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.

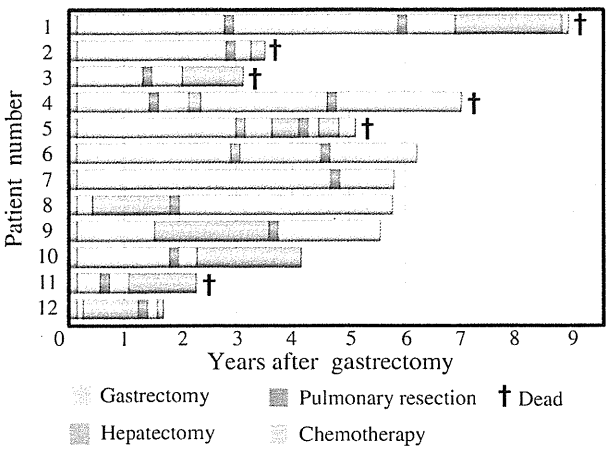

Fig. 1 The clinical courses of 12 patients with pulmonary metastases from gastric cancer. The overall survival following gastrectomy is shown. In total, five patients received chemotherapy, one of whom underwent a hepatectomy, and one patient underwent only a hepatectomy

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

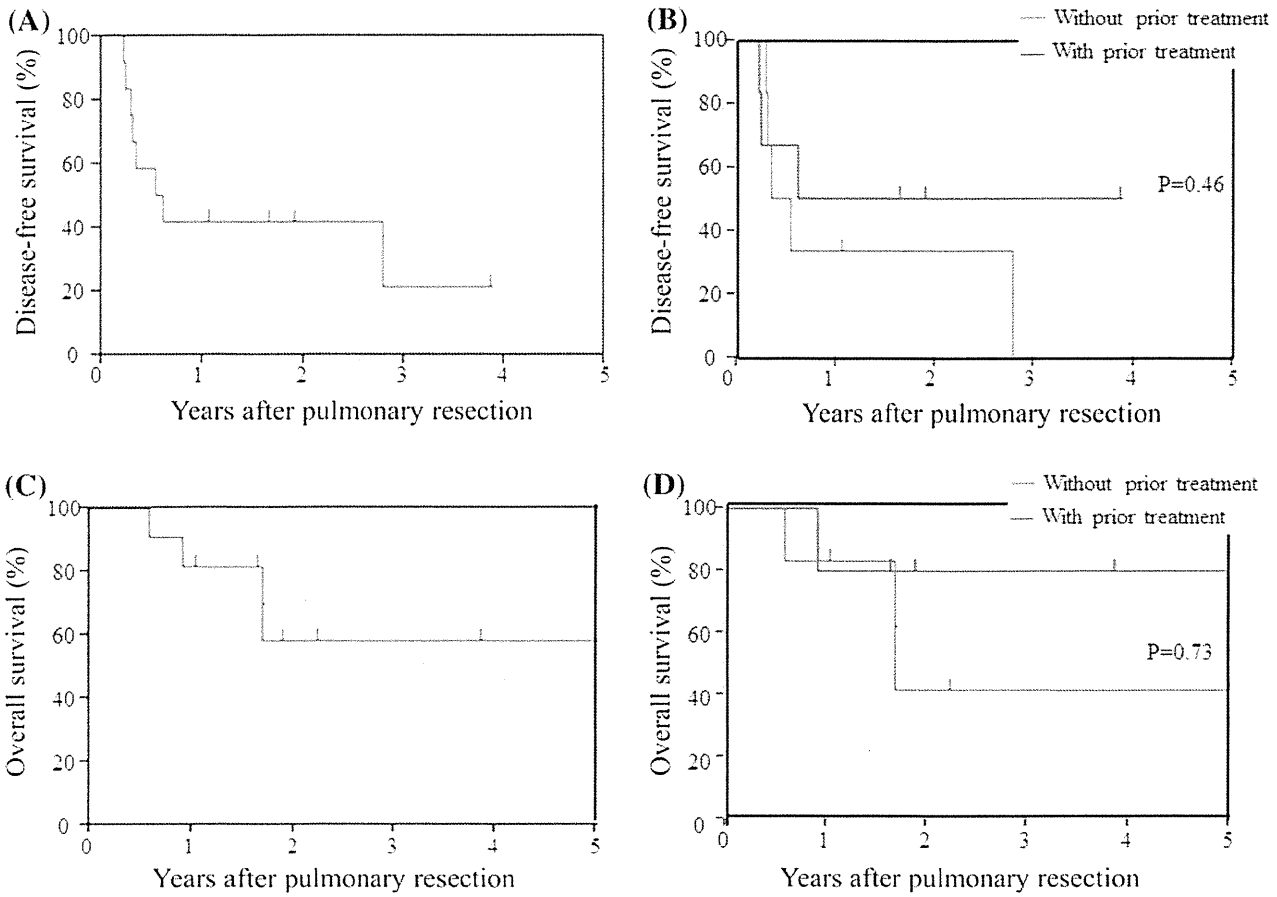

Fig. 2 The disease-free survival in the overall population (**a**) and in patient subgroups stratified according to prior treatment for metastases (**b**). No significant differences were observed between the groups ($p = 0.46$). The overall survival in the total population (**c**) and in patient subgroups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

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

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特集

特集2　胃がん治療の過去と未来

胃がんの集学的治療の近未来

伊藤誠二*1　伊藤友一*1　三澤一成*1　清水泰博*1
木下　平*1

Future Perspective of Multimodality Therapy for Gastric Cancer: Ito S*1, Ito Y*1, Misawa K*1, Shimizu Y*1 and Kinoshita T*1 (*1Department of Gastroenterological Surgery, Aichi Cancer Center Hospital)

Based on the result of ACTS-GC study, S-1 is used as standard postoperative chemotherapy for stage Ⅱ/Ⅲ gastric cancer in Japan, however, the outcome of stage Ⅲ patients is not satisfactory. In Japan, different adjuvant or neoadjuvant clinical trials are tested depending on the tumor stage and clinical condition. In global, the clinical trials of chemoradiation, molecular targeted agents, and triplet chemotherapies are tested in accordance with the standard care of each region. For improving the standard treatment, well-designed clinical trials are essential. Promoting patients accrual and development efficiency is an issue in the future.

Key words: Gastric cancer, Multimodality therapy
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はじめに

2007年に報告されたACTS-GC[1]の結果により，わが国ではStage Ⅱ/Ⅲの胃がん治癒切除症例に対してはS-1の1年間投与が標準治療となっている．一方，pStage Ⅲに対する補助療法の増強や，腹膜播種に対する適切な補助療法，高度リンパ節転移陽性症例に対する補助療法の開発，治療期間やレジメン選択の問題など，今後解決していかなければならないclinical questionも多い．本稿では，胃がんの集学的治療について，現在実施中の臨床試験と予想される方向性について述べる．

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1 国内で実施中の臨床試験

現在わが国においては，胃がんの集学的治療は進行度や病態に応じて異なる開発のアプローチが取られている（図1）．

1 pStage Ⅱに対するOPAS-1 trial (JCOG1104)

pStage Ⅱに対しては，ACTS-GCの結果，術後1年間のS-1投与により，約80％の症例で5年無再発生存が得られることから，手術を先行した上で，より低侵襲の治療として，標準治療である8コースのS-1投与と術後4コースとをRFSをprimary endpointとして比較する第Ⅲ相非劣性試験であるOPAS-1 trialが行われている．

2 pStage Ⅲに対する臨床試験

ACTS-GCの結果から，pStage Ⅲ治癒切除症

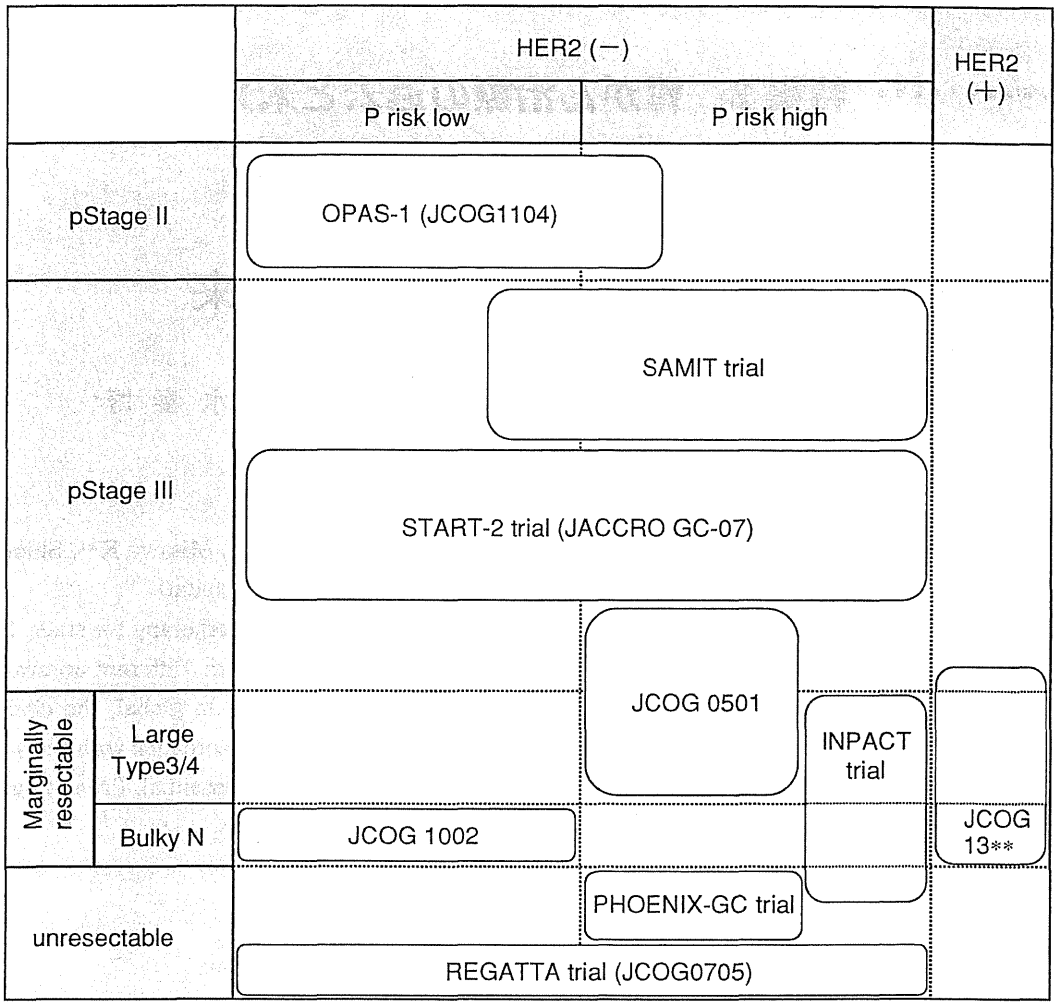

図1　国内で実施中の臨床試験

例に対する標準治療はS-1の1年間投与であるが，subset解析の結果から，pStage Ⅲに対しては，現在の標準治療である術後1年間のS-1投与では治療効果が不十分であり，何らかの併用療法が必要であることは間違いない．pStage Ⅲとは一部対象が異なるが，漿膜浸潤陽性胃癌を対象とした術後補助化学療法の比較試験であるSAMIT study[2]，これは2×2のFactorial Designにより，S-1に対するUFTの非劣性，5-FU系薬剤へのweekly paclitaxel 3コース追加の優越性を見るものであるが，すでに予定の1,500例の症例集積を終了し，まもなくprimary endpointである3年DFSの結果が判明する予定であり，結果が待たれる．

切除不能・再発胃癌において，S-1単剤療法とS-1/DOC併用療法を比較したSTART trial[3]において，S-1/DOC併用療法のTTPが有意に優れていたことを根拠として，pStage Ⅲに対する術後補助化学療法としてのS-1単剤療法とS-1/DOC併用療法を比較する第Ⅲ相試験であるSTART-2 trial（JACCRO GC-07）も，まもなく症例集積が開始される予定である．

3）大型3型/4型胃がんに対するJCOG0501

腹膜播種再発のリスクがきわめて高い大型3型/4型胃がんに対しては，治療完遂割合をprimary endpointとした第Ⅱ相試験の結果[4]を踏まえて，標準治療である手術先行と術前S-1/CDDP併用療法後手術とを全生存期間をprimary endpointとして比較する第Ⅲ相試験であるJCOG0501が行われており，まもなく症例集積が終了する予定である．

4 高度リンパ節転移症例に対するJCOG1002

大動脈周囲リンパ節転移やBulkyリンパ節転移を伴う高度リンパ節転移陽性症例に対しては，稀少疾患であること，手術単独の治療成績がきわめて不良であることから，CPT-11/CDDP NACのJCOG0001[5]，S-1/CDDP NACのJCOG0405[6]と，単アームの第Ⅱ相試験による開発が進められてきた．現在は術前DCS併用療法後に大動脈周囲リンパ節郭清を伴う胃切除を行う第Ⅱ相試験であるJCOG1002が行われており[7]，まもなく症例集積を終了する予定であるが，JCOG0405の段階でsurrogate endpointとして設定されていた治療完遂割合がすでに十分に高い成績を示しており，今後はS-1/CDDP NACを暫定標準とした第Ⅲ相試験に移行する予定である．

5 腹膜播種高危険群/腹膜播種症例に対する腹腔内化学療法

一方，腹膜播種高危険群/腹膜播種症例に対しては，腹膜播種に特化した治療として，腹腔内化学療法が注目されている．腹膜転移高リスク群および比較的軽微な腹膜転移例に限定したIN-PACT trial，腹膜播種陽性胃がんを対象とするPHOENIX-GC trialが症例集積中である．これらの臨床試験においては，腹腔内投与により，腹腔内の薬剤濃度が長期間持続することから，paclitaxelが使われているが，現時点ではpaclitaxelの腹腔内投与は保険適応がないため，高度医療制度のもとに行われている．

6 治癒切除不能進行胃がんに対するREGATTA trial

治癒切除不能進行胃がんに対する胃切除術の意義については，古くから議論されてきたところであるが，この議論に終止符を打つべく，日韓共同の第Ⅲ相試験として，REGATTA trial (JCOG0705) が行われている．これはH1/P1/M1のいずれか1つの非治癒因子のみを有する治癒切除不能進行胃がんを対象として，化学療法単独群と胃切除＋術後化学療法群を比較するもので，現在も症例集積中である．

2 海外で実施中の大規模臨床試験

海外においては，MAGIC trialの結果，3剤併用の術前補助化学療法へと移行している欧州，CLASSIC trialの結果，術後の2剤併用補助化学療法が標準となっている韓国などで，分子標的薬，放射線療法，3剤併用の臨床試験が行われている．

1 MRC-ST03 trial

MAGIC trialの結果，周術期のECF療法が標準となった欧州において，英国の研究グループにより行われている研究で，周術期のECX療法にbevasituzumabを上乗せした効果をみる第Ⅱ/Ⅲ相試験であり，現在も症例集積中である．

2 CRITICS trial

オランダの研究グループにより行われている研究で，術前のECX療法は共通とした上で，術後のECX療法とXP＋RTを比較する第Ⅲ相試験であり，現在も症例集積中である．

3 ARTIST-Ⅱ trial

韓国の研究グループにより行われた，術後XP adjuvantにXeloda＋RTを付加するARTIST trialは，全体では有効性を示せなかった[8]が，N＋症例に限定すれば，有意にDFSが良好とのsub group解析の結果から，現在，RTの有無と，併せて化学療法のregimeとしてS-1とSOXを比較するARTIST-Ⅱ trialの症例集積が始まったところである．

4 PROGIDY trial

同じく韓国の研究グループによる術前化学療法の臨床試験で，術後1年間のS-1療法を共通として，術前のDOSの付加をPFSをprimary enepointとして比較する第Ⅲ相試験で，現在も症例集積中である．

表1　cStageとpStageの乖離（愛知県がんセンター中央病院 2005～2007）

		pStage							
		ⅠA	ⅠB	ⅡA	ⅡB	ⅢA	ⅢB	ⅢC	Ⅳ
cStage	ⅠA	237	27	10	6	1	1	1	1
	ⅠB	12	18	14	11	3	6	1	
	ⅡA	3	9	9	7	7	4	4	4
	ⅡB	2	3	7	8	5	9	8	10
	ⅢA		1	2	2	5	12	5	9
	ⅢB			1	1	1	4	9	3
	ⅢC							2	1

表2　各種臨床試験におけるpT1の混入割合

	Depth in eligibility	Other eligibility	pT1 rate
JCOG9501	≧sMP	cM0 Not Type 4	4.4%
MAGIC trial (surgery arm)	≧cStage Ⅱ (through the submucosa)	cM 0	8.3%
D1 vs D3 Taiwan study	≧cMP	Eso inv. (−) No. 12/16 swelling (−)	23.5%
Dutch trial	?		26.4%

3 今後の方向性

1 術前か術後か？

術前化学療法（Neoadjuvant chemotherapy）には，化学療法のコンプライアンスが高いこと，腫瘍の縮小により，切除が容易となること，切除範囲外に存在する可能性のある微小転移に対し，早期に治療が開始できること，などのメリットがあり，その効果が期待されるが，わが国における，根治性の高い外科手術と術後補助化学療法を組み合わせた治療戦略に対して，術前化学療法が生存成績を向上させるか？という clinical question に対しては，いまだ答えはない．

胃がんの術前 staging は，通常，内視鏡所見，上部消化管造影所見，腹部 CT 所見などに基づいて行われる．胃がんにおいてもっとも頻度の高い腹膜転移の診断は，特に微小なものでは，staging laparoscopy あるいは開腹所見によってしか診断し得ないが，実際には施設の体制等により，すべての症例に staging laparoscopy を行うのは困難なことも多い．さらに，腹部 CT による深達度，リンパ節転移診断の正診率も必ずしも良好とはいえず，clinical stage と pathological stage の間には，一定の乖離が起こりうる（表1）．過去の種々の臨床試験においても，かなりの pT1 の混入が報告されているが（表2）[9~12]，術後補助化学療法の対象とならない pStage Ⅰ の混入頻度が著しく高い場合には，術前化学療法の導入そのものが困難となる．

現在の切除不能再発胃癌に対する標準治療である S-1/CDDP 療法は，消化器毒性が比較的強く，術後に行うことは困難と考えられていたが，regime の工夫[13]と最近の制吐薬の進歩により，術後の S-1/CDDP も必ずしも実現不可能とは言えなくなっている．一方，切除不能/再発胃癌において，S-1/CDDP 療法に対する SOX 療法の非劣性が示され[14]，S-1/CDDP 療法よりも消化器毒性の軽い SOX 療法も補助化学療法の候補のひとつとなってきており，術前か術後か？という問題も，なお未解決のままである．

まもなく症例集積を完遂する JCOG0501 の結

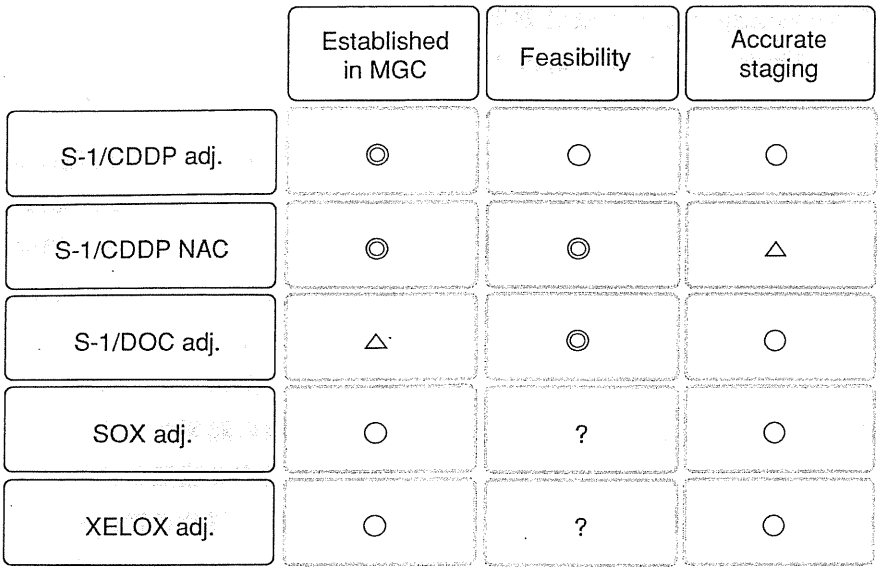

図2　pStage Ⅲに対する各種補助化学療法の候補

果や，現在JCOGにおいて計画中の術前診断の正診率に関する観察研究の結果が待たれるところである．

2 治療 regime は？

切除不能・再発胃癌において確立されたregimeを補助療法に導入する，という原則からいえば，S-1/CDDP療法はpStage Ⅲに対する有力な候補であることは間違いない．一方，その経緯に対して様々な指摘はあるが，updateされた解析においてS-1に対する優越性が示されたSTART trialで使われたS-1/DOC療法も有力な候補であるし，S-1/CDDP療法に対する非劣性が示されたSOX療法，韓国におけるCLASSIC trial[15]において，Stage Ⅲでも有効性を示したXELOX療法も候補となり得る．このように，次の胃がん補助化学療法臨床試験におけるregime選択は，なお混沌としており，XELOX療法や，SOX療法のわが国の患者集団のadjuvant settingにおけるfeasibilityなども参考にしながら，most promising regimeを選択していく必要がある（図2）．

また，術前・術後の治療期間も重要な問題である．術後の治療については，前述のようにOPAS-1 trialにより，pStage Ⅱに対する治療期間の短縮が検討されている．術前化学療法については，多くの研究で2コース程度の化学療法が行われているが，このコース数は，あまり強い根拠に基づいて決められたものではなく，微小転移の根絶，という観点から見れば，もう少し長い期間が必要な可能性もある．化学療法のregimeとコース数を比較するランダム化第Ⅱ相試験であるCOMPASS trial[16]の結果が間もなく明らかとなる予定であり，その結果が期待される．

3 分子標的薬の導入は？

ToGA trial[17]により，Her 2陽性胃がんに対するtrastuzumabの上乗せ効果が証明されたが，現時点では，海外においてもHer 2陽性胃がんに対する補助化学療法の臨床試験は，ドイツの研究グループによる，周術期5-FU/LV/DOC/Oxaliplatinに対するtrastuzumabの上乗せを検討するHerFLOT study，スペインの研究グループによる，周術期XELOXに対するtrastuzumabの上乗せを検討するNEXOH studyなど，第Ⅱ相試験レベルにとどまっている．わが国では，高度リンパ節転移陽性胃がんにおけるHer 2陽性率が高いことに着目し，Her 2陽性の高度リンパ節転移陽性胃がんに対する術前化学療法において，trastuzumabの上乗せを検討する臨床試験がJCOGにおいて企画されている．

英国のMRCでは，周術期補助化学療法とし

て，ECXに対するbevasituzumabの上乗せ効果を見るST03 trialが行われているが，切除不能・再発胃癌においては，有効なbiomarkerのない分子標的薬の多くは，その有効性を示すことができていない．ST03 studyの今後の症例集積，治療成績も期待はされるが，当面はHer2陽性胃がんに対する分子標的薬の導入が中心になるものと思われる．

4 Radiationの導入は？

INT-0116 study[18]により，手術単独に対する術後のCRTがsurvival benefitを示したが，リンパ節郭清度がわが国とはかなり異なること，手術単独群の治療成績が十分ではないことから，わが国ではその結果はガイドライン及び日常診療には反映されていない．韓国におけるARTIST trial[8]は，D2以上のリンパ節郭清を伴う治癒切除胃癌を対象としたもので，その結果が期待されたが，残念ながらCRTの有効性を示すことはできなかった．しかしながら，現在進行中のCRITICS trialやARTIST-II trialの結果によってはradiation therapyの導入も考慮されるべきかもしれない．

5 IPの導入は？

胃癌再発の半数は腹膜再発を伴っており，腹膜再発の制御は胃癌治療成績の向上のためにきわめて重要である．抗癌剤の腹腔内投与は，腹膜の微小転移に対し，高濃度の抗癌剤を直接接触させることができるため，より効果的な投与方法と考えられており，米国では卵巣癌の患者を対象にpaclitaxelの腹腔内投与が広く行われている．胃癌においても，過去，抗癌剤腹腔内投与の効果を示唆するpilot的な研究結果が国内学会を中心に報告されたが，標準治療との大規模な比較試験は行われてこなかった．現在，Phoenix-GC, INPACTの2つの比較試験が行われており，この結果によっては腹腔内化学療法も重要な集学的治療のオプションとなる可能性がある．

まとめ

ACTS-GC studyの結果により，わが国ではStage II/IIIの胃癌に対しては手術と術後補助化学療法による集学的治療が標準となったが，その後5年以上にわたって，標準治療を変えるような新たなevidenceは出ていない．標準治療を改善していくためには，適切にデザインされた大規模臨床試験の結果が必須であり，長い時間と多大な労力を要する困難な作業ではあるが，今後も，忍耐強く臨床試験を続けていくと共に，どのように症例集積ペースを上げていくか，どのように効率的に開発を進めていくか，が重要な課題であろうと考える．

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ORIGINAL ARTICLE – THORACIC ONCOLOGY

Clinicopathological Features and Prognostic Factors of Adenocarcinoma of the Esophagogastric Junction According to Siewert Classification: Experiences at a Single Institution in Japan

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ABSTRACT

Background. Treatment strategy for adenocarcinoma of the esophagogastric junction (AEG) remains controversial. The aims of this study are to evaluate results of surgery for AEG, to clarify clinicopathological differences according to the Siewert classification, and to define prognostic factors.

Methods. We retrospectively analyzed 179 consecutive patients with Siewert type I, II, and III AEG who underwent curative (R0) resection at the National Cancer Center Hospital East between January 1993 and December 2008.

Results. Patients with AEG were divided according to tumor: 10 type I (5.6%), 107 type II (59.8%), and 62 type III (34.6%). Larger, deeper tumors and nodal metastasis were more common in type III than type II tumors. No significant differences were seen in 5-year survival rates among the three types: type I (51.4%), type II (51.8%), and type III (62.6%). Multivariate analysis showed that depth of tumor and mediastinal lymph node metastasis were independent prognostic indicators. The recurrence rate for patients with mediastinal lymph node metastasis was 87.5%. The risk factors for mediastinal lymph node metastasis were length of esophageal invasion and histopathological grade.

Conclusions. Mediastinal lymph node metastasis and tumor depth were significant and independent factors for poor prognosis after R0 resection for AEG. Esophageal invasion and histopathological grade were significant and independent factors for mediastinal lymph node metastasis.

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In Western countries, incidence of adenocarcinoma of the esophagogastric junction (AEG) is rapidly increasing. This trend has not occurred in Eastern countries.[1–4] Siewert's classification into three types of tumors, proposed in 1996, defines AEG tumors according to the location of the tumor center in relation to the anatomical esophagogastric junction (EGJ) line. Characteristics differ for each type, making the classification useful for determining optimal treatment strategies.[5]

Surgical resection with lymphadenectomy is the mainstay of treatment for AEG. Though AEG consists of tumor arising from the proximal stomach and distal esophagus, there are various surgical options. Factors that surgeons need to consider are whether the esophagectomy should be subtotal or distal and if it should be combined with total or proximal gastrectomy via transhiatal or transthoracic approach. Currently, Siewert's classification is used to determine treatment strategy, but the approach is still controversial. An optimal surgical strategy has yet to be established.

The distribution of the three types of AEG differs markedly between Eastern and Western countries. In Eastern countries, type II and III cancers are more common than type I. In Western countries, however, the distribution is nearly equal between the three types of adenocarcinoma.[3,6,7] Only a few studies have addressed clinicopathological features of AEG in Japan, and most involved only type II and III cancers.[8,9] One reason for this might be that type I patients at most Japanese institutions are likely to be treated by the

esophageal surgical group, while those with type II or III are treated by the gastric surgical group. In such facilities, there can be two separate databases.

In the present study, we examined databases for both esophageal and gastric cancer to clarify the distribution and clinical outcomes of AEG at a single cancer center hospital in Japan. The aims of this study are to evaluate clinicopathological features and oncological outcomes of AEGs according to Siewert's subtype, and to define predictive factors for prognosis.

PATIENTS AND METHODS

Patients

We retrospectively reviewed a database of 179 consecutive patients with AEG (Siewert's type I, II, and III) who underwent curative surgical resection at the National Cancer Center Hospital East between January 1993 and December 2008. Type III tumors were defined as subcardial cancers infiltrating the EGJ, whose epicenter is within the proximal 5 cm of the stomach; therefore, subcardial cancers not extending into the EGJ were excluded from this study. Follow-up periods ranged from 1.5 to 173 months (median 33 months). Overall survival analysis contained all deaths, including those due to an unrelated cause. Exclusion criteria included prior history of surgery for gastric cancer or gastric stump cancer.

Before surgery, all patients underwent chest radiographs, an abdominal ultrasonography, or a computed tomography (CT) scan for tumor staging. Upper gastrointestinal endoscopy was performed and barium swallows taken. From these findings, we determined preoperative Siewert's subtype and surgical approach. The choice of operation was based on preoperative diagnosis and estimated length of esophageal invasion. The intent was complete surgical resection.

All surgical specimens were delivered to the pathology department after the operations. We took photographs and sketched the appearance of each one and made a detailed record. Pathologists recorded the margin of the tumor, the esophagogastric junction (EGJ), and the tumor center. Based on the pathological and preoperative findings, we measured the distance from the EGJ to the tumor center, then to the oral top of the tumor. This was defined as the length of esophageal invasion. We then recorded the Siewert's type for all specimens.

Data were evaluated based on gender, age, tumor appearance, tumor size, length of esophageal invasion, operative methods, perioperative chemotherapy, tumor pathology and lymph node staging, histological grading, lymphovascular and venous invasion, and recurrence patterns. We also compared these data among the AEG subtypes.

The UICC 7th tumor-node-metastasis (TNM) classification of esophageal cancer was used to describe tumor progression and histopathological grading.[10] The macroscopic appearances of the tumors were divided according to Borrmann's classification.[11] Number of regional lymph node stations was categorized according to the Japanese classification of gastric carcinoma.[12]

Statistical Analyses

Statistical analyses were performed by chi-square test and *t*-test. Cumulative survival rates were generated by the Kaplan–Meier method. Survival curves were compared with the log-rank test. Significant factors were identified by univariate analysis, and further examined by multivariate analysis. Multivariate regression analysis was carried out using the Cox hazards model. All statistical analyses were performed using SPSS (SPSS Inc., Tokyo, Japan) for Windows. *p*-Value < 0.05 was considered statistically significant.

RESULTS

Patient Population and Tumor Characteristics

Ten of 179 patients had type I (5.6%) tumors, 107 had type II (59.8%), and 62 had type III (34.6%). The characteristics of the patients and surgical approaches are presented in Table 1. There were no significant differences in age and gender between the three subtypes. The superficial tumor type was observed in 40% of patients with type I cancer, whereas it was less common in types II (19.6%) and III (9.7%). In types II and III, Borrmann 3 was the most common macroscopic appearance (42.1% and 56.5%). Borrmann 4 was generally rare, but observed mainly in type III (11.3%).

Tumor size was significantly larger in type III (81.6 mm) than types I (55.1 mm) and II (45.2 mm).There was no significant difference between types II and III in the length of esophageal invasion. The longest esophageal invasion was 70 mm in type I. In types II and III, the longest invasions were 55 mm and 50 mm, respectively. Surgical approaches varied by tumor type. The transthoracic technique was used most often on type I (80%) tumors, which included 50% of right thoracic and 50% of left thoracoabdominal approaches. In contrast, the transhiatal approach was common in type III. In type II, 34.6% of operations were performed transthoracically and 65.4% transhiatally. In type I, subtotal esophagectomy (50%) and proximal gastrectomy with distal esophagectomy (40%) were common, whereas total gastrectomy with distal esophagectomy was common in types II (71.0%) and III (90.3%). We saw no significant difference in the rate of patients who received perioperative chemotherapy.

TABLE 1 Baseline characteristics of patients and surgical approaches (n = 179)

Classification	Type I (n = 10)	Type II (n = 107)	Type III (n = 62)	p-value
Age (years)	63.5 (48–83)	65 (30–86)	65.5 (31–62)	NS
Male:female	7:3	85:22	41:21	NS
Macroscopic type				
Superficial	4 (40%)	21 (19.6%)	6 (9.7%)	
Borrmann 1	2 (20%)	7 (6.5%)	3 (4.8%)	
Borrmann 2	2 (20%)	29 (27.1%)	11 (17.7%)	
Borrmann 3	1 (10%)	45 (42.1%)	35 (56.5%)	
Borrmann 4	0	1 (0.9%)	7 (11.3%)	
Unclassifiable	1 (10%)	4 (3.7%)	0	
Tumor size (mm)	45.2 ± 5.1	55.1 ± 2.6	81.6 ± 4.5	<0.001(II/III)
				0.317 (I/II)
Esophageal invasion (mm)	46.3 ± 4.3	15.3 ± 1.1	13.6 ± 1.4	<0.001(II/III)
				0.359 (II/II)
Approaches				
Transthoracic	8 (80%)	37 (34.6%)	10 (16.1%)	0.005 (I/II)
(Right:left)	(4:4)	(7:30)	(0:10)	0.010 (I/III)
Transhiatal	2 (20%)	70 (65.4%)	52 (83.9%)	
Subtotal esophagectomy	5 (50%)	8 (7.5%)	0	
Total gastrectomy with distal esophagectomy	1 (10%)	76 (71.0%)	56 (90.3%)	
Proximal gastrectomy with distal esophagectomy	4 (40%)	23 (21.5%)	6 (9.7%)	
Neoadjuvant chemotherapy	0	0	3 (4.8%)	NS
Adjuvant chemotherapy	1 (10%)	13 (12.1%)	17 (27.4%)	NS

NS not significant

The pathological characteristics of the patients are presented in Table 2. Patients with type III classification had significantly deeper tumors than those with types I and II. Additionally, the frequency of lymph node metastasis was significantly higher in those with type III rather than type II tumors. Similarly, higher tumor stage was observed in those in the type III class than types I and II. The incidence of mediastinal lymph node metastasis was significantly higher in type I patients than in types II and III. Histopathological grading was significantly poorer in type III than type II tumors.

Patterns of Lymph Node Metastasis

Table 3 presents the frequency of lymph node metastasis as well as 5-year survival for each lymph node station. Using these results, we computed the index of estimated benefit from lymph node dissection (IEBLD) using the formula: IEBLD = frequency of metastasis to each lymph node station (%) × 5-year survival rate of metastatic cases (%)/100.[13]

These values are shown in Table 3. The rate of metastasis was high in lymph node stations 1, 2, 3, and 7, and their IEBLDs were also high (7.0–21.0). The metastatic rate of mediastinal lymph nodes was 22.2% in total (40.0% in type I, 21.3% in type II, and 12.5% in type III), and the 5-year survival rate was 17.6%. The IEBLD of the mediastinal lymph node was 3.9, the same as that for the 16th station.

Survival Outcomes

The survival curves for each Siewert type are shown in Fig. 1. We observed no significant difference in overall survival by subtypes. Five-year survival rates were 51.4% in type I, 51.8% in type II, and 62.6% in type III. The median follow-up period of survivors was 33 months. We used Kaplan–Meier survival analysis to assess 11 prognostic factors: age (<65 versus >65 years), gender, tumor size (<60 mm versus >60 mm), Siewert type (type I or II versus III), depth of tumor (T1–2 versus T3–4), existence of lymph node metastasis, existence of mediastinal lymph node metastasis, length of esophageal invasion (<20 mm versus >20 mm), degree of venous and lymphovascular invasion, and histopathological grade (G1, 2 versus G3, 4) (Table 4).

Univariate analysis showed that the following seven factors were associated with survival: depth of tumor

TABLE 2 Pathological characteristics of patients ($n = 179$)

Classification	Type I ($n = 10$)	Type II ($n = 107$)	Type III ($n = 62$)	p-value
UICC 7th T category				
T1a	0	1 (0.9%)	1 (1.6%)	
T1b	4 (40%)	23 (21.5%)	2 (3.2%)	(T1/T2~)
T2	2 (20%)	14 (13.1%)	7 (11.2%)	0.213 (I/II)
T3	3 (30%)	32 (29.9%)	18 (29.0%)	<0.001 (I/III)
T4a	1 (10%)	34 (31.8%)	29 (46.8%)	0.003 (II/III)
T4b	0	3 (2.8%)	5 (8.1%)	
UICC 7th N category				
N0	2 (20%)	43 (40.2%)	12 (193%)	(N0/N1~)
N1	5 (50%)	23 (21.5%)	12 (193%)	0.210 (I/II)
N2	3 (30%)	9 (8.4%)	16 (253%)	0.960 (I/III)
N3	0	32 (29.9%)	22 (355%)	0.005 (II/III)
UICC 7th TNM stage				
IA	1 (10%)	20 (18.7%)	2 (32%)	
IB	1 (10%)	7 (65%)	0	
IIA	0	4 (3.7%)	2 (32%)	(Stage I, II/III, IV)
IIB	3 (30%)	13 (12.1%)	7 (113%)	0.586 (I/II)
IIIA	3 (30%)	14 (131%)	10 (161%)	0.023 (I/III)
IIIB	1 (10%)	4 (3.7%)	7 (113%)	0.002 (II/III)
IIIC	1 (10%)	32 (29.9%)	24 (38.7%)	
IV	0	13 (12.1%)	10 (161%)	
Histopathological grade				
G1/2	6 (60%)	71 (66.4%)	31 (50.0%)	0.685 (I/II)
G3/4	4 (40%)	36 (33.6%)	31 (50.0%)	0.557 (I/III)
				0.036 (II/III)

($p = 0.003$), lymph node metastasis ($p = 0.002$), mediastinal lymph node metastasis ($p = 0.001$), esophageal invasion >20 mm ($p = 0.023$), venous invasion ($p = 0.005$), lymphovascular invasion ($p = 0.022$), and histopathological grade 3/4 ($p = 0.042$). Subsequent multivariate analysis confirmed that only depth of tumor ($p = 0.001$) [95% confidential interval (CI), 1.62–6.16] and mediastinal lymph node metastasis ($p = 0.001$) (95% CI, 1.74–5.92) were significant and independent prognostic indicators after curative resection for AEG (Table 4).

We performed multivariate analysis of seven factors to determine the risk for mediastinal lymph node metastasis. These included age (<65 versus >65 years), gender, tumor size (<60 mm versus >60 mm), Siewert type (types I and II versus III), depth of tumor (T1–2 versus T3–4), length of esophageal invasion (<20 mm versus >20 mm), and histopathological grade (G1, 2 versus G3, 4). We found that esophageal invasion (>20 mm) ($p < 0.001$) (95% CI, 4.28–108.2) and histopathological grade 3/4 ($p = 0.035$) (95% CI, 1.10–15.40) were significant and independent risk factors for mediastinal node metastasis (Table 5).

TABLE 3 Frequency of lymph node metastasis as well as 5-year survival for each station

Lymph node station	Rate of lymph node metastasis (%)				5-Year survival rate (%)	IEBLD
	Type I	Type II	Type III	Total		
1	30.0	42.1	58.1	46.9	44.8	21.0
2	20.0	20.6	24.2	27.9	33.7	9.4
3	30.0	23.4	43.5	36.9	43.4	16.0
4sa	0.0	5.6	14.5	8.4	25.7	2.2
4sb	0.0	2.8	8.1	4.5	0.0	0.0
4d	0.0	1.2	10.2	4.9	0.0	0.0
5	0.0	3.5	3.5	3.5	0.0	0.0
6	0.0	2.6	3.6	3.0	0.0	0.0
7	40.0	22.4	14.5	21.8	32.3	7.0
8	0.0	6.7	13.6	9.3	30.4	2.8
9	0.0	13.3	8.6	10.8	13.8	1.5
10	0.0	3.9	12.3	7.4	30.0	2.2
11p	0.0	14.0	15.5	14.4	38.7	5.6
11d	0.0	6.3	7.1	6.5	0.0	0.0
12	0.0	0.0	3.3	1.5	0.0	0.0
16	0.0	12.2	20.7	15.1	22.7	3.4
Mediastinal	40.0	21.3	12.5	22.2	17.6	3.9

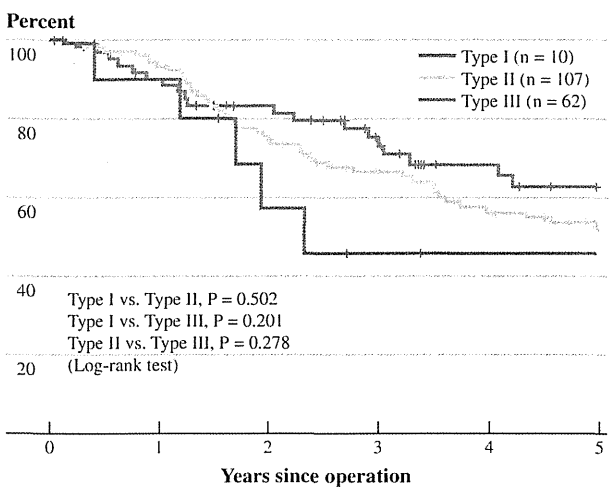

FIG. 1 Survival curves in each type of cancer (type I, II, or III). We saw no significant difference in overall survival by subtype

DISCUSSION

In this single-institution series of 179 AEGs in Japan, the proportions of types I, II, and III cancers were 5.6%, 59.8%, and 34.6%, respectively. After R0 resection, 5-year survival rates were 51.4% for type I, 51.8% for type II, and 62.6% for type III tumors. Mediastinal lymph node metastasis and a deeper tumor were significant and

TABLE 4 Univariate and multivariate predictors of overall survival

	No.	Univariate analysis *p*-value	Multivariate analysis	
			p-value	Hazard ratio (95% CI)
Age (years)				
<65	93	0.826		
≥65	86			
Sex				
Male	133	0.685		
Female	46			
Tumor maximal size (mm)				
<60	89	0.113		
≥60	90			
Siewert type				
Type I, II	117	0.255		
Type III	62			
UICC 7th N category				
T1–2	54	0.003	0.001	3.16 (1.62–6.16)
T3–4	125			
UICC 7th N category				
N0	57	0.002	0.242	
N1–3	122			
Mediastinal nodes				
Negative	163	0.001	0.0001	3.21 (1.74–5.92)
Positive	16			
Para-aortic nodes				
Negative	168	0.018	0.066	
Positive	11			
Esophageal invasion (mm)				
<20	124	0.023	0.351	
≥20	55			
Venous invasion				
Negative	33	0.005	0.395	
Positive	146			
Lymphovascular invasion				
Negative	67	0.022	0.182	
Positive	112			
Histopathological grade				
G1/2	71	0.042	0.363	
G3/4	108			

TABLE 5 Multivariate analysis of mediastinal lymph node metastasis

	Hazard ratio (95% CI)	*p*-value
Esophageal invasion ≥20 mm	21.5 (4.28–108.2)	<0.001
Histopathological grade G3/4	4.12 (1.10–15.10)	0.035

independent factors for poor prognosis. In patients with mediastinal lymph node metastasis, recurrence rate was quite high (87.5%). Although curative surgery is the primary treatment modality for AEG, survival rates in patients with poor prognostic factors are unsatisfactory.

This study shows a significantly higher prevalence of types II and III AEGs in Japan compared with Western nations. Nonetheless, data indicate that the prevalence of AEG is rising in Western countries, but not in the East.[1–4] The distribution of the three types of AEGs also differs between West and East, with type I tumors less frequent in the latter.[3,6,7] Most papers from Japanese institutions have reported on types II and III; data on all three types are scant.[7–9]

To establish the prevalence and trend of types I, II, and III in Japan, we reviewed the database of gastric and esophageal cancers in our hospital. Of the three types, 5.6% were type I, 59.8% type II, and 34.6% type III. These findings are similar to reports from Hasegawa et al. in Japan, Bai et al. in China, and Fang et al. in Taiwan.[6,7,14] The lower frequency of type I AEGs in Eastern countries may be explained by a lower prevalence of gastroesophageal reflux, obesity, and *Helicobacter pylori* infection.

In the present study, we saw no significant differences in age and gender among the three types of cancers, but clinicopathological features differed. Type III cancers were more aggressive than types I and II. Tumors were larger and deeper, with a higher rate of lymph node metastasis. This trend has been reported by other groups. Conversely, we observed no significant difference in rates of tumor progression between types I and II cancers. This may indicate that type III tumors include cardia cancer centered 2–5 cm below the EGJ that enlarges, and then subsequently infiltrates the EGJ. It may also be more difficult to detect early cancer around the cardia than in the distal esophagus by screening endoscopy.

The UICC 6th TNM classification did not include integrated staging criteria for AEGs. They were staged according to criteria for esophageal or gastric cancer.[15] The UICC 7th TNM classification, however, defined AEG as a new disease category to be classified according to staging for esophageal cancer.[10] Here we classified and staged 179 AEGs according to the latest criteria. However, surgeons should note that most type II and III tumors have features of subcardial gastric cancer, which originates in the gastric mucosa. Type I cancer is closely associated with intestinal epithelial metaplasia (Barrett's epithelium). Type II cancer may arise from either Barrett's epithelium or junction epithelium. The etiology of type III relates to the gastric mucosa, in particular an association with *Helicobacter pylori* or atrophic gastritis.

In this study, Barrett's epithelium accounted for 90% (9/10) of type I adenocarcinomas, 10.3% (11/107) of type II, and 0% of type III cancers. These results are similar to those of Siewert and Stein (76.9%, 9.8%, and 2%).[5] Our data suggest that the origins of AEG tumors are somewhat alike in Western and Eastern countries. However, several studies out of Japan disagree. Yuasa et al. found that prevalence of Barrett's epithelium in type II cancer is lower in Japan than in Western countries.[9] Okabayashi et al. suggested that the occurrence of superficial carcinoma of the cardia had no relationship to Barrett's epithelium in Japan.[3]

In the present study, 5-year survival rates were similar among the three types of cancers: 51.4% for type I, and 51.8% and 62.6%, respectively, for types II and III. Although our series only included R0 resection, these outcomes seem better than those from prior reports. Data from Western countries indicate that type I has the best prognosis, followed by types II and III.[5] Conversely, reports from Asian countries show no obvious differences between subtypes. Fang et al. reported similar survival rates between types II and III (59.6% versus 63.5%).[6] The reasons for this discrepancy are unclear. One explanation may be that surgeons in Asian countries are more accustomed to surgery for gastric cancer or D2 dissection, leading to better outcomes in type III tumors.

We also evaluated the frequency of lymph node metastasis as well as 5-year survival for each positive station. To estimate the therapeutic value of lymph node dissection, we calculated IEBLD.[13] Our data show that lymph node stations 1, 2, 3, and 7 (around the cardia, the lesser curvature of the proximal stomach, and root of the left gastric artery) had high rates of metastasis. Nonetheless, patients had relatively good prognoses, suggesting that dissections of the abdominal lymph nodes are vital to AEG patients.

Our data also show that IEBLD were relatively low in dissection of numbers 8 and 9 lymph nodes (around the common hepatic and the celiac artery). However, they suggest benefit from D2 lymphadenectomy in patients with type II and III tumors. At the least, data suggest the need to remove the lymph nodes around the root of the left gastric surgery (no. 7). The rate of mediastinal lymph node metastasis was 22.2% in the present study, but its IEBLD was low, as was the 5-year survival rate of patients (17.6%). This figure is consistent with previous reports. The JCOG 9502 trial (phase III) clearly showed that a thoracoabdominal approach with radical mediastinal node resection did not improve survival in patients with type II or III adenocarcinomas. It did, however, increase surgical risk.[16] Our data may support the results of that trial.

Multivariate analysis showed that depth of tumor and mediastinal lymph node metastasis were independent prognostic indicators after R0 resection for AEG. In our series, 16 patients had mediastinal lymph node metastasis, and the recurrence rate for these patients was 87.5% (14/16), whereas it was 38% (62/163) in those without mediastinal lymph node metastasis. Recurrence patterns in these patients were seven nodal (five para-aortic, two cervical), three hematogenous (liver, bone, brain), three peritoneal, and one anastomotic. Mediastinal lymph node metastasis at operation indicates more systemic spread of cancer cells, and that dissection may not improve the survival rate.

Further multivariate analysis showed that esophageal invasion and histopathological grade were independent risk factors for mediastinal lymph node metastasis. Patients with swollen mediastinal lymph nodes detected by preoperative CT scan are likely to have poor prognosis. Even in patients without swollen mediastinal lymph nodes, those with relatively long esophageal invasion (>20 mm) or poorly differentiated histological type may also have poor prognosis.

Radical surgery is the primary modality in the treatment of AEG cancer. However, long-term outcome in patients with mediastinal lymph node metastasis is still unsatisfactory. For such patients, effective perioperative chemotherapy may improve their prognosis. Phase III trials of perioperative chemotherapy for gastric cancer have been conducted in Japan (ACTS-GC) and the UK (MAGIC trial); both demonstrated significant improvement in survival with perioperative chemotherapy.[17,18] However, only 26% of patients in the MAGIC trial had AEG, and numbers are not available in the ACTS-GC study. A phase III trial to evaluate perioperative chemotherapy in AEG patients is needed. Their poor prognosis creates an urgent need for this research. Therefore, future studies to evaluate the efficacy of perioperative chemotherapy should focus on treatment of AEGs.

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