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ORIGINAL ARTICLE

Significant prognostic factors in patients with Stage IV gastric cancer with special reference to the curability of surgery

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Abstract
Purposes The purpose of this study was to determine an effective treatment strategy for patients with Stage IV gastric cancer.
Methods We analyzed the significant prognostic factors in 74 patients who underwent surgery between 1989 and 2005, and were finally determined to have Stage IV gastric cancer. These patients were classified as curability A ($n = 0$), B ($n = 29$) and C ($n = 45$) according to the criteria outlined by Japanese Gastric cancer society. Anti-tumor drugs were used after surgery in some cases. There were 32 patients who received either no treatment or an oral anti-tumor drug, and 42 patients who received new chemotherapeutic regimens.
Results According to a univariate analysis, the postoperative mean survival times were significantly different; tumor size $\leq$12 cm, a tumor without lymphatic involvement, more than D2 lymphadenectomy, and classification as curability B were favorable prognostic factors. The multivariate analysis revealed that tumor size, lymphadenectomy and curability were independent prognostic factors. In curability B patients, venous involvement was an independent prognostic factor. In curability C patients, both the tumor size and postoperative chemotherapy affected their prognosis.
Conclusions In patients with curable Stage IV gastric cancer, at least a D2 gastrectomy to reduce the absolute volume of tumor cells, followed by adjuvant chemotherapy, may be essential to improve their prognosis. In incurable cases, aggressive new chemotherapeutic regimens should be the treatment of choice for the prolongation of survival.

Keywords Gastric cancer · Stage IV · Prognostic factor

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Introduction

Although the mortality rate of gastric cancer has decreased in recent years, cancer of the stomach remains the second most common malignancy in the world. From 1991 to 1995, the 5-year survival rate of patients with gastric cancer who underwent surgical resection in Japan remained at a relatively high level of 66.6 % [1], however, the prognosis of patients with stage IV gastric cancer (those with liver metastasis, peritoneal metastasis, widespread lymph node metastasis, or the involvement of surrounding tissue beyond the stomach wall) is still extremely poor [2, 3], with an overall 2-year survival rate of 10 % [2].

Although various treatments, including surgery or postoperative aggressive chemotherapy, radiation and immunological therapies have been applied for the prolongation of survival time for such patients [4, 5], the prognosis remains poor and the standard treatment has not yet to be clarified. Therefore, an effective treatment strategy is needed to sustain or improve the patient quality of life and to improve the medical economics.

There have been a few recent studies on prognostic factors in gastric cancer performed using a multivariate analysis [2, 6]. However, most of these studies only evaluated the prognosis of gastric cancer of overall patients, with all stages of the disease. Little is known about the

prognostic factors in patients with stage IV cancer, especially from the standpoint of the curability of the disease.

We analyzed the prognosis of stage IV gastric cancer patients by the multivariate analyses in order to identify the independent factors that influence the postoperative survival. The most effective treatment strategy with special reference to the curability of surgery was also determined.

Materials and methods

Patients

This study was based on the data obtained from 74 patients with stage IV gastric cancer who had undergone gastrectomy between July 1989 and June 2005 at Fukuoka City Hospital. These patients were followed-up after the operation, and the ending date of the follow-up was September 2007. Thirteen patients survived and 61 patients died of the original disease. We treated the deaths due to causes other than gastric cancer as censored cases, and the deaths related to surgery (those who died within 30 days after the operation) as the objects for the analysis. These patients were classified into two categories, one consisted of curability B patients ($n = 29$), the other included curability C patients ($n = 45$). The definition of Stage IV, the classification of curability (Table 1) and other available information, including the tumor size, gross form, tumor differentiation, depth of tumor invasion (T), lymph node metastasis (N), distant metastasis (M), lavage cytology (CY), lymph node dissection and lymphatic/venous involvement were determined according to the criteria outlined by Japanese Gastric cancer society [7]. A peritoneal cytological examination at the time of laparotomy was done in 32 of 74 patients, since this study included some cases that were treated before the introduction of this procedure. With regard to postoperative chemotherapy, two groups were evaluated: (1) patients who received either no treatment or an oral anti-tumor drug, such as tegafur including UFT, 5′FUDR, etc., postoperatively (group A) and (2) those who received the new therapeutic regimen, S-1, an oral anti-tumor fluoropyrimidine containing tegafur, 5-chloro-2,4-dihydropyrimidine and potassium oxonate, a taxane (docetaxel or paclitaxel), calcium folinate (LV), fluorouracil (5-FU), methotrexate (MTX) and irinotecan hydrochloride (CPT-11) (group B). These new chemotherapeutic regimens were used during the postoperative clinical course either after surgery or at the time of recurrence. Patients treated with neoadjuvant chemotherapy using these drugs were not included in this study.

Table 1 Classification of the curability after surgery

Surgical curability	T	N × D	H	P	M	PM × DM
Curability A	T1 or T2	More than N0 × D1 or More than N1 × D2	H0	P0	M0	No cancer invasion Residual cancer cells within resection stump
Curability B	Other than curability A and C patients					
Curability C	Certain remaining cancer					

T depth of tumor invasion, *N* extent of lymph node metastasis, *M* other distant metastasis, *H* hepatic metastasis, *P* peritoneal metastasis, *M* other distant metastasis, *PM* proximal margin, *DM* distal margin

Statistical analysis

The following 12 items were included in the univariate statistical analyses: tumor size, gross form, tumor differentiation, TNM classifications, CY, lymphatic/venous involvement, lymph node dissection, curability of surgery and administration of postoperative chemotherapy. With respect to these 12 variables, the survival rates were determined by means of the Kaplan–Meier method, and differences in survival were determined by the log-rank test. For the purpose of a sequentially multivariate analysis, the Cox proportional hazards model was used to define the most pertinent prognostic factors.

Results

Patients' characteristics

The relationship between the reason why the patients was diagnosed with Stage IV disease and the curability of surgery is shown in Table 2. Of the 74 patients, there were 52 with a single prognostic factor, 19 with two factors and 3 with three factors, respectively. Most of the patients who were classified to have curability B status had a single prognostic factor, except for two cases with two factors, one of whom underwent liver resection for liver metastases (H1, P1), and one of whom underwent D3 lymph node dissection for a potential N3 lesion (N3, P1).

With regard to the indications for surgery in those with curability C classification, no patients underwent resection with curative intent. There were 22 patients who received palliative gastrectomy for the removal of pyloric stenosis, and nine for the prevention of tumor bleeding. In the remaining 14 patients, resection was performed with the intention of allowing postoperative chemotherapy to be more effective (reduction surgery).

Table 2 The reason for the classification as Stage IV, and the curability of surgery

Prognostic factor	Number of cases	Curability B ($n = 29$)	Curability C ($n = 45$)
One factor			
T4	9	6	3
N3	12	8	4
H1	7	3	4
P1	19	6[a]	13
M1 (N4)	5	4	1
Two factors			
T4, N3	5	0	5
T4, P1	1	0	1
N3, P1	4	1[a]	3
H1, N3	6	0	6
H1, P1	3	1[a]	2
Three factors			
T4, N3, H1	3	0	3

T4 tumor invasion of adjacent structures, *N3* metastasis to group 3 lymph nodes, *H1* liver metastasis, *P1* peritoneal metastasis, *M1* other distant metastasis

[a] There were a small number of disseminated metastases localized in the omentum, which were histologically confirmed and completely removed by means of omentectomy

Table 3 The type of surgery performed and postoperative complications in curability B patients

	Number of patients
Gastrectomy	
Total	21
Distal	8
Removal of invaded organs	
Transverse colon (T4)	2
Pancreas (T4)	4
Liver (H1)	4
Lymph node dissection	
D1	2
D2	15
D3	12
Post-operative complications	
Suture leakage	2
Abscess in the abdomen	3
Pancreatic fistula	3

D1 removal of primary nodes, *D2* removal of primary and secondary nodes, *D3* removal of primary, secondary and tertiary nodes

Table 3 shows the data on the type of surgery and postoperative complications. In curability B patients, gastrectomy with complete removal of invaded organs was carried out in 10 of 29 (34.5 %) patients. Gastrectomy with sufficient lymph node dissection (D2 or D3) was performed in 27 (91.3 %) patients. With regard to postoperative major complications, there was suture leakage in two, an abscess in the abdomen in three and a pancreatic fistula in three patients. The suture leakage was minor in these patients. Although the abscesses and pancreatic fistulas were probably due to the lymph node dissection (D2 or D3), there were no fatal complications resulting in surgical death. A complication occurred in 8 of 29 patients (27.5 %) in the curability B group, as opposed to 4 of 45 (8.9 %) in the curability C group.

Univariate analysis

Table 4 shows the postoperative mean survival time (MST) according to various prognostic factors. In all of the patients with stage IV resected gastric cancer, no statistically significant differences were found with regard to the gross form, tumor differentiation, TNM classifications, CY, venous involvement, and use of postoperative chemotherapy. In contrast, a significant correlation with the prognosis was found for tumor size ($\leq$12 vs. >12 cm), lymphatic involvement (ly0/1 vs. 2/3), lymph node dissection (D0/1 vs. $\geq$2) and curability of the operation (B vs. C). The favorable prognostic factors were found to be a tumor size $\leq$12 cm, ly0/1, $\geq$D2 lymph node dissection, and curability B, while the unfavorable factors were a tumor size >12 cm, ly2/3, D0/1 lymph node dissection and curability C. The 5-year survival rate was 12 % in all resected cases, 35.7 % in curability B patients and 0 % in curability C patients (Fig. 1). There was a significant difference between curability B and C patients ($p < 0.0001$). Table 5 shows data with regard to the curability B patients. The postoperative MST was significantly different only in cases with venous involvement (v0/1 vs. v2/3, MST: 1614 vs. 518 days). For the other factors, there was no statistically significant difference in the postoperative MST. In curability C patients, the postoperative MST was significantly different based not only on the tumor size ($\leq$12 vs. >12 cm vs. unclear, MST: 392 vs. 110 vs. 199 days), but also based on postoperative chemotherapy (group A vs. group B, MST: 232 vs. 402 days) (Table 6).

Multivariate analysis

Table 7 shows the results of the multivariate analysis of various factors identified to be significant in the univariate analysis. In all cases, the tumor size, lymph node dissection and curability of the operation proved to be the independent prognostic factors ($p < 0.01$). In the curability B patients, venous involvement was an independent prognostic factor ($p < 0.05$). In curability C patients, the tumor size ($p < 0.001$) as well as postoperative chemotherapy

Table 4 The results of a univariate analysis of various prognostic factors in patients with Stage IV gastric cancer (all patients who underwent resection)

Variable	No. of patients (%)	Postoperative MST (days)	1-year survival (%)	*p*
Tumor size				
≤12 cm	60 (81.1)	612	62.7	0.0108
>12 cm	8 (10.8)	505	12.5	
Unclear	6 (8.1)	270	16.7	
Gross form				
Types 1 and 2	26 (35.1)	684	65.4	NS
Types 3 and 4	41 (55.4)	722	42.6	
Unclassified	7 (9.5)	462	57.1	
Tumor differentiation				
Differentiated	27 (36.5)	561	55.6	NS
Undifferentiated	47 (63.5)	796	52.2	
pT				
T0 ~ 3	40 (54.1)	586	56.4	NS
T4	34 (45.9)	656	47.1	
pN				
N0 ~ 2	40 (54.1)	890	61.5	NS
N3	34 (45.9)	506	44.1	
M				
M0	56 (75.7)	599	58.2	NS
M1	18 (24.3)	513	38.9	
Lymphatic involvement				
ly0,1	31 (41.9)	1086	74.2	0.0061
ly2,3	43 (58.1)	430	38.1	
Venous involvement				
v0,1	52 (70.3)	856	58.8	NS
v2,3	22 (29.7)	406	40.9	
Lymph node dissection				
D0,1	26 (35.1)	274	20	<0.0001
≥D2	48 (64.9)	1037	70.8	
Curability				
Curability B	29 (39.2)	1340	75.9	<0.0001
Curability C	45 (60.8)	349	36.4	
Postoperative chemotherapy				
Group A	32 (43.2)	1001	45.3	NS
Group B	42 (56.8)	518	59.5	
Lavage cytology (CY)				
Negative (CY0)	19 (25.7)	947	57.9	NS
Positive (CY1)	13 (17.6)	411	23.1	
Not evaluated	42 (56.7)	607	59.5	

MST mean survival time, *pT* pathological depth of tumor invasion, *pN* pathological extent of lymph node metastasis, *M* other distant metastasis, *Group A* patients who received no treatment or an oral anti-tumor drug such as Tegafur, *Group B* patients who received new therapeutic regimens, such as TS-1, MTX, CPT, CDDP, TXL, etc

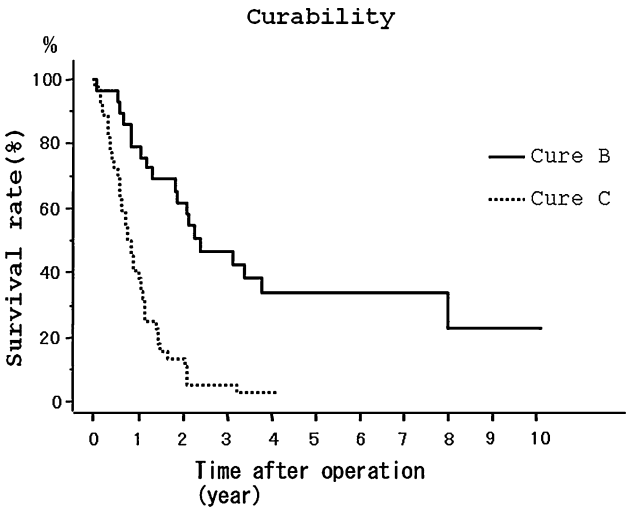

Fig. 1 The survival curves of patients with stage IV cancer. The *dotted line* represents curability C patients and the *heavy line* represents curability B patients

Table 5 The results of a univariate analysis of various prognostic factors in patients with Stage IV gastric cancer (curability B patients)

Variable	No. of patients (%)	Postoperative MST (days)	1-year survival (%)	*p*
Tumor size				
≤12 cm	23 (79.3)	943	87	NS
>12 cm	4 (5.4)	899	25	
Unclear	2 (6.9)	411	0	
Gross form				
Types 1 and 2	14 (48.3)	912	92.9	NS
Types 3 and 4	14 (48.3)	1383	57.1	
Unclassified	1 (3.4)	1097	0	
Tumor differentiation				
Differentiated	8 (27.6)	900	75	NS
Undifferentiated	21 (72.4)	1340	71.4	
pT				
T0 ~ 3	14 (48.3)	895	78.6	NS
T4	15 (51.7)	1142	73.3	
pN				
N0 ~ 2	16 (55.2)	1609	81.3	NS
N3	13 (44.8)	760	69.2	
M				
M0	23 (79.3)	919	78.3	NS
M1	6 (20.7)	837	50	
Lymphatic involvement				
ly0,1	16 (55.2)	1602	87.5	NS
ly2,3	13 (44.8)	703	53.8	

Table 5 continued

Variable	No. of patients (%)	Postoperative MST (days)	1-year survival (%)	*p*
Venous involvement				
v0,1	19 (65.5)	1614	84.2	0.0221
v2,3	10 (34.5)	518	60	
Lymph node dissection				
D0,1	2 (6.9)	701	50	NS
≥D2	27 (93.1)	1392	74.1	
Postoperative chemotherapy				
Group A	15 (51.7)	1702	80	NS
Group B	14 (48.3)	736	71.4	
Lavage cytology (CY)				
Negative (CY0)	11 (37.9)	1345	63.6	NS
Positive (CY1)	0 (0)	–	–	
Not evaluated	18 (62.1)	1053	92.9	

MST mean survival time, *pT* pathological depth of tumor invasion, *pN* pathological extent of lymph node metastasis, *M* other distant metastasis, *Group A* patients who received no treatment or an oral anti-tumor drug such as Tegafur, *Group B* patients who received new therapeutic regimens, such as TS-1, MTX, CPT, CDDP, TXL, etc

Table 6 The results of a univariate analysis of various prognostic factors in patients with Stage IV gastric cancer (curability C patients)

Variable	No. of patients (%)	Postoperative MST (days)	1-year survival (%)	*p*
Tumor size				
≤12 cm	37 (82.2)	392	44.4	<0.0001
>12 cm	4 (8.9)	110	0	
Unclear	4 (8.9)	200	0	
Gross form				
Types 1 and 2	12 (26.7)	402	25	NS
Types 3 and 4	27 (60)	317	34.7	
Unclassified	6 (13.3)	356	50	
Tumor differentiation				
Differentiated	19 (42.2)	410	42.1	NS
Undifferentiated	26 (57.8)	296	32	
pT				
T0 ~ 3	26 (57.8)	409	44	NS
T4	19 (42.2)	273	21.1	
pN				
N0 ~ 2	24 (53.3)	350	43.5	NS
N3	21 (46.7)	340	28.6	
M				
M0	33 (73.3)	364	40.6	NS
M1	12 (26.7)	275	25	

Table 6 continued

Variable	No. of patients (%)	Postoperative MST (days)	1-year survival (%)	*p*
Lymphatic involvement				
ly0,1	15 (26.7)	427	53.3	NS
ly2,3	30 (66.7)	303	27.6	
Venous involvement				
v0,1	33 (73.3)	358	40.7	NS
v2,3	12 (26.7)	293	25	
Lymph node dissection				
D0,1	43 (95.6)	345	33.4	NS
≥D2	2 (4.4)	436	50	
Postoperative chemotherapy				
Group A	17 (37.8)	232	12.5	0.0393
Group B	28 (62.2)	402	50	
Lavage cytology (CY)				
Negative (CY0)	8 (17.8)	400	62.5	NS
Positive (CY1)	13 (28.9)	168	0	
Not evaluated	24 (53.3)	383	42.9	

MST mean survival time, *pT* pathological depth of tumor invasion, *pN* pathological extent of lymph node metastasis, *M* other distant metastasis, *Group A* patients who received no treatment or an oral anti-tumor drug such as Tegafur, *Group B* patients who received new therapeutic regimens, such as TS-1, MTX, CPT, CDDP, TXL, etc

($p < 0.05$) were important factors that affected their prognosis.

Sequential Kaplan–Meier survival curves according to these prognostic factors were generated. In the curability B patients, a favorable prognosis was seen in those with venous involvement. On the contrary, in curability C patients, a favorable prognosis was noted for those with a tumor size ≤12 cm (Fig. 2) and in those treated by aggressive postoperative chemotherapy consisting of a new regimen (Fig. 3).

Discussion

Although various treatments, including surgery, have been performed for patients with stage IV gastric cancer in clinical studies, the optimal treatment strategy still remains controversial. In the current study, we performed the multivariate analyses in order to clarify the significant factors influencing the prognosis of patients with stage IV gastric cancer. We found the tumor size and lymph node dissection, as well as curability, to all be independent prognostic factors in all cases.

Table 7 A summary of the multivariate analyses of various prognostic factors in patients with Stage IV gastric cancers

Characteristics	Odds ratio	95 % CI	*p*
All patients			
Tumor size (≤12 vs. >12 cm)	5.325	(2.416–14.702)	0.0072
Lymph node dissection (D0,1 vs. ≥D2)	2.972	(1.447–6.104)	0.0030
Curability (B vs. C)	5.498	(2.209–14.912)	0.0003
Curability B patients			
Venous involvement (v0/1 vs. v2/3)	4.944	(1.018–14.011)	0.0228
Curability C patients			
Tumor size (≤12 vs. >12 cm)	6.238	(5.354–9.243)	0.0001
Postoperative chemotherapy (group A vs. group B)	2.156	(1.058–6.419)	0.0321

Group A patients who received no treatment or an oral anti-tumor drug such as Tegafur, *Group B* patients who received new therapeutic regimens, such as TS-1, MTX, CPT, CDDP, TXL, etc

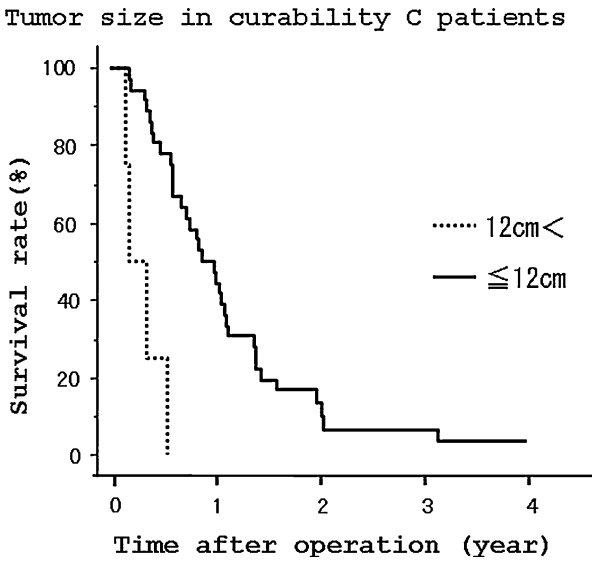

Fig. 2 The survival curves in curability C patients with stage IV cancer. The *dotted line* represents patients who had tumors >12 cm, and the *heavy line* represents patients who had tumors ≤12 cm

Concerning tumor size, there is general agreement that the prognosis is poorer in proportion to the increase of tumor size [8–11]. Shiraishi et al. [10] reported that gastric cancer with a diameter of more than 10 cm tends to be characterized by poor differentiation, invasiveness, serosal invasion and extragastric lymph node metastasis. Baba et al. [11] showed that the prognosis of advanced gastric cancer was poorer according to the increase in the width of serosal invasion, the influence of which was not as evident in expanding type carcinoma, but was for the infiltrative type carcinoma. These findings are similar to our results, in

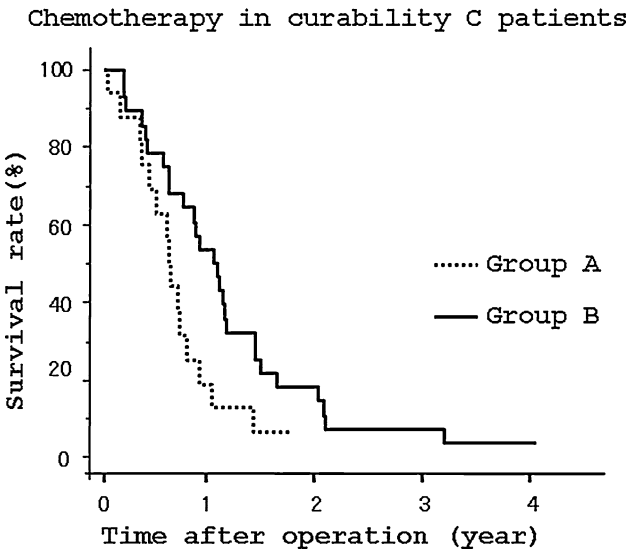

Fig. 3 The survival curves in curability C patients with stage IV cancer. The *dotted line* represents patients who received no treatment or an oral anti-tumor drug, such as Tegafur (group A), and the *heavy line* represents patients who received new therapeutic regimens, such as S-1, MTX, CPT-11, CDDP, or TXL (group B)

which there was a significantly lower survival rate in stage IV tumors with a diameter greater than 12 cm than in those with a diameter smaller than 12 cm. A possible explanation may be that patients with an unfavorable prognosis should actually be classified as belonging to the group with large tumors and they have a tendency for metastatic spread due to exfoliation of cancer cells from the serosa of the stomach into the peritoneal cavity, resulting in the occurrence of disseminated metastasis [9–11].

There still remains a problem whether lymph node dissection for stage IV gastric cancer is effective [2, 11–13]. Previous studies indicated a potential survival benefit for a D2 or more dissection [3, 14–16], and Baba et al. [14] suggested the usefulness of D2 lymph node dissection for advanced gastric cancer, even after non-curative gastrectomy. Korenaga et al. [3] observed the prolongation of survival in patients with stage IV gastric cancer who had undergone resection, especially for those with tertiary nodal involvement (N3) or directly invaded organs (T4) alone. These findings suggested that sufficient lymph node dissection of primary (N1), and secondary (N2) nodes, with or without complete removal of tertiary (N3) nodes may be necessary in potentially curable patients with stage IV gastric cancer. In the subsequent Japanese randomized control study (JCOG9501) [17], D3 extended lymph node dissection was not shown to be useful, with a higher evidence level. In that report, there were no significant differences between D2 lymphadenectomy and D2 lymphadenectomy plus para-aortic nodal dissection (PAND) in terms of the postoperative complications and 5-year overall

survival rate. However, the authors of that study noted that D2 lymphadenectomy plus PAND would have resulted in a better survival rate if there were more patients with para-aortic node metastasis. In the current study, we found that a D2 or greater dissection was an independent prognostic factor when the multivariate analyses were performed ($P = 0.0030$). In light of these findings, it is reasonable to consider that the effectiveness of D3 extended lymph node dissection may be controversial, but that at least D2 lymph node dissection is needed to reduce the absolute number of tumor cells in the body and for prolonging survival, provided that there is no evidence of incurable factors, such as peritoneal dissemination or liver metastasis. Although these findings are encouraging, it must be stressed that the number of patients was small, and there may be a higher occurrence of postoperative complications due to these aggressive procedures.

In curability B patients, we found that only venous involvement proved to be a prognostic factor in the multivariate analysis. The reason may be derived from the fact that potentially complete removal of metastatic nodes was performed by means of aggressive lymph node dissection in such curative cases.

In the curability C patients in our study, we found that a tumor size less than 12 cm was a favorable factor. However, our data did not always indicate the superiority of stage IV patients, including those with or without surgery. According to the Gastric Cancer Treatment Guidelines 2010 outlined by Japanese Gastric Cancer Association, the treatment for Stage IV (any T/N, M1) can be selected among chemotherapy, radiotherapy, palliative surgery, and/or best supportive care [4]. Several investigators have recently reported that chemotherapy, such as S-1 plus cisplatin (CDDP), showed a remarkably high response rate and good results in far advanced carcinoma of the stomach [18, 19]. In addition, recently advocated drugs, such as paclitaxel (TXL) and CPT-11, are expected to become the global standard regimen, because these drugs seem to be effective not only for unresectable or recurrent cases but also as postoperative chemotherapy for patients with stage IV gastric cancer [20–23]. Koizumi et al. [18] reported the improved prognosis of patients treated with S-1 plus the CDDP regimens (MST 13 months). Similar findings were made by Ohtsu et al. [24] (MST 7.4 months), with the rate being similar to that following palliative resection, as previously reported (MST 8.1–10.2 months) [25–27]. Therefore, our present policy is that when surgery would obviously result in palliation due to the presence of various incurative factors, aggressive chemotherapy seems preferable to non-curative gastrectomy for the curability C patients, except for those with pyloric stenosis or tumor bleeding. In comparison to the effect of postoperative chemotherapy in this study, however, it must be stressed that patients treated with either surgery alone or with an oral anti-tumor drug were considered to be the classical treatment group, and the number of patients was small. Since neo-adjuvant chemotherapy is reported to be effective for reducing widespread nodal involvement and eliminating disseminated metastatic foci or micro-metastases in the peritoneal cavity [28, 29], the subsequent gastric resection following this recently advocated treatment is recommended only when widespread metastatic lesions in the peritoneal cavity were eliminated and potentially curative surgery seems feasible.

The current study revealed some new information with regard to the effective treatment strategy for patients with stage IV gastric cancer. In potentially curable cases, at least a D2 gastrectomy to reduce the absolute volume of tumor cells, followed by adjuvant chemotherapy, may be needed to improve patient's prognosis. In incurable cases, we emphasize that postoperative chemotherapy of the new regimens comprising S-1, CPT-11, CDDP and TXL will lead to the prolongation of the survival time. Judgment will have to be reserved regarding whether the potentially curable stage IV patients should be treated by radical surgery or with new chemotherapeutic regimens alone (without surgery), until the outcome of these patients is elucidated by a future randomized controlled study.

Conflict of interest Shinohara S and the co-authors have no conflict of interest to declare.

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