treated in 2002 in Japan: 2009 annual report of the JGCA nationwide registry. Gastric Cancer. 2013;16:1-27.
37. Cunningham D, Allum WH, Stenning SP, Thompson JN, Van deVelde CJ, Nicolson M, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med. 2006;355:11–20.
38. Ychou M, Boige V, Pignon JP, Conroy T, Bouche O, Lebreton G, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. *J Clin Oncol.* 2011;29:1715–21.
39. Yoshikawa T, Sasako M, Yamamoto S, Sano T, Imamura H, Fujitani K, et al. Phase II study of neoadjuvant chemotherapy and extended surgery for locally advanced GC. *Br J Surg.* 2009;96:1015–22.
40. Tsuburaya A, Mizusawa J, Tanaka Y, Fukushima N, Nashimoto A, Sasako M. Neoadjuvant chemotherapy with S-1 and cisplatin followed by D2 gastrectomy with para-aortic lymph node dissection for GC with extensive lymph node metastasis. *Br J Surg.* 2014;101:653–60.
41. Hasegawa S, Yoshikawa T, Shirai J, Fujikawa H, Cho H, Doiuchi T, et al. A prospective validation study to diagnose serosal invasion and nodal metastases of gastric cancer by multidetector-row CT. *Ann Surg Oncol.* 2013;20:2016–22.
42. Dickersin K, Chan S, Chalmers TC, Sacks HS, Smith H Jr. Publication bias and clinical trials. *Control Clin Trials.* 1987;8:343–53.

Gastric Cancer (2014) 17:197–199
DOI 10.1007/s10120-013-0287-1

EDITORIAL

The earlier the better?

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Published online: 20 August 2013

In the past, post-gastrectomy patients had to undergo fasting with a nasogastric tube for as long as 5–7 days. Then, patients would be started on a liquid diet and gradually transitioned to a soft diet, upon confirming that the esophagogastrogram detected no sign of leakage. Early oral feeding was avoided because it was believed to increase the risk of postoperative complications.

In the late 1990s, however, a combination of early oral feeding, early mobilization, and sufficient pain control using epidural analgesia reportedly improved the recovery of patients with colorectal cancer [1]. This protocol was further refined and integrated into a fast-track methodology or enhanced recovery after surgery (ERAS) [2], which rapidly spread throughout the world with the widespread acceptance of laparoscopic minimal invasive surgery. Several randomized controlled trials (RCTs) [3, 4] and meta-analyses [5, 6] revealed that ERAS reduced the length of hospital stay and morbidity after colorectal surgery without compromising patient safety. European guidelines strongly recommend postoperative early feeding and perioperative oral nutritional support, such as carbohydrate administration, along with preoperative education, adequate postoperative analgesia, and early mobilization [7, 8].

In gastric cancer, introduction of early oral feeding has been very limited, possibly because of the fear of increasing postoperative complications related to upper gastrointestinal anastomosis. Hirao et al. [9] evaluated the feasibility of early oral feeding in patients with gastric cancer. In that study, patients in the early oral feeding group were started on a liquid diet on the 2nd postoperative day (POD 2) and transitioned to a solid diet on POD 6, and their outcomes were compared with those of control patients undergoing the conventional regimen, i.e., initiation of a solid diet on the POD 10. A significant decrease in the length of postoperative hospital stay and higher daily oral intake of calories on POD 10 were observed in the early oral feeding group. Although this study was the first to demonstrate the feasibility of early oral feeding in patients with gastric cancer, the regimen was far from being "fast track," as the length of postoperative hospital stay was 18.5 days even in the early oral feeding group.

Implementation of various ERAS programs for gastric cancer has been reported since 2010. Grantcharov and Kehlet [10] evaluated the efficacy of an ERAS program in 32 patients with gastric cancer, gastrointestinal stromal tumor (GIST), and benign diseases, who, after undergoing laparoscopic gastrectomy, were started on oral feeding on POD 2 with planned discharge on POD 3. Two major complications were reported, but morbidity was sufficiently low, with no deaths within 30 days. Median length of hospital stay was only 4 days. Yamada et al. [11] also evaluated the feasibility and efficacy of an ERAS program, in which 91 post-gastrectomy patients were placed on oral nutritional supplementation on POD 2 and then transitioned to a soft diet on POD 3. Compared with 100 control patients, those in the ERAS group had a significantly earlier oral intake start day, oral intake recovery, flatus, and defecation, and also had significantly less postoperative pain.

Two RCTs on ERAS have been reported in Korea. The first trial was conducted at Catholic University [12], where 54 patients scheduled to undergo gastrectomy were randomly allocated into control and early feeding groups; the control group was started on a soft diet on POD 4, whereas

This editorial refers to the article doi:10.1007/s10120-013-0275-5.

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the early feeding group was started on a liquid diet on POD 2 and transitioned to a soft diet on POD 3. The primary endpoint was the duration of hospital stay. The early oral feeding group had a significantly shorter duration of hospital stay and time of gas passage. The second RCT, reported by Yonsei University [13], included 47 patients who had undergone laparoscopic distal gastrectomy. The patients were randomly assigned to the fast-track or conventional pathway group. The fast-track protocol consisted of intensive preoperative education, short duration of fasting, preoperative carbohydrate load, early postoperative ambulation, early feeding, and sufficient pain control. In the fast-track and conventional groups, a liquid diet was started on POD 2 and POD 4, respectively, and a soft diet was started on POD 4 and POD 5, respectively. The possible and actual durations of postoperative hospital stay (primary endpoint) were significantly shorter in the fast-track group than in the conventional group. Moreover, the need for additional pain control was significantly less, and several QOL factors significantly improved, in the fast-track group.

In addition to these studies, the safety and efficacy of ERAS programs have been demonstrated even in gastric cancer surgery, albeit with delayed initiation of oral feeding. In ERAS programs for colorectal cancer, a normal diet is recommended as soon as patients become lucid after surgery. On the contrary, in most gastric cancer studies, a soft diet is started on POD 3 or POD 4 after safety is confirmed with a liquid diet on POD 2. It is speculated that surgeons might have concerns about anastomotic complications resulting from early oral feeding.

Jeong et al. [14] conducted a single-arm prospective trial to evaluate the feasibility of early oral feeding in patients with gastric cancer. In this trial, patients were started on a soft diet with lunch on POD 1, and their outcomes were compared with those of historical controls. In the early oral feeding group, the average diet start day was 1.8 days, and 39 % of patients were able to eat more than two-thirds of provided food on the 1st POD. There was no increase in postoperative complications. These observations led to the conclusion that postoperative oral nutrition is safe and feasible on POD 1 after gastrectomy. This report is meaningful in that the feasibility of early feeding in patients with gastric cancer was demonstrated. Yet, there were several limitations worth noting. First, the median age of this cohort was 59.9 years, which is about 10 years younger than those previously reported in studies targeting Japanese or Western patients. Furthermore, the authors indicated that compliance with early oral feeding was poor in patients aged 70 years or older. Thus, further confirmatory studies in other countries are required. Another major issue is the usefulness of the entire ERAS pathway. Despite the large difference in oral feeding start day, the difference in duration of hospital stay was only 1.5 days, suggesting that early oral feeding may not be the only factor affecting the duration of postoperative hospital stay.

Is it better to start a soft diet on POD 1 in patients with gastric cancer? The answer is both Yes and No. Caution is required when evaluating early oral feeding and ERAS programs. Previous ERAS studies are mostly single-institution studies with a small sample size. A comprehensive evaluation of ERAS programs, including early oral feeding, would require RCTs in a multi-institutional setting with a large sample size. Moreover, appropriate inclusion and exclusion criteria for each program, especially regarding age and comorbidities, are needed in future studies.

References

1. Bardram L, Funch-Jensen P, Jensen P, Crawford ME, Kehlet H. Recovery after laparoscopic colonic surgery with epidural analgesia, and early oral nutrition and mobilisation. Lancet. 1995; 345:763–4.
2. Kehlet H, Wilmore DW. Multimodal strategies to improve surgical outcome. Am J Surg. 2002;183:630–41.
3. Anderson AD, McNaught CE, MacFie J, Tring I, Barker P, Mitchell CJ. Randomized clinical trial of multimodal optimization and standard perioperative surgical care. Br J Surg. 2003;90: 1497–504.
4. Muller S, Zalunardo MP, Hubner M, Clavien PA, Demartines N. A fast-track program reduces complications and length of hospital stay after open colonic surgery. Gastroenterology. 2009;136: 842–7.
5. Varadhan KK, Neal KR, Dejong CH, Fearon KC, Ljungqvist O, Lobo DN. The enhanced recovery after surgery (ERAS) pathway for patients undergoing major elective open colorectal surgery: a meta-analysis of randomized controlled trials. Clin Nutr. 2010; 29:434–40.
6. Lv L, Shao YF, Zhou YB. The Enhanced Recovery After Surgery (ERAS) pathway for patients undergoing colorectal surgery: an update of meta-analysis of randomized controlled trials. Int J Colorectal Dis. 2012;27:1549–54.
7. Gustafsson UO, Scott MJ, Schwenk W, et al. Guidelines for perioperative care in elective colonic surgery: Enhanced Recovery After Surgery (ERAS(R)) society recommendations. Clin Nutr. 2012;31:783–800.
8. Nygren J, Thacker J, Carli F, et al. Guidelines for perioperative care in elective rectal/pelvic surgery: Enhanced Recovery After Surgery (ERAS(R)) society recommendations. Clin Nutr. 2012; 31:801–16.
9. Hirao M, Tsujinaka T, Takeno A, Fujitani K, Kurata M. Patient-controlled dietary schedule improves clinical outcome after gastrectomy for gastric cancer. World J Surg. 2005;29:853–7.
10. Grantcharov TP, Kehlet H. Laparoscopic gastric surgery in an enhanced recovery programme. Br J Surg. 2010;97:1547–51.
11. Yamada T, Hayashi T, Cho H, Yoshikawa T, Taniguchi H, Fukushima R, Tsuburaya A. Usefulness of enhanced recovery after surgery protocol as compared with conventional perioperative care in gastric surgery. Gastric Cancer. 2012;15:34–41.
12. Hur H, Kim SG, Shim JH, Song KY, Kim W, Park CH, Jeon HM. Effect of early oral feeding after gastric cancer surgery: a result of randomized clinical trial. Surgery (St. Louis). 2011;149:561–8.

13. Kim JW, Kim WS, Cheong JH, Hyung WJ, Choi SH, Noh SH. Safety and efficacy of fast-track surgery in laparoscopic distal gastrectomy for gastric cancer: a randomized clinical trial. World J Surg. 2012;36:2879–87.

14. Jeong O, Ryu S, Jung M, Choi W, Park Y. The safety and feasibility of early postoperative oral nutrition on the first postoperative day after gastrectomy for gastric carcinoma. Gastric Cancer 2013 (in press).

Gastric Cancer (2014) 17:206–212
DOI 10.1007/s10120-013-0299-x

REVIEW ARTICLE

Surgical resection of hepatic metastasis from gastric cancer: a review and new recommendation in the Japanese gastric cancer treatment guidelines

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Received: 30 April 2013 / Accepted: 22 August 2013 / Published online: 11 September 2013

Abstract Liver metastases from gastric cancer are rarely indicated for surgery because they are often diagnosed as multiple nodules occupying both lobes and coexist with extrahepatic disease. A literature search identified no clinical trials on hepatectomy for this disease; only retrospective studies of a relatively small number of cases collected over more than a decade, mostly from a single institution, were found. Five-year survival rates from these reports ranged from 0 % to 37 %, and long-term survivors were observed among carefully selected case series. The most commonly reported prognostic factor was the number of metastatic nodules, and patients with a solitary metastasis tended to have superior outcome. Patients diagnosed to have a small number of metastatic nodules by modern imaging tools could be indicated for surgery. Because both intrahepatic and extrahepatic recurrences are common, patients are likely to benefit from perioperative adjuvant chemotherapy, although it is not possible at this time to specify which regimen is the most appropriate.

Keywords Liver metastasis · Hepatectomy · Stage IV gastric cancer · Treatment guidelines

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Introduction

Hepatectomy for liver metastases should only be attempted when cure is the goal because hepatectomy usually does not relieve symptoms. Colorectal liver metastases are widely considered as targets of surgery with intent to cure, because they often present as a liver-only disease [1], which is not always the case with other types of cancer. A prognostic model based on several prognostic factors effectively stratified cancers of various origins into three groups in a comprehensive analysis of various noncolorectal nonendocrine liver metastases treated by hepatectomy in 41 French centers [2]. Gastric cancer metastasis in that report was classified into the intermediate-risk group in which 5-year survival rate was in the range of 15–30 %, with hepatic metastasis from pancreatic cancer, melanoma, and duodenal cancer. The low-risk group with a 5-year survival rate >30 % consisted of metastases from adrenal cancer, ovarian cancer, breast cancer, and renal cancer among others, and a high-risk group with 5-year survival

<15 % consisted of metastases from cancer of the lung, esophagus, head and neck, and gastroesophageal junction.

Gastric cancer is known to be heterogeneous in nature, consisting of cancer cells with varying biological characteristics. Gastric cancer can metastasize through the lymphatic pathway, the hematogenous pathway, and by direct dissemination into the peritoneal cavity from the serosal surface. Moreover, the fate of cancer cells that enter the portal circulation could vary. Hematogenous metastases can occur according to both the seed-and-soil hypothesis and the anatomical/mechanical hypothesis, neither of which needs to be mutually exclusive, and the extent to which either mechanism is operational depends on the tumor under investigation [3]. When gastric cancer cells spread through the hematogenous pathway, its first site of metastasis according to the anatomical/mechanical hypothesis would be the liver, followed by the lung. In addition, several gastric cancers spread along the seed-and-soil route, resulting in various distant metastases in the absence of hepatic metastases [4]. This result is in contrast with colorectal cancer in which the anatomical/mechanical hypothesis would seem more often applicable. The aggressive characteristics and unpredictable nature of gastric cancer cells are the reason that surgical resection of hepatic metastases has not been seriously considered.

However, some might not agree that gastric cancer even with solitary liver metastasis should always be considered as a contraindication for surgical treatment. The Japanese Gastric Cancer Treatment Guidelines recommend only chemotherapy, radiation, palliative surgery, and best supportive care for treatment of Stage IV or metastatic gastric cancer [5]. Recently, the guidelines committee of the Japan Gastric Cancer Association decided to revisit the treatment of potentially resectable M1 disease. A working group was organized to discuss whether any tentative comments could be added to the next version of the guidelines regarding surgical treatment with curative intent of (1) patients with resectable hepatic metastasis, (2) patients who are positive for cytological examination of peritoneal washes, and (3) patients with swollen nodes in the paraaortic region. This article is a summary of the literature search and discussion on gastric cancer hepatic metastasis by the members of the working group for this task.

Literature search

A search for relevant literature was conducted in March 2013 using PubMed and Scopus. Key search terms used included "gastric cancer," "liver metastasis," "hepatectomy," and "surgery" to find articles on hepatectomy for gastric cancer metastasis to the liver that were published in English after 2000. Sixty-eight articles were identified, of which the following were excluded: 15 articles that included either other types of distant metastases or hepatic metastasis from other cancer types with no independent outcome data for gastric cancer metastases, 15 articles with emphasis on treatment modalities other than hepatectomy, 6 articles with fewer than 15 cases, 5 articles on prediction and diagnosis of hepatic metastasis, 4 review articles, 3 articles on irrelevant subjects, and 1 article describing only hepatic metastasis from pT1 stage cancer. Three articles analyzed patients from the same institution, and the most recent report by Takemura et al. [6] was selected and added to a total of 17 articles to be analyzed in the current review [2, 6–21]. Most of the papers were retrospective single-institution analyses of consecutive patients who underwent hepatectomy during a given period, with two exceptions in which patients were recruited from multiple institutions [5, 7]. Wang et al. [8] analyzed only patients with synchronous liver metastases, but all other papers discussed both synchronous and metachronous metastases. Two papers analyzed all patients with hepatic metastasis who underwent gastrectomy, regardless of whether the patients underwent hepatectomy [9, 10]. Data of the patients who went on to receive hepatectomy could be retrieved from these reports for subsequent analyses. A paper by Adam et al. was a comprehensive analysis of noncolorectal nonendocrine liver metastases [2], from which patients with gastric cancer metastases could be retrieved for some of the analyses in this review.

Results and discussion

The median number of patients analyzed among the 17 series was 25 (range, 15–73), spanning a median period of 15 years (range, 5–36). Details such as the indication for surgery, diagnostic modalities used, type of surgery performed, and adjuvant treatments given were diverse and, in addition, could have changed substantially in each institution during the periods studied. Synopses of findings in the 17 papers are summarized in Table 1.

The type of hepatectomy performed was diverse. A greater proportion of patients underwent wedge or nonanatomic resection of the metastatic nodules, and major hepatectomy such as hemihepatectomy was reserved for 23.4 % of the patients (79 of 337). The selection was presumably based on the number, size, and location of the tumors rather than the surgeons' intent to perform anatomic resection for additional resection margin. In cases of colorectal liver metastasis, the preservation of hepatic parenchyma is considered to be of increasing importance in the setting of chemotherapy-associated steatohepatitis and the growing number of patients undergoing repeated metastectomy [22]. Even in gastric cancer metastasis, the most

Table 1 Outcome of the patients with gastric cancer liver metastasis

References	No. of cases	Enrolled	Age (years)	Synchronous	metachronous	No. with solitary metastasis	Operative death	Mortality (%)	Morbidity (%)	1-year survival rate (%)	3-year survival rate (%)	5-year survival rate (%)	No. of 5-year survivors	MST (months)
Takemura et al. [6]	64	1993–2011	65	34	30	37	0	0	23	84	50	37	27	34
Wang et al. [8]	30	2003–2008	60	30	0	22	0	0		43.3	16.7	16.7	5	11
Schildberg et al. [20]	31	1972–2008	65	17	14		2	6	29	75	25	13	4	14
Garancini et al. [19]	21	1998–2007	64	12	9	12	0	0	19	68	31	19	3	11
Miki et al. [18]	25	1995–2009	72	16	9					73.9	42.8	36.7	9	33.4
Makino et al. [10]	16	1992–2007	65.8	9	7	9	0	0		82.3	46.4	37.1	4	38.3
Tsujimoto et al. [17]	17	1980–2007	66.3	8	8	13	0	0		75	37.5	31.5	5	34
Cheon et al. [9][a]	41	1995–2005	61	30	11	28	1	3		75.3	31.7	20.8	3	17
Thelen et al. [16]	24	1988–2002	64	15	9	13	1	4.2	21	53	22	15	2	10
Morise et al. [15]	18	1989–2004	64	11	7	14	0	0		56.3	27.3	27.3	3	13
Sakamoto et al. [14]	37	1990–2005		16	21	21	0	0	24			11	2	31
Adam et al. [2]	64	1983–2004										27	17	15
Shirabe et al. [7]	36	1979–2001	66	16	20		0	0		64	26	26	4	
Zacherl et al. [13]	15	1980–1999		10	5	8	1	67	47	35.7	14.3	0	0	8.8
Okano et al. [12]	19	1986–1999	69	13	6	10	0	0		77	34	34	3	
Ambiru et al. [11]	40	1975–1999					0	0				18	6	12
Imamura et al. [21]	17	1990–1997		7	10	8	0	0		47	22	0	0	
Total	515					195 (61.1 %)	5	1.1				18.8	97	

MST median survival time

[a] Data include nine patients who were treated by radiofrequency ablation (RFA)

frequent pattern of recurrence was intrahepatic recurrence, observed in 79 % (166 of 209) of all the recurrences reported.

Mortality was 1.1 % (5/426) among the 15 studies in which the data were available, and morbidity ranged from 19 % to 47 % among 6 studies.

The 5-year survival reported from each series ranged from 0 % to 37 % and exceeded 30 % in five series [6, 10, 12, 15, 16]. Median survival time ranged from 9 to 38.8 months. The diversity in outcome may have reflected the diversity in patient selection and strategy taken, including the use of adjuvant therapies. The 5-year survival of all patients analyzed in the current study, calculated by dividing the number of 5-year survivors reported in each article by the total number of patients, was 18.8 % (97 of / 515). Although these series should be considered to represent a well-selected and more favorable population compared with patients with liver metastases who were treated with systemic chemotherapy and had poorer outcome, the 5-year survival rate at 18.8 % obtained cannot be ignored as futile. Gastric cancer with liver metastases has long been considered as a systemic disease with no indication for surgery with curative intent. This point has been made clear, both in the National Comprehensive Cancer Network (NCCN) Guidelines Version 1.2013 [23] and in the Japanese Guidelines [5]. However, there are occasions when such metastases are found as clinically resectable disease, and whether these exceptions should still be treated either by palliative chemotherapy or supportive care could be an issue for debate.

Indication for surgery has not been established but could be considered based on analysis of prognostic factors. Independent prognostic factors identified through multivariate analyses were varied, and included the number of metastatic nodules, unilobular distribution, solitary tumor, tumor diameter, and capsular formation regarding hepatic tumors (Table 2). Among these, the "number of metastatic nodules" was considered to be an important factor across several series if "solitary metastasis" was to be included. Among 319 patients with relevant information in the current series, 195 (61.1 %) actually had solitary metastases. One should note, however, that the number of nodules can differ, depending on the type of imaging studies used [24, 25]. Because most institutions needed more than a decade to accumulate 15 patients or more, there should have been much difference in the potential of imaging modalities at the beginning and the end of the study period. In the largest single-institution series, Takemura et al.[6] reported a 5-year survival of 37 %. It may be of note that they currently consider surgery when the number of metastatic nodules was diagnosed as three or fewer, using state-of-the-art imaging tools. As for other prognostic factors, some have found metachronous hepatic metastases to be a sign of favorable prognosis [11, 12, 20] whereas others consider this as irrelevant. In addition, status of the primary tumor such as serosal invasion, lymphatic invasion, and clinical stage were listed as relevant prognostic factors.

It may be worthwhile to mention that the incidence of clinically resectable hepatic metastasis may be lower than what a surgeon expects. Sakamoto et al. [14] reported that they found synchronous liver metastases in 2.2 % of the 5,209 patients who underwent gastrectomy at National Cancer Center, Japan, whereas 1.3 % developed metachronous metastases. About 20 % of these patients underwent hepatectomy for cure. In contrast, 1,013 of 10,259 patients (9.9 %) diagnosed as gastric cancer in the Yonsei University Health System, Korea, had synchronous or metachronous liver metastases [9]. Of these, 58 had metastases confined to the liver and 41 (only 4 % of all patients with liver metastases) underwent surgery with curative intent, which denotes management of both the primary tumor and the liver. The five-year survival rate of these 41 patients was 20.8 %, and the median survival time fell just short of 20 months. In short, 20 % of the patients with liver metastases can be treated surgically in a situation where only patients with potentially resectable disease are referred, a situation possibly encountered at the surgical department in a high-volume cancer center. In contrast, resectable liver metastasis undoubtedly is a rare disease when one attempts to carefully select patients from all gastric cancer patients who visit a hospital.

Indication for the adjuvant therapy given perioperatively was even more varied among the researchers, as no trial-based evidence exists for the population who underwent hepatectomy for gastric cancer metastasis. Takemura et al. [6] took an aggressive approach in which 18 of 73 patients received neoadjuvant chemotherapy and 31 received postoperative chemotherapy, including 5 cases that received arterial infusion (HAIC) postoperatively. In contrast, Sakamoto et al. [14] reported that they delivered chemotherapy only for those who subsequently had recurrences. There is no prospective trial showing the effect of perioperative adjuvant therapies for gastric cancer metastases to the liver. The high incidence of recurrence implies that micrometastases remain in situ after surgery, however. That micrometastases could be managed by modern chemotherapeutic agents has been proven by several adjuvant chemotherapy trials [26–28]. Thus, there is a rationale for perioperative chemotherapy, or even HAIC, given the high incidence of recurrence within the liver. Chemotherapy delivered preoperatively could be useful to identify cancers that do not respond to chemotherapy and progress rapidly and to avoid futile surgery. All five series with 5-year survival >30 % reported details on adjuvant strategies, including neoadjuvant chemotherapy and HAIC. In contrast, none of the patients received chemotherapy until

Table 2 Independent prognostic determinants of the patients with gastric cancer liver metastasis

	Indication for inclusion in the case series	Factors independently showing favorable prognosis
Takemura et al. [6]	All hepatectomy cases	No serosal invasion, diameter <5 cm
Wang et al. [8]	Hepatectomy cases of synchronous metastasis	Solitary liver tumor, absence of peritoneal metastasis
Schildberg et al. [20]	All hepatectomy cases	Solitary liver tumor, synchronous metastasis
Garancini et al. [19]	All hepatectomy cases	Solitary liver tumor, RO resection, capsule formation
Miki et al. [8]	All cases with hepatic metastasis	Stage of the primary cancer
Makino et al. [10]	All cases with hepatic metastasis who underwent gastrectomy	Unilobular distribution
Tsujimoto et al. [17]	All hepatectomy cases	Diameter <6 cm, D2 dissection
Cheon et al. [9]	All cases with hepatic metastasis who underwent laparotomy with curative intent	Smaller number of metastases
Thelen et al. [16]	All hepatectomy cases	Negative resection margin
Morise et al. [15]	All hepatectomy cases	
Sakamoto et al. [14]	All hepatectomy cases	Unilobular distribution, diameter <4 cm
Adam et al. [2]	All hepatectomy cases of noncolorectal nonneuroendocrine hepatic metastasis	
Shirabe et al. [7]	All hepatectomy cases who underwent RO resection	Number of metastases <3, no lymphatic or venous invasion of the primary tumor
Zacherl et al. [13]	All hepatectomy cases	
Okano et al. [12]	All hepatectomy cases	Solitary liver tumor, synchronous metastasis, well-differentiated phenotype, capsule formation
Ambiru et al. [11]	All hepatectomy cases	Synchronous metastasis
Imamura et al. [21]	All hepatectomy cases of gastric and colorectal liver metastasis	No extrahepatic metastasis

recurrence in another series by Sakamoto et al., who reported their 5-year survival at 11 % as unsatisfactory. These facts imply the relevance of perioperative chemotherapy, although outcomes obtained from retrospective case series should be interpreted with caution. Evidence at a higher level will not be available for the time being because the chances of conducting a decently designed trial to generate evidence for adjuvant therapies in a disease as rare as resectable gastric liver metastases would be sparse.

Systemic chemotherapy, HAIC, and radiofrequency ablation (RFA) are among other treatment modalities for gastric cancer metastasis to the liver. No prospective trial investigating systemic chemotherapy specified in hepatic metastases has been reported, with the exception of one small pilot study involving 8 patients [29]. In recent phase III trials of first-line chemotherapy against advanced/metastatic gastric cancer, median survival time ranged from 11 to 15 months [30–34]; 5-year survivors were rarely observed. In a report that integrated 643 patients enrolled in five separate prospective trials performed by the Japan Clinical Oncology Group, the 5-year survival rate of patients with metastasis confined to the liver and treated with systemic chemotherapy alone was 1.7 % [35]. Presumably, this series does not include patients with a relatively small cancer burden for whom indication for surgery was seriously considered, and comparison of survival data with those of highly selected patients who underwent surgical resection of the metastases needs to be interpreted with caution. Nevertheless, it remains impractical to hope to cure patients with gastric cancer metastases to the liver by systemic chemotherapy.

The rationale for HAIC is in high intrahepatic drug concentration in relationship to the systemic concentration [36]. A response rate >50 % has been reported that led to good local control [36, 37]. However, good local control did not necessarily lead to prolonged survival in cases of gastric cancer, in which extrahepatic metastases often emerge even during the course of successful liver-oriented treatment. In addition, an inadequately placed or malfunctioning catheter prevents efficient drug delivery [38]. Thus, catheter-related events such as occlusion, dislocation, and infection could result in interruption or termination of the treatment, even when the tumors are responding.

RFA has been attempted to treat selected patients with hepatic metastasis. The indication for RFA would include (1) liver-only disease; (2) size of the largest tumor less than

5 cm in diameter; and (3) location of tumor not adjacent to major vessels. RFA can be conducted either percutaneously under ultrasonic imaging guidance, laparoscopically, or by the open surgery approach. Reports on RFA applied to treat gastric cancer metastases to the liver remain scarce. Kim et al. [39] treated 20 patients by RFA or RFA and gastrectomy in case of synchronous metastases, achieving a median survival time of 30.7 months, whereas the experience by Kim et al. with 7 patients was more disappointing, with a median survival time of 11 months [40]. There is another report of 7 patients treated by HAIC followed by RFA who achieved a median survival time of 16.5 months [41]. This strategy was meant to select the patients so that RFA would only be delivered after confirming that new intrahepatic or systemic lesions do not develop during the HAIC. The chances of conducting a hepatectomy-versus-RFA trial for gastric cancer metastasis to the liver would seem unlikely. So far, the only clue of whether to perform hepatectomy or RFA comes from a meta-analysis of retrospective comparisons for colorectal liver metastases in which hepatectomy was significantly superior, even when conditions were limited to tumors >3 cm and solitary tumors [42]. Further prospective studies are needed to establish the position of RFA as an option for treatment of gastric liver metastases.

Conclusions

This working group reached the conclusion that hepatectomy could be considered in carefully selected cases of gastric cancer liver metastasis. The abstract of this article will appear in the forthcoming version of the Japanese gastric cancer treatment guidelines.

References

1. Shimada H, Tanaka K, Endou I, Ichikawa Y. Treatment for colorectal liver metastases: a review. Langenbecks Arch Surg. 2009;394:973–83.
2. Adam R, Chice L, Aloia T, Elias D, Salmon R, Rivoire M, et al. Hepatic resection for noncolorectal nonendocrine liver metastases. Analysis of 1425 patients and development of a prognostic model. Ann Surg. 2006;244:524–35.
3. Langley RR, Fidler IJ. The seed and soil hypothesis revisited: the role of tumor–stroma interactions in metastasis to different organs. Int J Cancer. 2011;128:2527–35.
4. Kodera Y, Ito S, Mochizuki Y, Yamamura Y, Misawa K, Ohashi N, et al. The number of metastatic lymph nodes is a significant risk factor for bone metastasis and poor outcome after surgery for linitis plastica-type gastric carcinoma. World J Surg. 2008;32:2015–20.
5. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines (ver. 3). Gastric Cancer. 2010;2011(14):113–23.
6. Takemura N, Saiura A, Koga R, Arita J, Yoshioka R, Ono Y, et al. Long-term outcomes after surgical resection for gastric cancer liver metastasis: an analysis of 64 macroscopically complete resections. Langenbecks Arch Surg. 2012;397:951–7.
7. Shirabe K, Shimada M, Matsumata T, Higashi H, Yakeishi Y, Wakiyama S, et al. Analysis of the prognostic factors for liver metastasis of gastric cancer after hepatic resection: a multi-institutional study of the indication for resection. Hepatogastroenterology. 2003;50:1560–3.
8. Wang Y-N, Shen K-T, Ling J-Q, Gao X-D, Hou Y-Y, Wang X-F, et al. Prognostic analysis of combined curative resection of the stomach and liver lesions in 30 gastric cancer patients with synchronous liver metastases. BMC Surg. 2012;12:20.
9. Cheon SH, Rha SY, Jeung HC, Im CK, Kim SH, Kim HR, et al. Survival benefit of combined curative resection of the stomach (D2 resection) and liver in gastric cancer patients with liver metastases. Ann Oncol. 2008;19:1146–53.
10. Makino H, Kunisaki C, Izumisawa Y, Tokuhisa M, Oshima T, Nagano Y, et al. Indication for hepatic resection in the treatment of liver metastasis from gastric cancer. Anticancer Res. 2010;30:2367–76.
11. Ambiru S, Miyazaki M, Ito H, Nakagawa K, Shimizu H, Yoshidome H, et al. Benefits and limits of hepatic resection for gastric metastases. Am J Surg. 2001;151:279–83.
12. Okano K, Maeba T, Ishimura K, Karasawa Y, Goda F, Wakabayashi H, et al. Hepatic resection for metastatic tumors from gastric cancer. Ann Surg. 2002;235:86–91.
13. Zacherl J, Zacherl M, Scheuba C, Steininger R, Wenzl E, Muhlbacher F, et al. Analysis of hepatic resection of metastasis originating from gastric adenocarcinoma. J Gastrointest Surg. 2002;6:682–9.
14. Sakamoto Y, Sano T, Shimada K, Esaki M, Saka M, Fukagawa T, et al. Favorable indications for hepatectomy in patients with liver metastasis from gastric cancer. J Surg Oncol. 2007;95:534–9.
15. Morise Z, Sugiokla A, Hoshimoto S, Kato T, Ikeda M, Uyama I, et al. The role of hepatectomy for patients with liver metastases of gastric cancer. Hepatogastroenterology. 2008;55:1238–41.
16. Thelen A, Jonas S, Benckert C, Lopez-Hanninen E, Neumann U, Rudolph B, et al. Liver resection for metastatic gastric cancer. Eur J Surg Oncol. 2008;34:1328–34.
17. Tsujimoto H, Ichikura T, Ono S, Sugasawa H, Hiraki S, Sakamoto N, et al. Outcomes for patients following hepatic resection of metastatic tumors from gastric cancer. Hepatol Int. 2010;4:406–13.
18. Miki Y, Fujitani K, Hirao M, Kurokawa Y, Mano M, Tsujie M, et al. Significance of surgical treatment of liver metastases from gastric cancer. Anticancer Res. 2012;32:665–70.
19. Garancini M, Uggeri F, Degrate L, Nespoli L, Gianotti L, Nespoli A, et al. Surgical treatment of liver metastases of gastric cancer: is local treatment in a systemic disease worthwhile? HPB (Oxf). 2012;14:209–15.
20. Schildberg CW, Croner R, Merkel S, Schellerer V, Muller V, Yedibela S, et al. Outcome of operative therapy of hepatic metastatic stomach carcinoma: a retrospective analysis. World J Surg. 2012;36:872–8.
21. Imamura H, Matsuyama Y, Shimada R, Kubota M, Nakayama A, Kobayashi A, et al. A study of factors influencing prognosis after resection of hepatic metastases from colorectal and gastric carcinoma. Am J Gastroenterol. 2001;96:3178–84.
22. Sarpel U, Bonavia AS, Grucela A, Roayaie S, Schwarz ME, Labow DM. Does anatomic versus nonanatomic resection affect recurrence and survival in patients undergoing surgery for colorectal liver metastasis? Ann Surg Oncol. 2009;16:379–84.
23. Ajani JA, Barthel JS, Bekaii-Saab T, Bentrem DJ, D'Amico TA, Das P, et al. Gastric cancer. J Natl Compr Canc Netw. 2010;8:378–409.
24. Wang Z, Chen J-Q. Imaging in assessing hepatic and peritoneal metastases of gastric cancer: a systemic review. BMC Gastroenterol. 2011;11:19.

25. Maas M, Rutten IJG, Nelemans PJ, Lambregts DM, Cappendijk VC, Beets GL, et al. What is the most accurate whole-body imaging modality for assessment of local and distant recurrent disease in colorectal cancer? A meta-analysis. Eur J Nucl Med Mol Imaging. 2011;38:1560–71.
26. Sasako M, Sakuramoto S, Katai H, Kinoshita T, Furukawa H, Yamaguchi T, et al. 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.
27. Bang YJ, Kim YW, Yang HK, Chung HC, Park YK, Lee KH, et al. Adjuvant vapecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. Lancet. 2012;379:315–21.
28. Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med. 2006;355:11–20.
29. Li Z-Y, Tang L, Zhang L-H, Bu Z-D, Wu A-W, Wu X-J, et al. Weekly docetaxel and cisplatin plus fluorouracil as a preoperative treatment for gastric cancer with synchronous multiple hepatic metastasis: a pilot study. Med Oncol. 2010;27:1314–8.
30. Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet. 2010;376:687–97.
31. Koizumi W, Narahara H, Hara T, Takagane A, Akiya T, Takagi M, et al. S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. Lancet Oncol. 2008;9:215–21.
32. Cunningham D, Starling N, Rao S, Iveson T, Nicolson M, Coxon F, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med. 2008;358:36–46.
33. Ohtsu A, Shah MA, Van Cutsem E, Rha SY, Sawaki A, Park SR, et al. Bevacizumab in combination with chemotherapy as first-line therapy in advanced gastric cancer: a randomized, double-blind, placebo-controlled phase III study. J Clin Oncol. 2011;29:3968–76.
34. Narahara H, Ishii H, Imamura H, Tsuburaya A, Chin K, Imamoto H, et al. Randomized phase III study comparing the efficacy and safety of irinotecan plus S-1 with S-1 alone as first-line treatment for advanced gastric cancer (study GC0301/TOP-002). Gastric Cancer. 2011;14:72–80.
35. Yoshida M, Ohtsu A, Boku N, Miyata Y, Shirao K, Shimada Y, et al. Longterm survival and prognostic factors in patients with metastatic gastric cancers treated with chemotherapy in the Japan Clinical Oncology Group (JCOG) study. Jpn J Clin Oncol. 2004;34:654–9.
36. Kumada T, Arai Y, Itoh K, Takayasu Y, Nakamura K, Ariyoshi Y, et al. Phase II study of combined administration of 5-fluorouracil, epirubicin and mitomycin-C by hepatic artery infusion in patients with liver metastases of gastric cancer. Oncology. 1999;57:216–23.
37. Ojima H, Ootake S, Yokobori T, Mochida Y, Hosouchi Y, Nishida Y, et al. Treatment of multiple liver metastasis from gastric carcinoma. World J Surg Oncol. 2007;5:70.
38. Inaba Y, Arai Y, Matsueda K, Takeuchi Y, Aramaki T. Right gastric artery embolization to prevent acute gastric mucosal lesions in patients undergoing repeat hepatic arterial infusion chemotherapy. J Vasc Interv Radiol. 2001;12:957–63.
39. Kim HR, Cheon SH, Lee KH, Ahn JR, Jeung HC, Lee SS, et al. Efficacy and feasibility of radiofrequency ablation for liver metastases from gastric adenocarcinoma. Int J Hypertherm. 2010;26:305–13.
40. Kim HO, Hwang SI, Hong HP, Yoo CH. Radiofrequency ablation for metachronous hepatic metastases from gastric cancer. Surg Laparosc Endosc Percutan Tech. 2009;19:208–12.
41. Yamakado K, Nakatsuka A, Takaki H, Mori Y, Tonouchi H, Kusunoki M, et al. Prospective study of arterial infusion chemotherapy followed by radiofrequency ablation for the treatment of liver metastasis of gastric cancer. J Vasc Interv Radiol. 2005;16:1747–51.
42. Weng M, Zhang Y, Zhou D, Yang Y, Tang Z, Zhao M, et al. Radiofrequency ablation versus resection for colorectal cancer liver metastases: a meta-analysis. PLoS One. 2012;7:e45493.