Yamasaki S, Miyagi-Maeshima A, Kakugawa Y, Matsuno Y, Ohara-Waki F, Fuji S, Morita-Hoshi Y, Mori M, Kim SW, Mori S, Fukuda T, Tanosaki R, Shimoda T, Tobinai K, Saito D, Takaue Y, Teshima T, Heike Y	Diagnosis and evaluation of intestinal graft-versus-host disease after allogeneic hematopoietic stem cell transplantation following reduced-intensity and myeloablative conditioning regimens.	Int J Hematol.	97(3)	421-6	2013
平家勇司	免疫療法の臨床試験を行う際に考えること	実験医学	12(2)	214-217	2013
平家勇司	細胞免疫療法の現状と展望	腫瘍内科	31(12)	137-142	2013
Sasaki, T., Tazawa, H., Hasei, J., Osaki, S., Kunisada, T., Yoshida, A., Hashimoto, Y., Yano, S., Yoshida, R., Kagawa, S., Uno, F., Urata, Y., Ozaki, T., Fujiwara, T.	A simple detection system for adenovirus receptor expression using a telomerase-specific replication-competent adenovirus.	Gene Therapy	20	112-118	2013
Hasei, J., Sasaki, T., Tazawa, H., Osaki, S., Yamakawa, Y., Kunisada, T., Yoshida, A., Hashimoto, Y., Onishi, T., Uno, F., Kagawa, S., Urata, Y., Ozaki, T., Fujiwara, T.	Dual programmed cell death pathways induced by p53 transactivation overcome resistance to oncolytic adenovirus in human osteosarcoma cells.	Molecular Cancer Therapeutics	12	314-325	2013
Yano, S., Tazawa, H., Hashimoto, Y., Shirakawa, Y., Kuroda, S., Nishizaki, M., Kishimoto, H., Uno, F., Nagasaka, T., Urata, Y., Kagawa, S., Hoffman, R. M., Fujiwara, T.	A genetically engineered oncolytic adenovirus decoys and lethally traps quiescent cancer stem-like cells into S/G2/M-phases.	Clinical Cancer Research	19	6495-6505	2013
Hashimoto, Y., Tazawa, H., Teraishi, F., Kojima, T., Watanabe, Y., Uno, F., Yano, S., Urata, Y., Kagawa, S., Fujiwara, T.	The hTERT promoter enhances the antitumor activity of an oncolytic adenovirus under a hypoxic microenvironment.	PLoS One	7	e39292	2013

Nishida S, Koido S, Takeda Y,Honma S, Kimita H, Takahara A, Morita S, Ito T, Morimoto S, Hara K, Tsuboi A, Oka Y, Yanagisawa S, Toyama Y, Ikegami M, Kitagawa T, Eguchi H, Wada H, Nagano H, Nakata J, Nakae Y, Hosen N, Oji Y, Tanaka T, Kawase I, Kumanogoh A, Sakamoto J, Doki Y, Mori M,Ohkusa T, Tajiri H, Sugiyama H.	Wilms Tumor Gene 1 (WT1) Peptide–based Cancer Vaccine Combined With Gemcitabine for Patients With Advanced Pancreatic Cancer.	J Immunother.			in press
Maeda T, Hosen N, Fukushima K, Tsuboi A, Morimoto S, Matsui T, Sata H, Fujita J, Hasegawa K, Nishida S, Nakata J, Nakae Y, Takashima S, Nakajima H, Fujiki F, TatsumiN, Kondo T, Hino M, Oji Y, Oka Y, Kanakura Y, Kumanogoh A and Sugiyama H.	Maintenance of complete remission after allogeneic stem cell transplantation in leukemia patients treated with Wilms tumor 1 peptide vaccine.	Blood Cancer Journal.	3	e130	2013
Tachino S, Fujiki F, Oka Y, Tsubboi A, Morimoto S, Lin Y, Tamanaka T, Kondo K, Nakajima H, Nishida S, Hosen N, Oji Y, Kumanogoh A, Sugiyama H.	Functional human Th17 clones with WT1-specific helper activity.	Cancer Immunol Immunother.	62(4)	801-810	2013
Lin Y, Fujiki F, Katsuhara A, Oka Y, Tsuboi A, Aoyama N, Tanii S, Nakajima H, Tatsumi N, Morimoto S, Hosen N, Nishida S, Oji Y, Kumanogoh A, Sugiyama H.	HLA-DPB1*05:01-restricted WT1332-specific TCR-transduced CD4(+) T lymphocytes display a helper activity for WT1-specific CTL induction and a cytotoxicity against leukemia cells.	J Immunother.	36(3)	159-170	2013
Nagata Y.	Stereotactic body radiotherapy (SBRT) for early stage lung cancer..	Cancer Research and Treatment..	45(3)	155-161	2013

Kimura T., Takahashi S., Kenjo M., Nishibuchi I., Takahashi I., Takeuchi Y., Doi Y., Kaneyasu Y., Murakami Y., Honda Y., Aikata H., Chayama K., Nagata Y.	Dynamic computed tomography appearance of tumor response after stereotactic body radiation therapy for hepatocellular carcinoma: How should we evaluate treatment effects?	Hepatol Res.	43	717-27	2013
Honda Y., Kimura T., Aikata H., Kobayashi T., Fukuhara T., Masaki K., Nakahara T., Naeshiro N., Ono A., Miyaki D., Nagaoki Y., Kawaoka T., Takaki S., Hiramatsu A., Ishikawa M., Kakizawa H., Kenjo M., Takahashi S., Awai K., Nagata Y., Chayama K.	Stereotactic body radiation therapy combined with transcatheter arterial chemoembolization for small hepatocellular carcinoma.	J Gastroenterol Hepatol.	28(3)	530-536.	2013
Takahashi S, Kimura T, Kenjo M, Nishibuchi I, Takahashi I, Takeuchi Y, Doi Y, Kaneyasu Y, Murakami Y, Honda Y, Aikata H, Chayama K, Nagata Y	Case reports of portal vein thrombosis and bile duct stenosis after stereotactic body radiation therapy for hepatocellular carcinoma.	Hepatol Res.	Epub ahead of print		2013
永田 靖	【特集 高精度放射線治療のピットフォール】はじめに	臨床放射線	58(5)	649-650	2013
Satoi S, Yamaue H, Kato K, Takahashi S, Hirono S, Takeda S, Eguchi H, Sho M, Wada K, Shinchi H, Kwon AH, Hirano S, Kinoshita T, Nakao A, Nagano H, Nakajima Y, Sano K, Miyazaki M, Takada T.	Role of adjuvant surgery for patients with initially unresectable pancreatic cancer with a long-term favorable response to non-surgical anti-cancer treatments: results of a project study for pancreatic surgery by the Japanese Society of Hepato-Biliary-Pancreatic Surgery.	J Hepatobiliary Pancreat Sci	Epub ahead of print		2013
Sugimoto M, Gotohda N, Kato Y, Takahashi S, Kinoshita T, Shibasaki H, Nomura S, Konishi M, Kaneko H.	Risk factor analysis and prevention of postoperative pancreatic fistula after distal pancreatectomy with stapler use.	J Hepatobiliary Pancreat Sci.	20(5)	538-544	2013

Sugimoto M, Takahashi S, Gotohda N, Kato Y, Kinoshita T, Shibasaki H, Konishi M.	Schematic pancreatic configuration: a risk assessment for postoperative pancreatic fistula after pancreaticoduodenectomy.	J Gastrointest Surg	17(10)	1744-1751	2013
Kobayashi S, Gotohda N, Kato Y, Takahashi S, Konishi M, Kinoshita T.	Infection control for prevention of pancreatic fistula after pancreaticoduodenectomy.	Hepatogastroenterology	60(124)	876-82	2013
高橋進一郎, 小西 大, 池田公史, 大野 泉, 小林達伺.	Borderline resectable の膵癌とは何か詳しく教えてください(Q&A).	膵・胆道癌 FRONTIER	3巻1号	34-6	2013
Takashima A, Boku N, Kato K, Nakamura K, Mizusawa J, Fukuda H, Shirao K, Shimada Y, Ohtsu A.	Survival prolongation after treatment failure of first-line chemotherapy in patients with advanced gastric cancer: combined analysis of the Japan Clinical Oncology Group Trials JCOG9205 and JCOG9912.	Gastric Cancer. [Epub ahead of print]			2013
Ohtsu A, Ajani JA, Bai YX, Bang YJ, Chung HC, Pan HM, Sahmoud T, Shen L, Yeh KH, Chin K, Muro K, Kim YH, Ferry D, Tebbutt NC, Al-Batran SE, Smith H, Costantini C, Rizvi S, Lebwohl D, Van Cutsem E.	Everolimus for Previously Treated Advanced Gastric Cancer: Results of the Randomized, Double-Blind, Phase III GRANITE-1 Study.	J Clin Oncol.	31(31)	3935-43	2013
Yamada Y, Boku N, Nishina T, Yamaguchi K, Denda T, Tsuji A, Hamamoto Y, Konishi K, Tsuji Y, Amagai K, Ohkawa S, Fujita Y, Nishisaki H, Kawai H, Takashima A, Mizusawa J, Nakamura K, Ohtsu A.	Impact of excision repair cross-complementing gene 1 (ERCC1) on the outcomes of patients with advanced gastric cancer: correlative study in Japan Clinical Oncology Group Trial JCOG9912.	Ann Oncol.	24(10)	2560-5	2013
Kaneko K, Yano T, Minashi K, Kojima T, Ito M, Satake H, Yajima Y, Yoda Y, Ikematsu H, Oono Y, Hayashi R, Onozawa M, Ohtsu A.	Treatment strategy for superficial pharyngeal squamous cell carcinoma synchronously combined with esophageal cancer.	Oncology	84(1)	57-64	2013
Fuse N, Nagahisa-Oku E, Doi T, Sasaki T, Nomura S, Kojima T, Yano T, Tahara M, Yoshino T, Ohtsu A.	Effect of RECIST revision on classification of target lesions and overall response in advanced gastric cancer patients.	Gastric Cancer	16(3)	324-8	2013

Yano T, Yoda Y, Satake H, Kojima T, Yagishita A, Oono Y, Ikematsu H, Kaneko K.	Radial incision and cutting method for refractory stricture after nonsurgical treatment of esophageal cancer.	Endoscopy.	45(4)	316-9	2013
矢野友規, 小田柿智之, 森本浩之, 依田雄介, 大野康寛, 金子和弘.	【食道表在癌の診断と治療】 食道癌 ESD up-to-date.	日本消化器病学会雑誌.	110(10)	1731-7	2013

Ⅴ．研究成果の刊行物・別刷

Gastric Cancer
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

Yasuhiro Kodera · Kazumasa Fujitani · Norimasa Fukushima · Seiji Ito · Kei Muro · Norifumi Ohashi · Takaki Yoshikawa · Daisuke Kobayashi · Chie Tanaka · Michitaka Fujiwara

Received: 30 April 2013 / Accepted: 22 August 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

Y. Kodera (✉) · D. Kobayashi · C. Tanaka · M. Fujiwara
Department of Gastroenterological Surgery, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya, Aichi 466-8550, Japan
e-mail: ykodera@med.nagoya-u.ac.jp

K. Fujitani
Department of Surgery, Osaka General Medical Center, Osaka, Japan

N. Fukushima
Department of Surgery, Yamagata Prefectural Central Hospital, Yamagata, Japan

S. Ito
Department of Gastroenterological Surgery, Aichi Cancer Center Hospital, Aichi, Japan

K. Muro
Department of Clinical Oncology, Aichi Cancer Center Hospital, Aichi, Japan

N. Ohashi
Department of Gastroenterological Surgery, Aichi Medical University, Aichi, Japan

T. Yoshikawa
Department of Gastroenterological Surgery, Kanagawa Cancer Center, Kanagawa, Japan

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

Published online: 11 September 2013

<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.

Surg Today (2013) 43:1382–1389
DOI 10.1007/s00595-012-0432-1

ORIGINAL ARTICLE

Pulmonary metastasectomy for gastric cancer: a 13-year single-institution experience

Yoshihisa Kobayashi · Takayuki Fukui · Seiji Ito · Kohei Shitara · Simon Ito · Shunzo Hatooka · Tetsuya Mitsudomi

Received: 3 July 2012 / Accepted: 6 September 2012 / Published online: 27 November 2012

Abstract
Purpose Pulmonary metastases from gastric cancer are rare, and the role of surgery is unclear. The purpose of this study was to determine which patients with metachronous metastatic gastric cancer (MGC) might benefit from pulmonary resection.
Methods Between 1998 and 2011, 12 patients underwent 14 pulmonary resections for MGC. We reviewed their clinical courses and evaluated their radiological findings.
Results Solitary pulmonary lesions were identified for 11 metastases, and the remaining three showed multiple pulmonary lesions. Six patients received treatment for the metastases before pulmonary resection. Lobectomy was performed for five lesions and wedge resection was performed for the remaining nine lesions. At the median follow-up time of 23.0 months, four patients were alive without disease, and the median DFS following pulmonary resection was 6.6 months. The overall 5-year survival rate following pulmonary resection was 58.4 %. In a univariate analysis, the number of lesions and the tumor doubling time (TDT) were significant predictors of the DFS, although prior treatment was not a significant predictor of the DFS.
Conclusion Pulmonary resection for MGC might be an effective therapeutic option when there is a solitary metastatic lesion that has a long TDT, even if the patient has been previously treated for metastases.

Keywords Metastatic lung tumor · Pulmonary resection · Metastatic gastric cancer · Tumor doubling time · Tumor disappearance rate

Y. Kobayashi · Simon Ito · S. Hatooka
Department of Thoracic Surgery, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusa-Ku, Nagoya 464-8681, Japan

T. Fukui
Department of Thoracic Surgery, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan

Seiji Ito
Department of Gastroenterological Surgery, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusa-Ku, Nagoya 464-8681, Japan

K. Shitara
Department of Gastrointestinal Oncology, National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwa 277-0882, Japan

T. Mitsudomi (✉)
Department of Thoracic Surgery, Kinki University Faculty of Medicine, 377-2 Ohno-higashi, Osaka-Sayama 589-8511, Japan
e-mail: mitsudom@surg.med.kindai.ac.jp

Introduction

Worldwide, gastric cancer ranks second of all causes of deaths from cancer, with approximately 700,000 confirmed deaths annually. The gastric cancer incidence and death rates vary considerably among racial and ethnic groups, with higher rates in Asian countries than in Western countries [1]. In Japan, approximately 50,000 people die from gastric cancer annually [2].

After a curative resection for gastric cancer, recurrence can develop in a variety of forms: distant, peritoneal or local. The most common site of distant recurrence is the liver, followed by the lungs, brain and bones [3]. Most cases with lung metastases are also associated with metastasis to other organs. In addition, most pulmonary metastases are associated with carcinomatous lymphangitis and malignant pleural effusion [4]. Therefore, the

pulmonary metastasis of a solitary nodule is regarded as extremely rare.

The role of surgical resection for pulmonary metastases of gastric cancer is unclear, whereas there have been some reports of favorable outcomes of colorectal cancer [5] and hepatocellular cancer [6]. Although the standard treatment for metastatic gastric cancer (MGC) is systemic chemotherapy, the clinical outcome has not been satisfactory. Koizumi et al. [7] reported that the median survival is 13.0 months in patients with advanced gastric cancer treated with S-1 plus cisplatin. Kodera et al. [8] reported that the median post-recurrence survival was approximately 1 year in 197 gastric cancer patients at our institution. However, pulmonary resection for selected patients resulted in a relatively favorable clinical outcome, although the study cohorts of all previous reports included a relatively small number of cases and were without a control group [9, 10]. To the best of our knowledge, all of the previous studies reported a maximum of seven patients who underwent pulmonary resection for MGC at each institution [6].

In this study, we reviewed the clinicopathological features of a relatively large number of patients with MGC who underwent pulmonary resection, and evaluated their radiological findings to determine which patients with MGC may benefit from pulmonary resection.

Methods

Patient cohort

Between October 1998 and September 2011, 393 consecutive pulmonary metastasectomies were performed at the Aichi Cancer Center Hospital. We basically used Thomford's criteria as a guideline for performing the resection of pulmonary metastases [11]. The inclusion criteria were as follows: (1) medical status adequate for tolerating pulmonary resection, (2) a controlled primary organ site, (3) no other extrapulmonary metastases, and (4) pulmonary metastasis limited to one lung. Although these criteria were originally proposed for colon cancer, we extended them to gastric cancer.

In this study, we reviewed the clinical courses of 12 patients with MGC who underwent pulmonary resection; seven underwent a gastrectomy for primary gastric cancer at our institution, and the remaining five underwent a gastrectomy at another institution. During the same period, 2,645 consecutive gastrectomies were performed for gastric cancer at our institution, and the incidence of pulmonary resections for MGC was 0.26 % (7/2,645).

Approval for this study was obtained, and the need for individual patient consent was waived by the institutional review board.

Radiological evaluation of the tumors

A contrast-enhanced chest CT was preoperatively performed in each patient. When a patient had multiple lesions, the largest lesion was evaluated. We evaluated the tumor disappearance rate (TDR), the ground glass opacity (GGO) ratio, and the tumor doubling time (TDT) to distinguish MGC from primary lung cancer. TDR was defined as [1 − (maximum diameter of the mediastinal windows/maximum diameter of the lung windows)] × 100 [12].

We scored the GGO ratio by visually estimating the proportion of the GGO component in each tumor, without measuring the diameter. GGO was defined as an area of a slight, homogenous increase in density that did not obscure the underlying vascular markings [13].

TDT was calculated using a modified Schwartz equation of exponential growth [14, 15]. When data from more than two CT examinations were available, the measurements from the first and last examinations were used to calculate the TDT.

CT examinations were performed with the following window settings: lung, a window level of −500 to −700 Hounsfield units (HUs) and a window width of 1,000–2,000 HUs; mediastinum, a window level of 20–60 HUs and a window width of 350–600 HUs.

Pathological diagnosis

The initial stage of gastric cancer was classified using the tumor-node-metastasis classification of the International Union Against Cancer, 7th edition [16]. The histological types were classified according to the Lauren classification as either the intestinal type (well-differentiated) or the diffuse (poorly differentiated) type. The well-differentiated type includes papillary and tubular adenocarcinomas, poorly differentiated medullary carcinoma, and well-differentiated mucinous carcinoma. The poorly differentiated type includes poorly differentiated scirrhous carcinoma, signet ring cell carcinoma, and poorly differentiated mucinous carcinoma [17]. All of the patients in this cohort were diagnosed in the manner described.

Statistical analyses

Statistical calculations were carried out using a statistical software program (JMP version 8.0.2; SAS Institute Inc., Cary, NC, USA). The overall survival (OS) was calculated using the Kaplan–Meier method. The differences between survival curves were analyzed using the log-rank test. Hazard ratios (HRs) in patient subsets were calculated using the Cox proportional hazards model. Differences were considered significant when there was a two-sided p value ≤ 0.05.

Results

Clinicopathological features of patients with metastatic gastric cancer

All patients in this study had metachronous pulmonary metastases. We defined metachronous pulmonary metastases as those that were not detected at the initial staging of gastric cancer. The clinicopathological features of patients with MGC are shown in Table 1. Pulmonary metastases were observed even if the patients were initially classified as stage IA. Tumor differentiation displayed a characteristic tendency, in which all patients had well-differentiated tumors, including the tubular and papillary types. The median disease-free survival (DFS) after initial gastric resection was 16.9 months (range 0.2–49.2 months). For nine patients, the first site of recurrence was the lung. The median interval between the initial gastric resection and the detection of pulmonary metastases was 17.2 months (range 0.2–54.8 months). One patient suffered thoracic empyema caused by an anastomotic leak after gastrectomy. Chest CT was performed during the early postoperative period, and pulmonary metastases were detected by chance. As a result, the DFS after initial gastrectomy was 0.2 months. In this patient, the pulmonary metastases were not detected at the initial staging of gastric cancer, so we regarded them as metachronous.

We reviewed 14 resected pulmonary metastases, including two repeat resections. The clinical courses and prior treatments for metastases are shown in Fig. 1. In total, five patients received chemotherapy and two patients underwent hepatectomy. Among the five patients who received chemotherapy before pulmonary resection, two patients received chemotherapy to treat pulmonary metastases. In the remaining three patients, chemotherapy was indicated to treat peritoneal dissemination in one patient, multiple liver and pulmonary metastases in one patient, and celiac lymph node and pulmonary metastasis in one patient. In our study, the targets of prior treatment were not limited only to extrapulmonary metastases, but also included pulmonary metastases, because all of the patients underwent pulmonary resection after the progression of disease.

Radiological evaluation of pulmonary metastases

Solitary pulmonary lesions were identified for 11 of the 14 metastases, and the remaining three were multiple lesions (Table 2). The median tumor size was 1.6 cm (range 1.0–5.0 cm). The median TDT and TDR were 70.1 days (range 13.6–156.5 days) and 11.2 % (range 0–60 %), respectively. No GGO components were identified using CT for any of the lesions.

Pulmonary metastasectomy

The surgical procedures and subsequent clinical courses of the 12 patients are shown in Table 2. An intraoperative frozen section diagnosis was performed for eight patients, and six were diagnosed with MGC. Only one patient was preoperatively diagnosed with MGC based on a percutaneous lung biopsy. A lobectomy was performed for five lesions for the following reasons: difficulty distinguishing MGC from primary adenocarcinoma of the lung using an

Table 1 The clinicopathological features of the patients with primary gastric cancers

Patient	Age at gastrectomy	Gender	Type of gastrectomy	Pathological stage	Histological type	DFS following gastrectomy (months)	First site of recurrence	Interval between gastrectomy and pulmonary metastases (months)
1	45	Female	Subtotal	IIIA	W/D	28	Lung	28
2	50	Male	Subtotal	IIIA	W/D	35	Lung	35
3	31	Male	Subtotal	IA	W/D	13	Lung	13
4	67	Male	Total	IIIA	W/D	15	Lung	15
5	60	Female	Subtotal	IA	W/D	36	Liver	44
6	62	Male	Subtotal	IA	W/D	35	Liver	55
7	69	Male	Total	IIIA	W/D	49	Lung	49
8	61	Male	Total	IIIA	W/D	5	Lung	5
9	69	Male	Total	IIIB	W/D	18	Lung and celiac LN	19
10	75	Male	Subtotal	IIIC	W/D	12	Lung	12
11	48	Male	Total	IIIB	W/D	6	Lung	6
12	33	Male	Total	IIIA	W/D	0	Lung	0

CT computed tomography, *DFS* disease-free survival, *LN* lymph nodes, *PET* positron emission tomography, *W/D* well differentiated

intraoperative frozen section diagnosis (2 cases), large tumor size (2 cases), and local recurrence in the lung (1 case). No postoperative complications were observed.

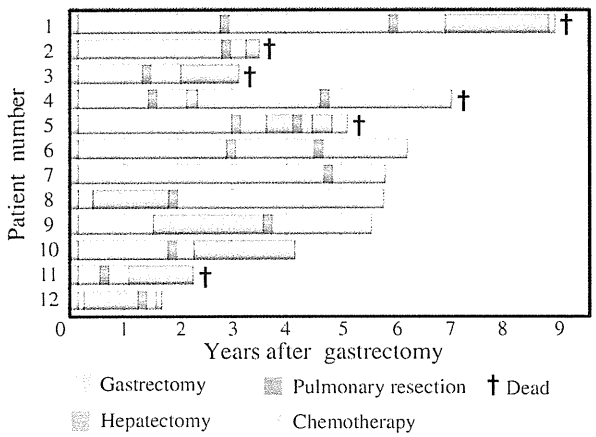

Fig. 1 The clinical courses of 12 patients with pulmonary metastases from gastric cancer. The overall survival following gastrectomy is shown. In total, five patients received chemotherapy, one of whom underwent a hepatectomy, and one patient underwent only a hepatectomy

Seven patients received adjuvant chemotherapy after pulmonary resection; S-1 in three patients, tegafur uracil in one patient, paclitaxel in one patient, docetaxel in one patient, and S-1 and cisplatin plus trastuzumab in one patient.

At the median follow-up time of 23.0 months, four patients (33 %) were alive without disease, three of whom had undergone a wedge resection of the lung. The survival curves are shown in Fig. 2. The median survival time following pulmonary resection was 66.7 months, and the overall 5-year survival rate was 58.4 %. The median survival time following gastrectomy was 85.4 months. A univariate analysis indicated that only the pathological stage of the primary gastric cancer was a significant predictor of the OS following pulmonary resection. The HR for stage III in comparison to stage I/II was 7.56 (95 % CI 0.92–157.37; $p = 0.048$).

The median DFS following pulmonary resection was 6.6 months, and no significant difference was observed between the patients with and without prior treatment. A univariate analysis indicated that the number of lesions and TDT were significant predictors of the DFS (Table 3).

Table 2 Radiological evaluation of the pulmonary metastases and pulmonary metastasectomy

Patient	Number of lesions	Tumor size on CT (cm)	TDT (days)	TDR (%)	Surgical procedure	Pattern of recurrence	DFS following pulmonary resection (months)	OS following pulmonary resection (months)	OS following gastrectomy (months)	Status
1	1	2.2	115	27	Wedge	Local recurrence in lung	34	74	109	Dead
1*	1	2.0	136	20	Lobectomy + ND					
2	2	5.0, 0.8	74	4	Lobectomy + wedge	Liver	4	7	43	Dead
3	1	1.2	38	17	Wedge	Lung, brain	7	21	38	Dead
4	1	1.8	NA	28	Wedge⇒	Peritoneal dissemination, lung	7	67	85	Dead
4*	1	1.3	157	0	Wedge					
5	2	1.0, 0.4	31	60	Wedge	Lung, mediastinal LN, liver, brain	3	11	62	Dead
6	1	4.6	51	4	Lobectomy + ND	Disease free	20	20	76	Alive
7	1	1.1	168	9	Wedge	Disease free	13	13	71	Alive
8	1	3.0	92	20	Wedge	Disease free	47	47	70	Alive
9	1	1.3	70	0	Wedge	Disease free	23	23	68	Alive
10	2	1.3, 0.9	63	11	Wedge	Mediastinal LN	4	28	51	Alive
11	1	2.0	14	NA	Lobectomy + ND	Mediastinal LN, lung, brain	4	21	28	Dead
12	1	1.0	55	60	Wedge	Lung	3	5	19	Alive

*1*4** repeat pulmonary resection, *CT* computed tomography, *DFS* disease-free survival, *LN* lymph nodes, *NA* not available, *ND* nodal dissection, *OS* overall survival, *TDR* tumor disappearance rate, *TDT* tumor doubling time

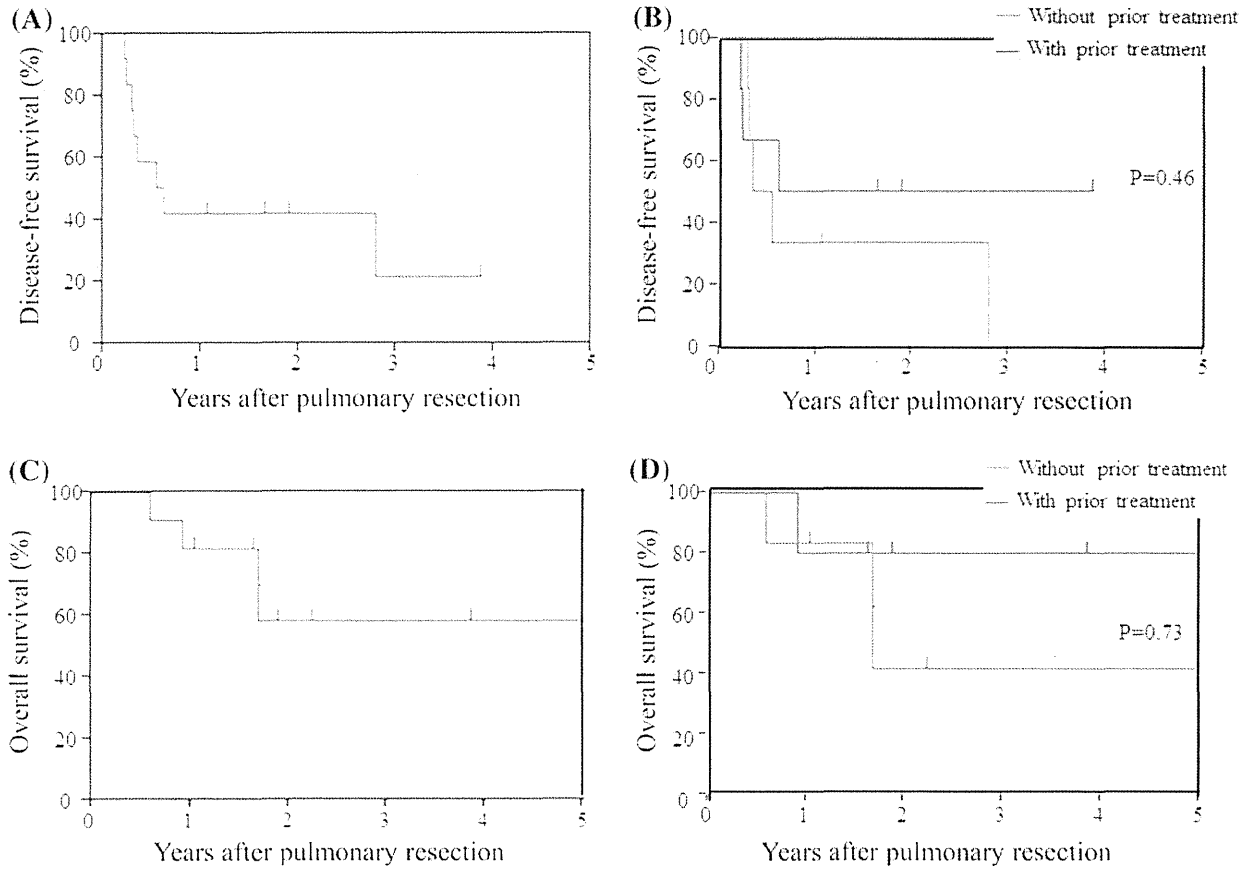

Fig. 2 The disease-free survival in the overall population (**a**) and in patient subgroups stratified according to prior treatment for metastases (**b**). No significant differences were observed between the groups ($p = 0.46$). The overall survival in the total population (**c**) and in patient subgroups stratified according to prior treatment for metastases (**d**). No significant differences were observed between the groups ($p = 0.73$)

Discussion

In this study, relatively favorable survival was observed in patients who underwent a pulmonary resection for MGC, which was similar to previous reports [9]. Our results indicate that pulmonary resection for MGC might be an effective therapeutic option when there is a solitary metastatic lesion, even if a patient has been previously treated for metastases. To the best of our knowledge, this is the first report to evaluate the detailed radiological findings of MGC. Our results indicate that the TDT was also a prognostic factor for the DFS.

Generally, a solitary pulmonary metastasis from gastric cancer is rare. Sakaguchi et al. [18] reported seven pulmonary resections for MGC among 3,219 patients with gastric cancer, and Kanemitsu et al. [19] reported four pulmonary resections for MGC among 3,076 patients with gastric cancer. These incidences of resection were 0.1 and 0.2 %, respectively, which were similar to our data (0.26 %). Previous studies reported relatively favorable outcomes in these patients [9, 10]. In this study, we reviewed not only the clinical outcomes, but also the detailed radiological findings of a relatively large number of MGC patients.

A correlation was previously reported to exist between the histological types of gastric cancer and the clinical features. For example, Adachi et al. [17] reported that patients with well-differentiated types are characterized by old age, male gender, and hematogenous metastasis, whereas patients with poorly differentiated types are characterized by serosal invasion, lymph node metastasis, and peritoneal dissemination. In agreement with that report, all of our cases were classified as well-differentiated type tumors.

According to previous studies, the median DFS following gastrectomy ranged from 11.8 to 21.8 months [20, 21]. The median interval from gastrectomy to pulmonary metastases in our cohort was 17.2 months. After gastrectomy, chest CT was not routinely performed at our institution, and as a result, solitary pulmonary metastases may

Table 3 Results of the univariate analysis for the DFS and OS following pulmonary resection

Baseline and clinical features	Patients	DFS			OS		
		HR	95 % CI	*P*	HR	95 % CI	*P*
Gender							
Male	10	1.00			1.00		
Female	2	1.66	0.22–7.85	0.557	0.78	0.04–5.86	0.833
Age (years)							
<65	7	1.00			1.00		
≥65	5	2.64	0.56–18.71	0.234	3.66	0.54–71.58	0.215
Initial stage of gastric cancer							
I/II	4	1.00			1.00		
III	8	1.81	0.35–8.37	0.435	7.56	0.92–157.37	0.048
DFS following gastrectomy							
<Median (17 months)	6	1.00			1.00		
≥Median (17 months)	6	0.61	0.12–2.81	0.521	0.87	0.11–5.44	0.879
Prior treatment							
No	6	1.00			1.00		
Yes	6	0.58	0.12–2.41	0.458	0.731	0.10–4.42	0.731
Number of lesions							
One	9	1.00			1.00		
Two	3	14.11	1.75–289.83	0.003	4.230	0.50–35.88	0.122
Tumor size on CT							
<Median (16 mm)	6	1.00			1.00		
≥Median (16 mm)	6	0.503	0.10–2.30	0.362	0.889	0.11–7.43	0.907
TDT							
<Median (63 days)	6	1.00			1.00		
≥Median (63 days)	5	0.15	0.01–0.95	0.049	0.31	0.02–2.49	0.293
TDR							
<Median (17 %)	5	1.00			1.00		
≥Median (17 %)	6	1.93	0.37–13.95	0.442	1.495	0.14–32.54	0.743
Surgical procedure							
Wedge resection	8	1.00			1.00		
Lobectomy	4	1.32	0.26–6.05	0.714	3.38	0.53–26.78	0.174

DFS disease-free survival, *OS* overall survival, *TDR* tumor disappearance rate, *TDT* tumor doubling time

not have been detected. Patients with well-differentiated gastric cancer might be good candidates for routine chest CT after a gastrectomy. However, even if routine follow-up chest CT might contribute to the early detection of pulmonary metastases, it is unclear whether it would contribute to a more favorable survival.

Generally, the standard treatment for operable non-small-cell lung cancer is a lobectomy with dissection of the hilar and mediastinal lymph nodes [22]. However, a lobectomy is not always essential for a metastasectomy if a normal margin of the resection is ensured. To determine the appropriate surgical procedure, it is important to preoperatively distinguish MGC from primary lung cancer. Compared with previous reports concerning lung cancer, this study identified some differences in the radiological findings between MGC and primary adenocarcinoma of the lung. We previously evaluated the radiological findings of 140 primary adenocarcinomas of the lung and observed that the median TDR was 33 %, and half of the tumors (69/140) exhibited some GGO components [23]. The median TDT of MGCs was 70 days, which was 258 days shorter than that of the lung adenocarcinomas [24]. The median TDR of our MGCs was 11 %, which was lower than the 33 % observed for lung adenocarcinoma. Takamochi et al. [25] reported a median lung adenocarcinoma TDR of 59 %.

Therefore, a short TDT and a low TDR appear to be useful for preoperatively distinguishing MGC from primary adenocarcinoma of the lung. It is sometimes difficult to distinguish MGC from primary lung cancer using

intraoperative frozen section diagnosis. In our cases, six of eight patients were diagnosed with MGC based on an intraoperative frozen section diagnosis, and the remaining two underwent a lobectomy because the diagnosis was uncertain. Similarly, Tanai et al. [10] reported that two of six MGC patients underwent a lobectomy due to the possibility of primary lung cancer. To select the appropriate surgical procedure, clinicians should suspect MGC based on CT findings and attempt to preoperatively make a diagnosis by CT-guided transthoracic needle aspiration biopsy or transbronchial lung biopsy. If the differentiation is impossible before or during surgery, lobectomy with dissection of the hilar and mediastinal lymph nodes should be performed because there is a possibility that the tumor is primary lung cancer. If the patient can tolerate a two-stage operation and the normal margin of resection is ensured, an initial wedge resection might be another therapeutic option. Of course, an additional lobectomy with dissection of lymph nodes is necessary if the tumor does turn out to be primary lung cancer.

Although we performed metastasectomies based on Thomford's criteria, it was still unclear which patients with MGC might benefit from pulmonary resection. To assess the role of surgery for MGC, it is necessary to compare the outcomes of patients who underwent surgery with those of patients who received standard chemotherapy.

To accomplish this, we first attempted to review the outcomes of patients who received chemotherapy for pulmonary metastases after gastrectomy. During this 10-year period, approximately 1,000 patients received chemotherapy for gastric cancer at our institution. Among them, seven patients had only postoperative lung metastases, three of whom underwent a pulmonary resection after receiving chemotherapy. As a result, only four patients were included in the nonsurgical group. Three of those patients had bilateral multiple lesions, and the remaining patient was unable to tolerate pulmonary resection because of low pulmonary function. Therefore, it is difficult to directly compare the outcomes of the surgical group and the nonsurgical group because the favorable results in the surgical group could undoubtedly reflect a selection bias in terms of the tumor burden and patient condition.

Next, we attempted to determine the prognostic factors present in the surgical group. Pastorino et al. [26] reported that complete resectability, disease-free intervals of 36 months or more, and the number of metastases were independent prognostic factors among 5,206 lung metastasectomies. Similar to the study by Pastorino et al., the number of lesions was a prognostic factor for the DFS in our study. Moreover, we also identified the TDT as a prognostic factor for the DFS.

In conclusion, pulmonary resection for MGC might be an effective therapeutic option when there is a solitary metastatic lesion that has a long TDT, even if the patient has been previously treated for metastases.

Acknowledgments The authors thank the American Journal Experts for editing the English in this manuscript.

Conflict of interest T. Mitsudomi and the co-authors have no conflict of interest to declare.

References

1. Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. J Clin Oncol. 2006;24:2137–50.
2. Vital Statistics Japan (Ministry of Health, Labour and Welfare, National Cancer Center, Japan. http://ganjoho.jp/public/statistics/backnumber/2011_jp.html. Accessed 14 June 2012.
3. Maehara Y, Hasuda S, Koga T, Tokunaga E, Kakeji Y, Sugimachi K. Postoperative outcome and sites of recurrence in patients following curative resection of gastric cancer. Br J Surg. 2000;87:353–7.
4. Nakayama H, Ichinose S, Kato Y, Ito H, Masui K, Kameda Y. Long-term survival after a surgical resection of pulmonary metastases from gastric cancer: report of a case. Surg Today. 2008;38:150–3.
5. Suemitsu R, Takeo S, Kusumoto E, Hamatake M, Ikejiri K, Saitsu H. Results of a pulmonary metastasectomy in patients with colorectal cancer. Surg Today. 2011;41:54–9.
6. Ohba T, Yano T, Yoshida T, Kawano D, Tsukamoto S, Shoji F, et al. Results of a surgical resection of pulmonary metastasis from hepatocellular carcinoma: prognostic impact of the preoperative serum alpha-fetoprotein level. Surg Today. 2012;42:526–31.
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. Kodera Y, Ito S, Yamamura Y, Mochizuki Y, Fujiwara M, Hibi K, et al. Follow-up surveillance for recurrence after curative gastric cancer surgery lacks survival benefit. Ann Surg Oncol. 2003;10:898–902.
9. Kemp CD, Kitano M, Kerkar S, Ripley RT, Marquardt JU, Schrump DS, et al. Pulmonary resection for metastatic gastric cancer. J Thorac Oncol. 2010;5:1796–805.
10. Tanai C, Hamaguchi T, Watanabe S, Katai H, Tochigi N, Shimada Y. A case of long-term survival after surgical resection of solitary pulmonary metastasis from gastric cancer. Jpn J Clin Oncol. 2009;40:85–9.
11. Thomford NR, Woolner LB, Clagett OT. The surgical treatment of metastatic tumors in the lungs. J Thorac Cardiovasc Surg. 1965;49:357–63.
12. Saito H, Kameda Y, Masui K, Murakami S, Kondo T, Ito H, et al. Correlations between thin-section CT findings, histopathological and clinical findings of small pulmonary adenocarcinomas. Lung Cancer. 2011;71:137–43.
13. Suzuki K, Koike T, Asakawa T, Kusumoto M, Asamura H, Nagai K, et al. A prospective radiological study of thin-section computed tomography to predict pathological noninvasiveness in peripheral clinical IA lung cancer (Japan Clinical Oncology Group 0201). J Thorac Oncol. 2011;6:751–6.