Changes in Standard Treatments and Postoperative Outcomes for Advanced Gastric Cancer at One Institute over an 11-Year Period

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ABSTRACT

Background Reportedly, the recently established postoperative adjuvant chemotherapies (ADJs) with tegafur and uracil (UFT) or fluoropyrimidine S (S-1) show better survival than surgery alone in patients with advanced gastric cancer (GC). We analyzed chronological changes in postoperative prognosis of patients with advanced GC in our institute, and investigated the efficacy of ADJ in patients with stage II–III GC.

Methods Of 143 patients with stage II–III GC who underwent curative gastrectomy at Tottori University Hospital between 1998 and 2008, three died with operative complications within 1 month after surgery. The remaining 140 patients were followed to the end of 2013. We compared disease-free survival (DFS) and clinicopathological differences between 82 patients who underwent gastrectomy during 1998–2002 (Group A) and 58 patients who underwent gastrectomy during 2003–2008 (Group B).

Results Operative quality, as represented by number of dissected lymph nodes, was similar in both groups, but the recurrence rate of Group A (51.2%) was higher than in Group B (37.9%, $P = 0.12$) and the 5-year DFS rate of Group B (62.3%) was higher than that of Group A (50.2%, $P = 0.095$). In stage II, the 5-year DFS rate of patients in Group B (73.3%) was similar to Group A (77%), but at tumor stage III, the 5-year DFS rate of patients in Group B increased to 48.7%, compared with 33.1% of Group A. Between 2003 and 2008, S-1 was widely used as ADJ for stage II–III GC.

Conclusion Postoperative ADJ with S-1 improved DFS of patients with stage III gastric cancer.

Key words adjuvant chemotherapy; gastric cancer; S-1; tegafur and uracil

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Abbreviations: ADJ, adjuvant chemotherapy; DFS, disease-free survival; GC, gastric cancer; S-1, fluoropyrimidine S; UFT, tegafur and uracil

Gastric cancer (GC) is the fourth most common malignancy worldwide[1] and the second leading cause of cancer-related death, with the highest mortality rates reported in East Asia including Japan, Korea and China; approximately 60% of gastric cancers in the world are diagnosed in this area.[2] Early detection and curative surgery can improve survival of loco-regional GC but the survival rates of advanced or recurrent GC remain low.

Surgery is the main modality for the treatment of resectable GC. Surgical technique is the most important factor for patients' outcome and has progressed rapidly in recent years with newly developed operative apparatus. Furthermore, tegafur and uracil (UFT) and its derived anticancer drug, fluoropyrimidine S (S-1) reportedly to have survival benefits for patients with curatively operated advanced GC as adjuvant chemotherapy (ADJ), as shown in large randomized studies in Japan.[3, 4] Thus, from 2007, fluoropyrimidine-based therapy has been used as standard ADJ for stage II–III GC.[5]

However, the improvement of GC patients' survival from single institutions has not been widely discussed. In the present study, we selected patients with stage II–III GC who were treated over an 11-year period (1998–2008) and we followed these patients at least 5 years. We divided these patients into two sub-groups (Group A, who were treated between 1998 and 2002; and Group B, who were treated between 2003 and 2008) and compared clinicopathological characteristics and prognoses between the two groups.

MATERIALS AND METHODS

Patients

Between 1998 and 2008, 143 patients with stage II–III GC underwent curative gastrectomy with D2 or more extensive lymph node dissection for adenocarcinoma of the stomach. Three patients died with operative complications within 1 month after surgery. We excluded these three patients and we enrolled the remaining 140 patients for this study. All 140 patients (average age: 62.7 years; range 34–89 years) had pathological stage II–III gastric adenocarcinomas.[6] Clinicopathological characteristics of the patients were described according with the Japanese Classification of Gastric Carcinoma.[6]

All patients provided informed consent for the treatment including ADJ. The study design was approved by the Ethics Review Board of Tottori University. We divided the patients into two sub-groups (Group A, who were treated between 1998 and 2002; and Group B, who were treated between 2003 and 2008). All patients were followed at our hospital or at our affiliated hospital till the end of 2013.

ADJ

DFS was defined as the time from the date of registration to the date of detection of progressive disease, death, or treatment discontinuation. The recurrence sites were detected by clinical findings, enhanced computed tomography (CT), or magnetic resonance imaging (MRI). Between 1998 and 2008, ADJ was applied to 36 patients (40%) of Group A, and 34 patients (24%) of Group B. Of Group A patients, 30 (21.4%) received UFT and 6 (4.9%), S-1. While in Group B, 5 patients (3.6%) were treated with UFT and 29 patients (20.7%), S-1. Before 2001, UFT (300–600 mg/day) was mainly used; UFT-based ADJ was applied for a total of 35 patients. By 2002, S-1 began to be used as ADJ for advanced GC; S-1 (80 mg/m2) was given for a total of 35 patients. A summary of ADJ is listed in Table 1.

Table 1. Patients' characteristics

	Group A	Group B	*P* value
n	82	58	
Age (mean, SD)	67.5 (11.4)	66.9 (12)	0.934
Sex (male/female)	58/24	36/22	0.282
Histological type (well differentiated/poorly differentiated)	51/31	27/31	0.301
Tumor stage (II/III)	32/50	32/26	0.059
Gastrectomy (Total/proximal/distal)	46/1/35	25/3/30	0.166
Dissected number of lymph nodes (mean, SD)	35.5 (19.5)	38.9 (18.1)	0.156
Adjuvant chemotherapy (yes/no)	36/46	34/24	0.086
Chemotherapy (UFT-based/S-1)	30/6	5/29	< 0.001
Recurrence (yes/no)	42/40	22/36	0.12

Group A patients underwent gastrectomies during 1998–2002 and Group B patients, during 2003–2008. UFT, tegafur and uracil.

Statistical analysis

The terminology used in this study conforms to the Japanese Classification of Gastric Carcinoma, 3rd English edition.[6] Differences between two parameters were compared using the chi-squair test for independence, Fisher's exact probability test, and the Mann-Whitney *U* test. Disease-free survival (DFS) was defined as time from date of registration to date of detection of progressive disease, death, or treatment discontinuation. Survival curves were estimated using the Kaplan-Meier method, and differences were analyzed using the stratified log-rank test. P value < 0.05 was regarded as statistically significant.

RESULTS

Table 1 shows the clinicopathological differences between Group A (82 patients who were treated between 1998 and 2002) and Group B (58 patients who were treated between 2003 and 2008). Patients in Group A tended to be at more advanced stages, although not significantly different. However, operative quality (number of dissected lymph nodes) did not differ between the groups. ADJ was administered to a larger percentage of Group B patients. The main ADJs for patients in Group A were UFT-based, but S-1 was the main adjuvant drug in Group B.

The recurrence rate of Group A (51.2%) was higher than that of Group B (37.9%, $P = 0.12$). Major sites of metastases were the lymph node in 14.6%/15.5% (Group A/B) patients, peritoneum in 23.1%/12.0% patients, liver in 7.3%/10.3% patients, lung in 4.8/3.9% patients and others in 4.8%/3.4% patients. Sites of metastases are summarized in Table 2. The 5-year DFS rate of Group A (50.2%) was lower than that of Group B (62.3%, $P = 0.095$, Fig. 1), but not significantly different for both recurrence and DFS.

Table 2. Sites of metastasis

	Group A	Group B	*P* value
Metastatic sites			0.665
Lymph nodes	12	9	
Peritoneum	19	7	
Liver	6	6	
Lung	4	2	
Others	4	2	
Recurrence (yes/no)	42/40	22/36	0.12

We also analyzed the survival effect of ADJ for these 140 patients. The 5-year DFS rate of 70 patients who received ADJ (54%) was close to that of 70 patients without ADJ (57%, $P = 0.904$). The 5-year DFS of the 35 patients treated with S-1 (62.2%) was better than that of 35 patients treated with UFT-based chemotherapy (45%) but not significantly different ($P = 0.208$). For patients with stage III disease, 5-year DFS of 22 patients treated with UFT-based ADJ (30.3%) was close to that of 36

patients without chemotherapy, but increased to 46.6% in 18 patients treated with S-1. This difference was not significant ($P = 0.654$).

Subgroup analysis

DFS rates in eligible patients were analyzed according to the disease stage (Japanese Classification, 14th edition) and histological type. Kaplan-Meier estimates of DFS are shown according to disease stage. Among patients with stage II disease, 5-year DFS rates were very close in the 2 groups (Fig. 2); but, for those with stage III disease, 5 year DFS for Group B was better than for Group A (Fig. 3).

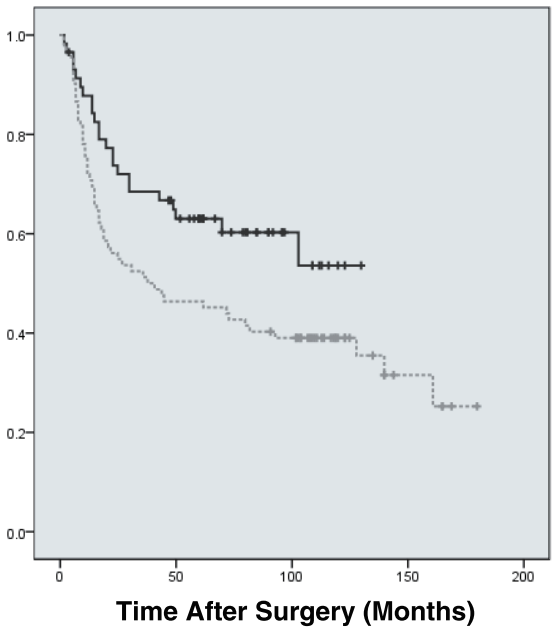

Fig. 1. Disease-free survival for the 58 patients in Group B (who underwent gastrectomies during 2003–2008; solid line) was better than that of the 82 patients in Group A (who underwent gastrectomies during 1998–2002; dotted line), but not significantly different ($P = 0.095$).

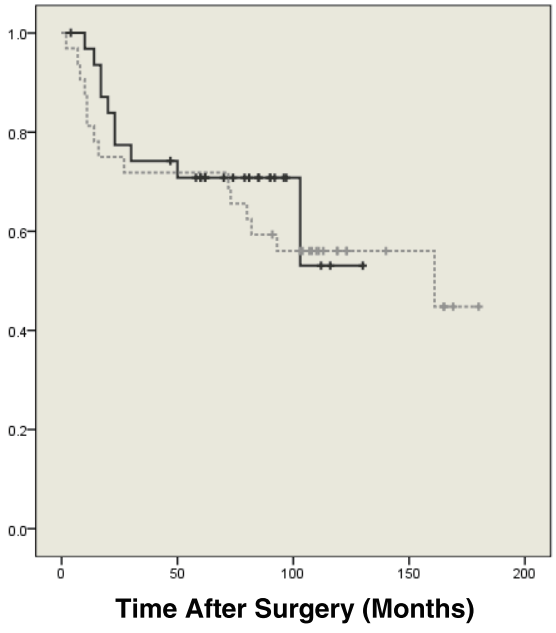

Fig. 2. Disease-free survival for the 32 patients in Group B with stage II (who underwent gastrectomies during 2003–2008; solid line) was better than that of the 32 patients in Group A with stage II (who underwent gastrectomies during 1998–2002; dotted line), but not significantly different ($P = 0.903$).

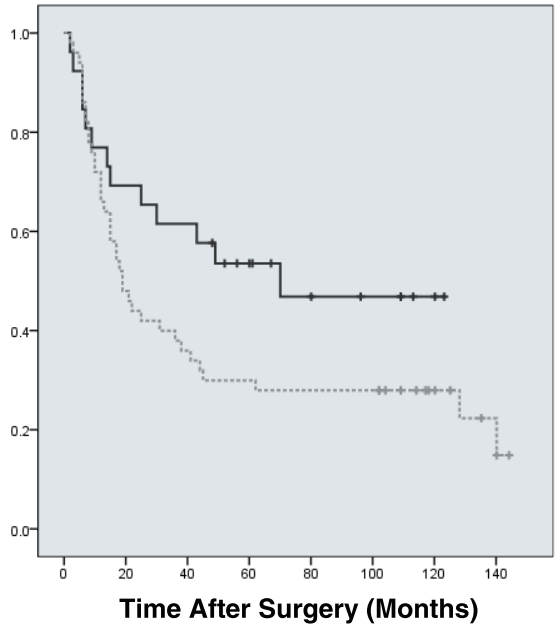

Fig. 3. Disease-free survival for the 50 patients in Group B with stage III (who underwent gastrectomies during 2003–2008; solid line) was better than that of the 26 patients in Group A with stage III (who underwent gastrectomies during 1998–2002; dotted line), but not significantly different ($P = 0.350$).

DISCUSSION

As ADJ has become more sophisticated, the survival of patients with operable advanced GC has improved. In the present study, we analyzed changes in outcome as standard treatments for advanced GC have changed. We found that DFS for patients treated between 2003 and 2008 was longer than that of patients treated between 1998 and 2002. The quality of surgery for advanced GC (as represented by the number of dissected lymph nodes) did not change between the 2 periods. The prognostic improvement was most conspicuous in patients with stage III disease who were treated with S-1 ADJ.

The UFT has been used as adjuvant drug for advanced GC for a long time in Japan. Even though our sample size was small, the effectiveness of UFT as ADJ for GC was confirmed.[3] However, since S-1 has become widely used in this clinical context, the situation has changed completely. S-1 was developed as an oral anticancer agent that combines tegafur (a prodrug of fluorouracil) with 5-chloro-2,4-dihydropyrimidine and potassium oxonate at a molar ratio of 1:0.4:1 (Taiho Pharmaceutical, Tokyo, Japan).[7] The Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer (ACTS-GC) confirmed that oral S-1 administration for 1 year significantly improved DFS in patients with stage II–III GC after curative surgery.[4] From 2007 on, oral S-1 administration for 1 year has therefore been recognized as the standard postoperative ADJ for advanced GC in Japan,[5] and has been widely used in that setting since 2002.

In this study, a small amount of cancer cells remained after gastrectomy in stage II. S-1 and UFT were effective in killing the cancer cells in this stage. In stage III, S-1 was effective but UFT (serosa-negative, locally advanced) was not effective in killing cancer cells because a small amount of cancer cells remained. So, DFS for S-1 was better than that of UFT in stage III whereas it was close in stage II.

We had little data for our patients. In the ACTS-GC trail, 5-year DFS rates for S-1 were 65.4%.[8] Survival rates of S-1 ADJ in the present study were close to the ACTS-GC trail.

No randomized study comparing UFT versus S-1 as ADJ for patients with stage II–III GC has been conducted in Japan. This study is limited by its small sample size, retrospective design and single-institution cohort. In our hospital, procedures for GC are performed by specialists in GC treatment. Although surgical quality was not changed, the prognosis of patients with stage III GC improved in more recently treated patients. These data indicate the usefulness of S-1 as ADJ for these patients.

The authors declare no conflict of interest.

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