Long-term survival and prognosis associated with conversion surgery in patients with metastatic gastric cancer

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Abstract. In gastric cancer, primary systemic chemotherapy is the standard approach for the management of patients with initially unresectable metastasis, and it occasionally leads to a reduction in the size of the lesion, which facilitates surgical resection. The aim of this study was to examine the prognosis of patients who were able to undergo complete resection following chemotherapy. A total of 10 patients who underwent radical surgery for stage IV primary gastric cancer after chemotherapy between 2009 and 2015 at the Department of Surgery of Hokkaido Social Work Association Obihiro Hospital (Obihiro, Japan) were retrospectively investigated. Three regimens were used (S-1, n=1; S-1 + cisplatin, n=8; and S-1 + docetaxel, n=1). The mean time from chemotherapy to surgery was 210 days. One total gastrectomy + splenectomy + colectomy, one total gastrectomy + splenectomy, four total gastrectomies and three distal gastrectomies were performed. There were two cases of pancreatic fistula formation postoperatively. All the patients survived for >1 year. Of the 10 patients, 5 survived without recurrence. The median survival time was 871.1 days after diagnosis. Therefore, curative resection after chemotherapy is associated with a better prognosis in stage IV gastric cancer patients.

Introduction

Gastric cancer is the second most prevalent malignancy worldwide (1). With the advances in chemotherapy, a standard treatment for gastric cancer has been established and it has been published in the Japanese treatment guidelines for gastric cancer (2). Certain randomized controlled trials have reported improved patient survival, but the median survival time (MST) is limited to 13-16 months (3-7). Therefore, novel therapeutic approaches should be considered to improve the survival of stage IV gastric cancer patients.

Recently, the response rate to new chemotherapy regimens has improved markedly, whereas the role of surgery for stage IV gastric cancer patients responsive to induction chemotherapy remains fairly uncertain. Performing surgery in such patients may result in a survival benefit following curative resection. This type of surgery is referred to as conversion surgery. However, the clinical value of conversion surgery for stage IV gastric cancer remains controversial.

The aim of this study was to retrospectively evaluate conversion surgery for stage IV gastric cancer patients in terms of operative morbidity, mortality, prognostic factors, recurrence and overall survival.

Patients and methods

Patients. This study was performed with the approval of the Internal Review Board on Ethical Issues of the Hokkaido Social Work Association Obihiro Hospital. Patients diagnosed with stage IV gastric cancer who underwent chemotherapy in our hospital between January, 2009 and December, 2015 were retrospectively reviewed. The inclusion criteria were as follows: i) Histologically confirmed gastric cancer; ii) distant metastatic sites confirmed by computed tomography and/or positron emission tomography; iii) patient receiving a chemotherapeutic regimen for at least one cycle; iv) Eastern Cooperative Oncology Group performance status of 0 or 1; and v) no history of prior chemotherapy or radiotherapy. Surgery was then performed within 5-6 weeks after the last cycle of chemotherapy.

A total of 10 patients underwent conversion surgery for stage IV gastric cancer (Table I). The patients were also stratified into two categories, according to recurrence after conversion surgery (recurrence or non-recurrence groups) and according to the histological type [differentiated-type

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Table I. Characteristics of the 10 gastric cancer patients who underwent conversion surgery.

Case	Age (years)	Gender	Incurable factor	Histopathological type	Macroscopic type	Preoperative chemotherapy	Period of chemotherapy (days)
1	85	M	LNM	tub2	2	S-1	213
2	70	M	LNM	tub2-por	2	S-1+CDDP	500
3	72	M	LNM	tub2-por	2	S-1+CDDP	143
4	74	M	LM	tub1>tub2>por	2	S-1+CDDP	136
5	69	M	CY	sig>por	5	S-1+CDDP	133
6	81	F	PM	por-sig	3	S-1+DOC	150
7	63	F	PM	por>tub2	3	S-1+CDDP	123
8	60	M	LNM	por	3	S-1+CDDP	95
9	59	M	Other organ invasion (colon)	tub1-tub2	4	S-1+CDDP	139
10	72	F	LNM	tub1-tub2	4	S-1+CDDP	467

M, male; F, female; LNM, lymph node metastasis; LM, liver metastasis; PM, peritoneal metastasis; CDDP, cisplatin; CY, cytology; DOC, docetaxel; tub1, well-differentiated tubular adenocarcinoma; tub2, moderately differentiated tubular adenocarcinoma; por, poorly differentiated adenocarcinoma; sig, signet ring cell carcinoma.

Table II. Demographics of conversion surgery for gastric cancer and postoperative outcome.

Case	Operation	Postoperative complications	Postoperative chemotherapy	Pathological response	Recurrence region	DFS (days)	OS (days)	Patient status
1	TG + SC	None	None	1b	None		1,417	Alive
2	DG	None	S-1	1a	None		1,178	Alive
3	TG	None	S-1	1a	None		1,385	Alive
4	DG + Hr0	None	S-1	1b	None		920	Alive
5	TG	None	CY^+	2	None		515	Alive
6	TG + SC	None	None	1b	Peritoneal	174	406	Dead
7	DG + Hr0 + P	None	S-1 + CDDP	1b	Liver	75	430	Dead
8	DG	None	S-1 + CDDP	1a	Lymph node	333	672	Dead
9	TG + SC + colectomy	Pancreatic fistula	S-1	1a	Liver	839	1,090	Dead
10	TG	None	S-1	3	Lymph node	511	1,175	Alive

DFS, disease-free survival; OS, overall survival; TG, total gastrectomy; SC, splenectomy; DG, distal gastrectomy; Hr, hepatic resection; P, peritoneal resection; CDDP , cisplatin; CY, cytology.

(well- or moderately differentiated tubular adenocarcinoma, tub1 and tub2, respectively), and undifferentiated-type (poorly differentiated or signet ring cell carcinoma, por and sig, respectively)].

Treatment regimen. The chemotherapeutic regimens were as follows: 1 patient was assigned to receive S-1 (S-1 case) administered at a dose of 80 mg/m^2/day divided into two daily doses for 28 days, followed by 14 days of rest; 8 patients were assigned to S-1 plus cisplatin (CDDP) and received oral S-1 (80 mg/m^2/day divided into two daily doses for 21 days) plus intravenous CDDP (60 mg/m^2 on day 8) repeated every 5 weeks; and 1 patient was assigned to the S-1 plus docetaxel (DOC) group and received oral S-1 (80 mg/m^2/day divided into two daily doses for 14 days) plus intravenous DOC (40 mg/m^2 on day 1) repeated every 3 weeks.

Follow-up schedule. Physical examinations and laboratory tests were performed every 2 weeks during the treatments. Tumor response was evaluated by computed tomography every 4-8 weeks using the Response Evaluation Criteria In Solid Tumors guidelines (8).

Indications for conversion surgery. Candidates for conversion surgery were those for whom R0 resection could be achieved on the basis of the response to chemotherapy, if there were no non-curative factors. The majority of the patients received adjuvant chemotherapy, mainly with S-1.

Results

Characteristics of patients undergoing conversion surgery. The preoperative characteristics of the 10 patients who

Table III. Comparison between recurrence and non-recurrence groups.

A, Non-recurrence group

Case	Histopathological type	Macroscopic type
1	tub2	2
2	tub2-por	2
3	tub2-por	2
4	tub1>tub2>por	2
5	sig>por2	5

B, Recurrence group

Case	Histopathological type	Macroscopic type
6	por-sig	3
7	por>tub2	3
8	por	3
9	tub1-2	4
10	tub1-2	4

tub1, well-differentiated tubular adenocarcinoma; tub2, moderately differentiated tubular adenocarcinoma; por, poorly differentiated adenocarcinoma; sig, signet ring cell carcinoma.

underwent conversion surgery are summarized in Table I. The patients included 8 men and 2 women with a median age of 70.5 years (range, 59-86 years). All 10 patients had one incurable factor prior to chemotherapy: 1 patient had T4b, 3 had P1, 1 had H1, 4 had M1 (distant lymph node metastasis) and 1 had CY1 disease. All the patients were assessable regarding their response. After chemotherapy, all the cases were considered as resectable gastric cancer, achieving R0 resection. The median interval between diagnosis and surgery was 210 days (range, 95-500 days).

Three regimens were used (S-1, n=1; S-1 + CDDP, n=8; and S-1 + DOC, n=1). One total gastrectomy + splenectomy + colectomy, one total gastrectomy+splenectomy, four total gastrectomies and three distal gastrectomies were performed. There were 2 cases of pancreatic fistula postoperatively. All the patients survived for >1 year after the diagnosis. Of the 10 patients, 5 survived without recurrence. The median survival time was 871.1 days after diagnosis (Table II).

Comparison between the recurrence and non-recurrence groups. In the recurrence group, the metastatic sites included 2 peritoneal disseminations, 1 multiple visceral invasion and 2 lymph node metastases prior to chemotherapy. In the non-recurrence group, the metastatic sites included 1 case of positive peritoneal cytology, 1 case of liver metastasis and 3 cases of lymph node metastasis prior to surgery. The pathological findings prior to chemotherapy were 3 undifferentiated-type and 2 differentiated-type patients in the recurrence group, and 1 undiffentiated-type and 4 differentiated-type patients in the non-recurrence group (Table III).

Table IV. Comparison of prognosis in stage IV gastric cancer patients.

Trial (chemotherapy regimen)	OS (months)	Refs.
JCOG9912 (S-1)	11.4	(22)
SPIRITS (SP)	13.0	(3)
ToGA (HXP)	13.8	(7)
Our cases (conversion surgery)	29.0	

OS, overall survival; SP, S-1 + cisplatin; HXP, trastuzumab + capecitabine + cisplatin.

Discussion

According to the Japanese guidelines for gastric cancer (2), S-1/CDDP is the standard first-line systemic chemotherapy for human epidermal growth factor (HER)2-negative patients (3), whereas trastuzumab + capecitabine + CDDP (XP regimen) is considered as the first-line treatment for HER2-positive patients (7). More recently, as significant progress has been made by improving chemotherapeutic regimens, conversion surgeries have been performed for stage IV gastric cancer patients (9-14). In colorectal metastases, complete resection was found to achieve a 5-year survival rate of 35-58% (15-17).

Our data revealed that patients who underwent conversion surgery exhibited a longer survival compared with those who received chemotherapy alone, which was consistent with previous findings (10,13,18-20) (Table IV). Furthermore, among patients undergoing conversion surgery, higher differentiation and non-invasive macroscopic type are favorable survival predictors. If chemotherapy leads to a transient response and conversion surgery is achievable, conversion surgery may prolong survival in selected patients.

Based on our data, 3 of 5 cases exhibited the same relapse patterns prior to chemotherapy. In colorectal cancer, macroscopic residual disease was found during surgical exploration at the site of liver metastases that were considered to have disappeared on imaging. In patients without detection of further tumors and in whom the site of the complete response remained intact, *in situ* recurrence was observed in 74% of the cases after 1 year (21). These data demonstrated that removing the region of metastasis that was present prior to chemotherapy may improve the prognosis with conversion surgery.

All cases with peritoneal dissemination recurred after conversion surgery. In the case of macroscopic peritoneal metastasis, it is insufficient to completely remove macroscopic cancer after conversion surgery. However, such patients exhibited a better prognosis compared with those who were treated with chemotherapy alone, and cytology-positive patients survived without recurrence. S-1 is effective as postoperative chemotherapy for gastric cancer patients with positive peritoneal lavage cytology following macroscopically curative resection (22). According to these results, additional treatments may be required before or after conversion surgery for peritoneal dissemination.

Therefore, conversion surgery may be associated with a more favorable prognosis in stage IV gastric cancer patients. According to our results, patients without peritoneal dissemination and with more highly differentiated tumors have a better prognosis following conversion surgery.

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