Role of Surgery in the Management for Gastric Cancer with Synchronous Distant Metastases

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Abstract Optimal treatment of patients with gastric cancer with synchronous distant metastases is palliative chemotherapy. However, occasionally gastrectomy should be selected due to control bleeding from tumors, perforation, or obstruction. The aim of this study is to evaluate the survival benefits of non-curative gastrectomy for patients with synchronous distant metastasis. Total 78 gastric cancer patients with synchronous distant metastasis treated in our hospital *between 2003 and 2012* were enrolled in this study. Of these, 74 patients (95 %) received S1 based chemotherapy. During the treatment, 37 patients (47.4 %) underwent palliative gastrectomy because of bleeding from tumors ($n=15$), tumor perforation ($n=6$), and obstruction ($n=16$). Survival benefits were compared in resected and non-resected patients, retrospectively. The two groups were clinicopathologically similar. Palliative gastrectomy was performed safely (morbidity: 10.8 % and mortality: 0) in resection group. However, resection showed survival benefits only in 13 patients (16.7 %) with single metastasis and without peritoneal metastasis. Their 2-year survival rate was 40 % and their median survival was 19 months. Non-curative gastrectomy with precise surgical techniques followed careful postoperative nutrition management may improve survival only for patients with a single metastatic site, except for peritoneal dissemination.

Keywords Gastric cancer · Gastrectomy · Synchronous distant metastasis · Survival

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Introduction

Although treatment outcomes have improved for patients with gastric cancer, many patients are diagnosed at a late stage. Gastric cancer patients with hematogenic (lung, liver, brain, or bone), peritoneal, or extended lymph node (cervical, mediastinal, or para-aortic) metastases are regarded as non-resectable, with a very poor prognosis. These patients frequently undergo gastrectomy to reduce symptoms caused by advanced gastric cancer, including obstruction, abdominal pain due to perforation, and bleeding. Several studies reported that non-curative resection may also have survival benefits in gastric cancer patients with distant metastasis [1–3]. Other studies, however, found that non-curative gastrectomy had no survival benefits, but only increased postoperative morbidity and prolonged hospital stay [4–8]. Thus, the optimal therapeutic strategy for patients with gastric cancer and synchronous distant metastases remains unclear.

The new Japanese Gastric Cancer Association (JGCA) classification 14th edition (3rd English edition) [9] has defined sites of distant metastasis as the liver, lungs, brain, ovaries, bones, bone marrow, skin, peritoneum, and distant lymph nodes (extra-abdominal). The basic treatment for gastric cancer patients with synchronous distant metastases has been systemic chemotherapy and never gastrectomy. However, the role of gastrectomy in patients with positive peritoneal lavage cytology and low peritoneal metastatic foci is controversial. Definitive demonstration of the survival advantages of palliative gastrectomy requires large scale, randomized control trials. However, trials like this are difficult to perform, since patients undergo gastrectomy to relieve symptoms (e.g., obstruction, perforation, bleeding) resulting from gastric cancer, and it would be unethical to withhold such treatment. Thus, retrospective evaluations are required to compare survival in patients who did and who did not undergo palliative

gastrectomy. We have therefore evaluated the survival benefit of non-curative gastrectomy for gastric cancer patients with synchronous distant metastases.

Materials and Methods

We evaluated 78 patients with histologically proven primary gastric cancer, with synchronous distant metastases who were treated at Tottori University Hospital from January 2003 to August 2012. Patients with low Eastern Cooperative Oncology Group Performance Status Scale (ECOG PS 3 and 4) were excluded from this study and they were treated with best supportive care without chemotherapy or surgical intervention [10]. Informed consent was obtained from all these 78 patients about their treatment. The study protocol has been approved by the ethics committee of Tottori University (approval number: 357).

Of the 78 patients, 41 had a single metastatic site (11 in the liver, 2 in bone, 13 in extra-abdominal metastatic lymph nodes, and 15 with peritoneal dissemination) and 37 had multiple metastatic sites. Thirty-seven underwent gastrectomy with macroscopic residual tumors (R2 operation) because of bleeding from tumors ($n=15$), tumor perforation ($n=6$), and obstruction ($n=16$). In obstructive cases, we usually chose gastrectomy rather than a bypass operation for patients with good PS and without tumor invasion to duodenum and pancreas.

Patients were followed-up until death or the cut-off date of February 28, 2013. The median follow-up period was 14.3 months (range, 2–83 months). The Mann–Whitney *U* test, Chi-squared test and Fisher's exact probability test were used to compare the clinicopathological characteristics of the two groups, as appropriate. Survival rates were analyzed using the life table method, with differences evaluated using the log-rank test. A *P*-value <0.05 was considered statistically significant.

Results

Complications of Palliative Gastrectomy

Of the 37 patients who underwent resection, 22 underwent total gastrectomy and 15 underwent distal partial gastrectomy. Four patients (10.8 %) experienced postoperative complications, two after total (2/22, 9.1 %) and two after distal (2/15, 13.3 %) gastrectomy. The two patients who underwent total gastrectomy experienced postoperative intra-abdominal bleeding, for which they underwent re-operation. Of the two patients who underwent partial gastrectomy, one experienced anastomotic leakage and the other experienced an intra-abdominal abscess. No patient died because of postoperative

complications. Of the 41 non-resected patients, 11 underwent bypass surgery and 2 underwent laparotomy, with none of these patients experiencing any complications.

Clinicopathological Characteristics of the Resected and Non-Resected Groups

The clinicopathologic characteristics of the two patient groups are shown in Table 1. Of the 78 patients, 74 (95 %) received S1 based chemotherapy, usually S1+cisplatin or S1+docetaxel. In four patients (one in the resection and three in the non-resection group), because of a decline in ECOG performance status, we used weak anticancer drugs of effect, such as 5-fluorouracil or uracil-tegafur. No significant differences were observed between the groups.

Patient Survival

The 2-year overall survival (OS) rate was higher (16.3 % vs. 11 %) and median OS was longer (14 vs. 10 months) in the resection than in the non-resection group ($P=0.039$). In 78 patients, the 2-year OS rate was higher (16.7 % vs. 10 %) and median OS was longer (13 vs. 10 months) in the 41 patients with single a metastatic site than in the 37 patients with multiple metastatic sites ($P=0.009$). In addition, the 2-year OS rate was higher (25 % vs. 5.1 %) and the median OS was longer (12 vs. 10 months) in the 34 patients without than in the 44 with peritoneal metastases ($P=0.021$). However, ECOG PS and presence or absence of liver metastases did not affect patient survival. The details were shown in Table 2.

Table 1 Clinicopathologic characteristics of patients who did and did not undergo non-curative resection

	Resection	Non-resection	<i>P</i>
<i>N</i>	37	41	
Age (mean $\pm$ SD)	65.9 $\pm$ 12.5	67 $\pm$ 13.3	0.896
Gender (Male/Female)	28/9	24/17	0.109
ECOG PS (0/1/2)	22/13/2	24/13/4	0.76
Initial chemotherapy			
S1	5	5	
S1+Cisplatin	16	16	
S1+Docetaxel	11	15	0.721
S1+Camptotesin	4	2	
Others	1	3	
Number of distant metastatic site			
(Single/Multiple)	20/17	21/20	0.802
Liver metastasis			
(No/Yes)	25/12	25/16	0.545
Peritoneal metastasis			
(No/Yes)	15/22	19/22	0.606

SD standard deviation

Table 2 Prognostic differences between resection and non-resection groups

Variables	Resection (MST/N)	Non-resection (MST/N)	<i>P</i>
ECOG PS			
0 (<i>N</i> =46)	11/22	10/24	0.218
1 and 2 (<i>N</i> =32)	18/15	8/17	0.132
Number of distant metastatic site			
Single (<i>N</i> =41)	18/20	10/21	0.028
Multiple (<i>N</i> =37)	11/17	8/20	0.725
Liver metastasis			
No (<i>N</i> =50)	17/25	10/25	0.235
Yes (<i>N</i> =28)	13/12	8/16	0.118
Peritoneal metastasis			
No (<i>N</i> =34)	19/15	10/19	0.022
Yes (<i>N</i> =44)	11/22	8/22	0.638

MST median survival time (month)

In non-resection group, ECOG PS, number of distant metastatic sites, presence or absence of liver metastasis, and presence or absence of peritoneal metastasis did not affect patients' survival. However, in the resection group, we found that single metastatic site ($P=0.011$) and absence of peritoneal metastasis ($P=0.011$) were better prognostic factors.

Palliative gastrectomy showed the survival benefit in patients with single metastatic site and the absence of peritoneal metastases. We analyzed the survival benefits of gastrectomy relative to both single metastatic site and the absence of peritoneal metastases. Of the 20 patients with a single metastatic site who underwent palliative gastrectomy, 13 did not have peritoneal metastasis, whereas 7 did. The 2-year OS rate was extremely higher (40 % vs. 0 %) and the median OS was longer (19 vs. 11 months) in the 13 patients without than in the 7 with peritoneal metastases ($P=0.044$, Fig. 1).

Discussion

The prognosis of gastric cancer patients diagnosed at advanced stage is poor. The 2009 annual report of the Japanese Gastric Cancer Association estimated that the 5-year OS rate in unresected patients was 1.5 %. In resected patients without residual tumors, the 5-year OS rate was 88.6 %, whereas, in resected patients with residual tumors, the rate was only 9.9 % [11], indicating that the curative potential of gastric resection is an important prognostic factor for patient survival. Indeed, survival rates after gastrectomy plus metastasectomy were found to be higher if the surgery was curative (R0 operation), especially compared with patients with liver or lymph node involvement [12, 13]. In contrast, the survival benefits of non-curative gastrectomy (with macroscopically residual tumors,

Fig. 1 Survival outcomes in gastric cancer patients with a single metastatic site who underwent gastrectomy. Survival was significantly greater in 13 patients without peritoneal metastasis (solid line) than that of 7 patients with peritoneal metastasis (dotted line, $P=0.044$)

R2 resection) are unclear. Moreover, recent advances in chemotherapy, especially the introduction of S1 plus cisplatin regimens, have been found to prolong median OS of patients with incurable gastric cancer to 13 months [14]. These results indicated that first-line treatment of patients with advanced gastric cancer and synchronous distant metastases in Japan should consist of S-1 plus cisplatin. Patients with advanced gastric cancer and synchronous distant metastases undergo gastrectomy only for life-threatening symptoms, including obstruction, perforation, or bleeding, to improve quality of life.

We have compared clinical outcomes in patients who did and did not undergo palliative gastrectomy (R2 operation), with both groups receiving S-1 based chemotherapy. Despite its retrospective design, we found that non-curative gastrectomy had survival benefits for patients with a single metastatic site and without peritoneal metastasis. Palliative gastrectomy was previously found to have significant survival advantages in patients with one metastatic site, but this survival advantage was no longer observed in patients with more than two sites [8, 15]. Thus, the number of metastatic sites should be considered prior to performing a non-curative gastrectomy.

In agreement with previous studies, we also found that gastrectomy did not improve survival in patients with peritoneal metastases [16–18]. Computed tomography (CT) has limited ability to diagnose peritoneal metastasis, but diagnostic laparoscopy, which is less invasive than laparotomy, was found to be more sensitive than CT in detecting peritoneal metastases [19]. Thus, diagnostic laparoscopy should be utilized to evaluate patients at risk for peritoneal metastasis.

Non-curative gastrectomy was reported significantly associated with higher postoperative mortality and morbidity rates, and longer hospital stay. In one study, palliative gastrectomy was performed in 33 % of Stage IV patients, with surgical morbidity rate higher in those who underwent R2 (32.4 %)

than R1 (19 %) operations [20]. That study reported that the low immunonutritional status of the R2 group was primarily responsible for the high morbidity and mortality rates in this group. Although our patient cohort was small, our results suggest that careful pre- and postoperative nutrition management and precise surgical techniques may allow even elderly patients to undergo palliative gastrectomy safely, with acceptable operative risks. Thus, it is important to balance the survival benefits and complications of non-curative gastrectomy for gastric cancer patients with distant metastases.

Our results should be interpreted with caution, because of the retrospective nature of this study and between group differences in patient characteristics. There may be bias in the selection of treatment strategies, including chemotherapeutic regimens and indications for gastrectomy, which may affect survival of patients. These limitations may be overcome and conclusive results obtained by performing well-designed prospective trials investigating the efficacy of gastrectomy in gastric cancer patients with a single incurable factor. Such a trial is currently underway [21] and may reveal the survival benefits of palliative gastrectomy in gastric cancer patients with distant metastases.

Although we did not focus on patient symptoms, palliative gastrectomy in patients with advanced gastric cancer is performed to relieve symptoms. In cases of tumor perforation and tumor bleeding, gastrectomy will be chosen to save the life of the patients. However, in cases of tumor obstruction, we have three palliative methods to cure the quality of patients' life, such as non-surgical methods like pyloric stenting or bypass operation and surgical resection. Keränen et al. [22] reported that the median symptom-free and overall survival were longest in the resection group than stenting or bypass operation. And, they concluded palliative resection followed by chemotherapy is important to prolong the patients' survival.

In conclusion, we found that overall survival was longer in gastric cancer patients with distant metastases who did than did not undergo non-curative resection. However, these survival benefits were not observed in patients with multiple metastatic sites or peritoneal metastasis. Non-curative resection with precise surgical techniques followed careful postoperative nutrition management may improve survival only for patients with a single metastatic site, except for peritoneal dissemination.

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