Risk Factors for Recurrence After Curative Conversion Surgery for Unresectable Gastric Cancer

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Abstract. *Aim: To evaluate the recurrence risk after curative conversion surgery following chemotherapy for initially unresectable gastric cancer. Patients and Methods: We retrospectively analyzed clinicopathological and postoperative recurrence-free survival (RFS) data for 34 patients who underwent curative conversion surgery. Results: Recurrence was observed in 17 (50%) patients, with a median time to recurrence of 22 months (range=1-98 months). In nine (53%) patients with recurrence, the pattern was consistent with their initial metastatic disease. According to multivariate Cox regression analysis, initial clinical T4b disease (cT4b; odds ratio=6.44, 95% confidence interval=1.59-23.9; p=0.01) was the only significant independent risk factor affecting RFS. Pathological T4a or T4b disease was recorded in five-out of six (83%) patients with cT4b. Conclusion: Initial cT4b disease appears to predict recurrence in patients with initially unresectable gastric cancer treated with curative conversion surgery. Effective use of additional chemotherapy may be required for patients with this risk factor.*

Gastric cancer is the fourth most prevalent cancer and the second leading cause of cancer-related death worldwide (1). It is generally diagnosed in the late stages, and exhibits a high frequency of invasion and metastasis. The prognosis of patients with unresectable gastric cancer characterized by invasion or metastasis is usually very poor. These patients are currently not considered candidates for surgery and are usually offered systemic chemotherapy. The phase III SPIRITS trial established S-1 plus cisplatin as a standard first-line chemotherapy regimen for unresectable or metastatic gastric cancer in Japan (2). Our previous phase II trial noted that S-1 plus paclitaxel, an alternative drug combination, has similar efficacy (3). Several novel combined chemotherapy regimens occasionally allow conversion of initially unresectable gastric cancer to resectable cancer. Additional (conversion) surgery after a response to chemotherapy results in long-term survival in certain patients (4-6). We have previously reported that patients with unresectable gastric cancer obtained survival benefit from combination chemotherapy, such as S-1 plus cisplatin or paclitaxel, and subsequent conversion surgery (7). Postoperative chemotherapy after non-curative surgery using the same chemotherapeutic regimen, as administered preoperatively, is often performed in clinical practice. Although understanding the recurrence risk after potentially curative surgery is helpful for determining the optimal treatment, only limited information is available from previous studies (4-6). In the present study, we selected patients with initially unresectable gastric cancer who underwent curative conversion surgery following chemotherapy and retrospectively examined their clinicopathological and postoperative survival data in order to evaluate the recurrence risk after curative surgery.

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Patients and Methods

Patients. We retrospectively reviewed a database of 163 patients with unresectable gastric cancer who underwent combination chemotherapy with S-1 plus cisplatin or paclitaxel at Saitama Medical Center of Saitama Medical University or Gunma University Graduate School of Medicine from February 2003 to July 2014. We performed conversion procedures in 43 out of the 163 patients, 34 of which resulted in curative surgery. The study was approved by the local Ethics Committee of Saitama Medical Center of Saitama Medical University (Approval No. 1059).

Table I. *Preoperative characteristics of 34 patients with gastric cancer who underwent curative conversion surgery.*

Preoperative characteristic	
Median age (range), years	63 (42-76)
Gender, n	
Male/female	25/9
Performance status, n	
0/1	31/3
Location, n	
U/M/L	9/17/8
Macroscopic types, n	
Type2/3/4	8/22/4
Histological grading, n	
G12/3	6/11/17
Clinical tumor depth, n	
T2/3/4a/4b	1/10/17/6
Clinical nodal stage, n	
N0/12/3	3/9/10/12
Peritoneal metastasis, n	
P0/1	24/10
Hepatic metastasis, n	
H0/1	30/4
Distant metastasis, n	
M0/1	12/22
Peritoneal cytology, n	
Negative/positive	33/1
Number of noncurative factors, n	
1/2	28/6
First-line chemotherapy	
S-1+cisplatin/S-1+paclitaxel	21/13
Median number of cycles (range)	4 (2-17)
Toxicity grade, n	
Grade 1/2/3/4	23/5/5/1
Response, n	
Partial response/stable disease	28/6
Type of gastrectomy, n	
Distal/total	10/24

U: Upper; M: middle; L: lower.

Table II. *Postoperative characteristics of 34 patients with gastric cancer who underwent curative conversion surgery.*

Postoperative characteristic	
Histological tumor size (mm)	
Median (range)	64 (2-130)
Pathological response, n	
Grade 0/1a/1b/2	3/9/12/10
Pathological tumor depth, n	
ypT2/3/4a/4b	8/12/11/3
Pathological nodal stage, n	
ypN0/1/2/3	10/11/11/2
Pathological stage, n	
ypStage I/II/III	2/15/17
Second-line chemotherapy	
No/Yes	7/21
Median number of cycles (range)	6.5 (1-28)
Toxicity grade, n	
Grade 1/2/3/4	22/7/5/0
Recurrence, n	
Hematogenous	6
Lymphatic	7
Peritoneal	4

Tumor staging was performed according to the seventh edition of the Union for International Cancer Control pTNM staging guidelines (8). Tumor classification after preoperative chemotherapy is designated by the prefix "y," and the pathological classification following preoperative chemotherapy is designated ypTNM (8, 9). Terminology defined by the Japanese Gastric Cancer Association was used to avoid unnecessary confusion (9). In addition, eligible patients were required to have an Eastern Cooperative Oncology Group performance status (PS) of 0-2. The tumor response was objectively assessed after each treatment course according to the Response Evaluation Criteria in Solid Tumors (10). Adverse events were evaluated according to the Common Terminology Criteria for Adverse Events, version 4.0 (11). Patients with unresectable gastric cancer were considered if they had at least one initially proven lesion with any non-curative factor, such as tumor invasion of adjacent structures (T4b); peritoneal (P1), hepatic (H1), and distant (M1) metastasis; or positive peritoneal cytology (CY1). The main indication for conversion surgery was anticipation of curative resection based on the response to chemotherapy.

Assessment of recurrence. Recurrent disease was assessed by physical examination, histological findings, clinical follow-up, and imaging, as described in a previous study (12). The first site of recurrence was recorded. The time to recurrence was defined as the period from the date of surgery until detection of the first recurrence. The mode of recurrence was classified as hematogenous metastasis (liver, lung, bone, skin, brain, and adrenal), lymphatic metastasis (cervical, mediastinal, and abdominal para-aortic), or dissemination (peritoneal and pleural).

Statistical analysis. Continuous variables are expressed as median or mean values and range. Patients' characteristics were compared using the χ^2 test, Fisher's exact probability test, and the Mann–Whitney *U*-test, as appropriate. We calculated cumulative survival rate after curative surgery by the Kaplan–Meier method and compared survival curves with the log–rank test. To assess the independence of prognostic factors, we subjected significant variables from the log rank test with *p*-values less than 0.05 to a multivariate Cox proportional hazard regression analysis. In the multivariate analysis, we calculated odds ratios (ORs) with 95% confidence interval (CI). All statistical analyses were performed with JMP 5.0 software (SAS Institute Inc., Cary, NC, USA) and *p*-values less than 0.05 were considered statistically significant.

Results

Patients' characteristics. The preoperative characteristics of the 34 patients who underwent curative conversion surgery are presented in Table I. There were 25 male and nine female patients with a median age of 63 years (range=42-76 years). All patients had a PS of 0 or 1. Out of 34 patients with one

Table III. *Univariate and multivariate predictors of recurrence in 34 patients with gastric cancer who underwent curative conversion resection.*

Variable	Univariate			Multivariate	
	Number	2-Year PFS rate (%)	*p*-Value	Odds ratio (95% CI)	*p*-Value
Macroscopic type			<0.01		0.67
Type2, 3	30	64		1	
Type4	4	0		1.71 (0.11-15.9)	
Clinical tumor depth			<0.01		0.01
T2, 3, 4a	28	66		1	
T4b	6	17		6.44 (1.59-23.9)	
Non-curative factors			<0.01		0.10
1	28	66		1	
2	6	0		6.25 (0.71-61.5)	
Toxicity grade of first-line CT			<0.01		0.34
1, 2	28	64		1	
3, 4	6	0		2.54 (0.35-14.7)	
Pathological tumor depth			0.02		0.63
ypT2, 3, 4a	31	59		1	
ypT4b	3	30		2.06 (0.07-26.1)	
Toxicity grade of second-line CT			<0.01		0.60
1, 2	29	62		1	
3	5	0		1.97 (0.16-21.6)	

CT: Chemotherapy.

or two non-curative factors preoperatively, six (18%), 10 (29%), four (12%), 22 (65%), and one (3%) had T4b, P1, H1, M1, and CY1 disease, respectively. Twenty-one patients (62%) were assigned to the S-1 plus cisplatin group and 13 (38%) to the S-1 plus paclitaxel group. The median number of cycles administered per patient for first-line chemotherapy was four (range=2-17). No complete response was noted; most patients (n=28, 82%) had a partial response. Six patients (18%) had grade 3 or 4 toxicities. Three patients (9%) remained ypT4b, whereas two (18%), 15 (29%), and 17 (3%) patients transitioned to ypStages I, II, and III, respectively. Twenty-seven patients (79%) underwent chemotherapy, 21 of whom (78%) received S-1 monotherapy. The median number of cycles administered per patient for second-line chemotherapy was 6.5 (range=1-28). Five patients (15%) had grade 3 toxicity but none had grade 4 toxicity (Table II).

Recurrence. The postoperative 5-year overall survival (OS) rate of the 34 patients who underwent curative conversion surgery was 46%, with a median follow-up of 25 months (range=2-113 months). Recurrence was observed in 17 (50%) patients, and hematogenous, lymphatic, and peritoneal recurrences were observed in six, seven, and four patients, respectively (Table II). The median time to recurrence was 22 months (range=1-98 months) and the cumulative rate of recurrence at 2 and 3 years was 56% and 47%, respectively. More than 82% of recurrences occurred within 2 years. In nine (53%) of the patients with recurrence, the pattern of recurrence was mostly consistent with their initial metastatic disease. We selected the following 25 factors for Kaplan–Meier analysis using the 2-year recurrence-free survival (RFS) rate: age (<63 years *vs*. ≥63 years), sex (male *vs*. female), PS (0 *vs*. 1), location (upper part *vs*. middle/lower part), macroscopic type (type 2/3 *vs*. type 4), histological grade (G1/G2 *vs*. G3), clinical tumor depth (T2-4a *vs*. T4b), clinical nodal stage (T2-4a *vs*. T4b), P1 (yes *vs*. no), H1 (yes *vs*. no), M1 (yes *vs*. no), CY1 (positive *vs*. negative), number of non-curative factors (1 factor *vs*. 2 factors), cycles of first-line chemotherapy (<4 *vs*. ≥4), toxicity grade of first-line chemotherapy (grade 1/2 *vs*. grade 3/4), response (partial response *vs*. stable disease), type of gastrectomy (distal *vs*. total), histological tumor size (<64 mm *vs*. ≥63 mm), pathological grade (grade 0-1b *vs*. grade 2), pathological tumor depth (T2-4a *vs*. T4b), pathological nodal stage (N0-2 *vs*. N3), ypStage (I, II, *vs*. III), second-line chemotherapy (yes *vs*. no), cycles of second-line chemotherapy (<6.5 *vs*. ≥6.5), and toxicity grade of second-line chemotherapy (grade 1/2 *vs*. grade 3).

According to the log-rank test, the following six variables were significantly associated with a worse postoperative RFS: macroscopic type 4 ($p<0.01$), cT4b ($p<0.01$), two non-curative factors ($p<0.01$), grade 3 or 4 toxicity of first-line chemotherapy ($p<0.01$), ypT4b ($p=0.02$), and grade 3 toxicity of second-line chemotherapy ($p<0.01$). In multivariate Cox regression analysis, cT4b (OR=6.44; 95% CI=1.59-23.9; $p=0.01$) was the only significant independent predictor of postoperative RFS (Table III).

Table IV. *Characteristics and recurrence pattern of six patients with clinical T4b disease.*

Case	Age	Gender	Location	Initial involved organ	Initial metastatic organ	First-line chemotherapy	Pathological response	Pathological tumor depth	Second-line chemotherapy	Site of recurrence
1	48	Male	M	Transverse mesocolon	Peritoneum	S-1+paclitaxel	Grade 1b	ypT4b	None	Liver, lung
2	50	Female	U	Pancreas	None	S-1+cisplatin	Grade 2	ypT4a	S-1	Liver
3	58	Male	L	Pancreas	Abdominal para-aortic nodes	S-1+paclitaxel	Grade 2	ypT3	S-1+cisplatin	Peritoneum
4	63	Male	L	Liver, Transverse mesocolon	Abdominal para-aortic nodes	S-1+cisplatin	Grade 1b	ypT4b	S-1	Liver
5	58	Male	LD	Pancreas	None	S-1+cisplatin	Grade 2	ypT4a	Paclitaxel	Abdominal para-aortic nodes
6	55	Female	L	Pancreas, Transverse mesocolon	Abdominal para-aortic nodes	S-1+cisplatin	Grade 1b	ypT4a	S-1	Ovary

M: Middle part; U: upper part; L: lower part; LD: lower part + duodenum.

Profile of patients with clinical T4b. Among six patients with cT4b disease, the initial involved organs were the pancreas in four patients, transverse mesocolon in three patients, and liver in one patient. All patients had recurrence involving various organs such as the liver, lung, ovary, peritoneum, and abdominal para-aortic nodes. These organs were not consistent with the initial organ of non-curable metastases. Two patients remained with ypT4b disease with pathological response grade 1b, whereas disease in one and three patients transitioned to ypT3 and T4a, respectively. Among all 34 patients who underwent curative conversion surgery, stages ypT4a or T4b were recorded in five (83%) of six patients with cT4b and nine (32%) of 28 patients with non-cT4b disease. In five patients, second-line chemotherapy with a modification of the regimen used for first-line chemotherapy was offered (Table IV).

Discussion

Patients with unresectable gastric cancer usually have a poor prognosis and are initially considered for systemic chemotherapy rather than surgery. However, when chemotherapy has produced a transient response and curative surgery can be accomplished, conversion surgery is occasionally associated with prolonged survival in selected patients (4-7). Although the survival benefit for these patients has been recently discussed, the recurrence risk after curative conversion surgery should also be evaluated to determine the optimal treatment. Our data clearly show that disease of initial stage cT4b is an independent risk factor for recurrence in patients who undergo curative conversion surgery. Effective postoperative chemotherapy appears to be required for patients with a high risk of recurrence, such as those with initial cT4b disease.

In the present study, the rate of recurrence of gastric cancer after curative conversion surgery was 50% with a median time to recurrence of 22 months, which is higher than the rate for initially resectable gastric cancer (14%) reported in our previous studies (13). Multivariate analysis showed that initial cT4b disease is a significant independent risk factor for recurrence after curative conversion surgery. All six patients with cT4b had recurrence patterns that were not consistent with their initial metastatic disease. The rate of ypT4a or ypT4b disease among patients with cT4b was 83%, which is higher than that among patients with non-cT4b disease (32%), although the pathological response for these cT4b patients was either grade 1b or 2. A previous study showed that patients with gastric cancer with histological tumor size of 5.0 cm or more have a poorer survival after conversion surgery than those with smaller tumors, irrespective of whether they were treated with curative or non-curative resection (6). Based on these findings, a residual primary lesion in gastric cancer patients undergoing curative conversion surgery may primarily reflect progression of the cancer itself because initial metastatic factors associated with the noncurative status are mostly resolved after first-line chemotherapy.

When conversion surgery has been performed after a response to chemotherapy for patients with initially unresectable gastric cancer, the primary treatment modality is curative resection. The rate of prevention of recurrence in these patients, including those with cT4b disease, is still unsatisfactory, although the optimal regimen or number of cycles of additional chemotherapy after curative conversion surgery has not been established. For patients in Japan with initially resectable gastric cancer, the major regimen for those with pStage II and III disease who receive adjuvant

chemotherapy after curative surgery is S-1 monotherapy for 1 year (up to eight cycles) (14). In the present study, most patients received S-1 monotherapy as second-line chemotherapy, with the exception of two patients with ypStage I. Patients with ypStage II and III who received more than eight cycles of S-1 monotherapy showed improved long-term postoperative survival, probably because of low resistance to S-1 (data not shown). While this suggests that S-1 monotherapy may be effective for patients with ypStage II and III disease even after curative conversion surgery, these results remain preliminary.

Although this was a retrospective study with a small sample size, our data indicate that initial disease of cT4b predicts recurrence in patients with initially unresectable gastric cancer who are treated with curative conversion surgery. Because curative conversion surgery alone may not prevent recurrence in this patient group, effective additional (single or combination) chemotherapy is required for patients with a high risk of recurrence. A prospective study with a larger series of cases is required to evaluate the value of conversion surgery and subsequent additional chemotherapy for this type of cancer.

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