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Original Article

Ten-Year Survival of Curability B Gastric Cancer Patients Treated by Tegafur-Uracil as Postoperative Adjuvant Chemotherapy in a Common Public Hospital
—Univariate and Multivariate Analyses—

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Abstract *Purpose* : The prognosis of gastric cancer patients undergoing curability B surgery was retrospectively examined to determine the effectiveness of the administration of oral anti-cancer drugs as postoperative adjuvant chemotherapy.

Methods : This study was based on the outcomes of 86 potentially curative patients who had undergone curability B resection of gastric cancer with or without the subsequent administration of oral 5-fluorouracil analogue. There were 21 patients who underwent surgery alone with no oral anti-cancer agents (group A) and 65 patients who were treated postoperatively, mainly with UFT (Tegafur and uracil ; group B). This study compared the ten-year survival times of these two groups using univariate and multivariate analyses.

Results : The amount of UFT in group B was 354.2 ± 122.0mg and the administration period was 11.7 ± 7.2 months. The backgrounds showed significantly more older patients in group A compared than group B (P = 0.0002). A univariate analysis showed the ten-year survival rate in group B to be higher than group A (P = 0.0079). A multivariate analysis showed that the postoperative administration of UFT was an independent factor associated with prolongation of survival times as well as the extent of lymph nodes metastasis and pathological stage (P = 0.0096).

Conclusion : This study provided conventional evidence that postoperative administration of oral 5-fluorouracil analogue is associated with better long-term prognoses in patients undergoing curability B resection for gastric carcinoma.

Key words : Gastric cancer, Curability B, Ten-year survival, Postoperative adjuvant chemotherapy

Introduction

Many studies have evaluated the effectiveness of postoperative adjuvant chemotherapy after curative resection of gastric cancer[1)~4)]. The usefulness of postoperative adjuvant chemotherapy for curative resection of gastric carcinoma has previously been confirmed by meta-analyses[5)~8)].

Two randomized control studies confirmed the significant survival benefits of postoperative adjuvant chemotherapy for gastric cancer patients treated with oral UFT (5-fluorouracil (5-FU) analogue, tegafur combined with uracil in a ratio of 1 : 4, Taiho Pharmacology Tokyo, Japan) or with a S-1 (a new oral fluoropyrimidine containing tegafur, 5-chloro-2, 4-dihydropyrimidine and potassium oxonate, Taiho Pharmacology Tokyo, Japan)[9)10)]. These studies clarified the efficacy of

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adjuvant chemotherapy using a tegafur-based regimen for curatively resected gastric cancer with extensive lymph node dissection[11].

Although these reports revealed the effectiveness of chemotherapy based on the five-year survival rates, there have been no studies that reported the ten-year survival rates of gastric cancer, especially studies that focused on the correlation between curability B and adjuvant chemotherapy. The classification of postoperative curability for gastric cancer proposed by *Japanese Classification of Gastric Carcinoma*[12] defines curability B as patients with no gross residual tumors following resection with a strong possibility that some occult cancer cells may remain in the body.

The current study focused on curability B cases after surgical resection for gastric cancer and clarified the effectiveness of postoperative adjuvant chemotherapy using oral administration of uracil and tegafur. The ten-year survival rates were analyzed using univariate and multivariate methods in such patients.

Patients and Methods

Patients

This study evaluated 86 patients who underwent surgery with primary gastric cancer pathologically diagnosed as curability B in Fukuoka City Hospital from October 1989 to July 2005. The patients had no double cancer history and the causes of death were limited to the original diseases. No neoadjuvant chemotherapy had been given to the patients enrolled in this study.

The mean age of these patients was 63.7 ± 11.8 years old (ranged 33-92 y.o.) and included of 56 males and 30 females. These 86 were divided into a surgery alone group (group A, n = 21) and a UFT administration group (group B, n = 65) according to the drugs administered postoperatively. Group B received conventional oral tegafur based drugs, mainly UFT. The prognosis of patients was compared between groups A and B.

Clinicopathological investigation

Clinicopathological factors were evaluated according to *the Japanese Classification of Gastric Carcinoma* outlined by the Japanese Gastric Cancer Association[12]. Resection A indicates no residual disease with a high probability of cure with resections satisfying all of the following conditions : T1 or T2 ; N0 treated by D1, 2, 3 resection or N1 treated by D2, 3 resection ; M0, P0, H0, CY0 and proximal and distal margins > 10 mm. Resection B indicates no residual disease but it does not fulfill the criteria for "resection A". Resection C indicates definite residual disease. The curability C group included the resection C category cases that underwent a simple gastrectomy, by-pass operation and only exploration with no surgical treatment. Curability A, B and C are the categories that include the patients who underwent resection A, B and C operations, respectively.

Follow-up of the patients

Follow-up for the patients continued until their deaths and only the patients that died of gastric cancer was included. The interval of the follow-up period after the operation ranged from 99 to 5760 days (mean 1695 ± 1368, median 1272.5 days).

Statistical analysis

Univariate and multivariate analyses were performed to determine the association of age, sex, depth of tumor invasion, histological type, stage, lymph node metastasis and adjuvant chemotherapy with the ten-year survival. Statistical analyses were performed among the groups using the chi-square or non parametric Wilcoxon tests or Cochran-Armitage trend test. Survival curves were generated by the Kaplan-Meier method and the log-rank test was used to analyze the equality of the survival curves. A Cox proportional hazard model was

used for the multivariate analyses to determine the independent prognostic factors. A P value of less than 0.05 was considered to indicate significance.

Results

Profiles of the patients on each group

Table 1 shows the clinical findings of the patients of each group. The postoperative findings showed that regarding incidence, there were significantly more elderly patients in group A than in group B (P = 0.0002). There were no significant differences between the two groups regarding other factors such as sex, depth of tumor invasion, histological type stage and lymph nodes dissection.

Table 2 shows the profile of group B. The patients received 354.2 ± 122.0 mg of UFT (300 mg median and 200–600 mg range) and the administration period was 11.7 ± 7.2 months (12 months in median and 1–24 months in range).

Table 1 Background of the patients in each group

Factors		Group A (n = 21)	Group B (n = 65)	p value
age[a]		71.8 ± 10.8	60.6 ± 11.5	0.0002
male vs. female		11 vs. 10	45 vs. 20	0.159
depth of tumor invasion				
	t1, 2	3 (14.2%)	24 (36.9%)	0.052
	t3, 4	18 (85.8%)	41 (63.1%)	
Extent of lymph node metastasis				
	n0, 1	8 (38.1%)	22 (33.8%)	0.722
	n2, 3	13 (61.9%)	43 (66.2%)	
Histological type				
	Undifferentiated	10 (47.6%)	39 (60.0%)	0.3191
	differentiated	11 (52.4%)	26 (40.0%)	
Stage				
	I	0 (0%)	0 (0%)	
	II	3 (14.3%)	13 (20.0%)	0.192
	IIIA	7 (33.3%)	26 (40.0%)	
	IIIB	6 (28.6%)	20 (30.8%)	
	IV	5 (23.8%)	6 (9.2%)	
Lymph node dissection				
	D0, 1	2 (9.5%)	3 (4.6%)	0.705
	D2	16 (76.3%)	53 (81.6%)	
	D3, 4	3 (14.2%)	9 (13.8%)	

[a] : Mean ± standard deviation.
Group A : patients with surgery alone with no oral anti-cancer agents
Group B : patients that received UFT postoperatively as adjuvant chemotherapy

Table 2 Amount and length of administration of UFT for group B

	amount of UFT (mg/day)	length of administration (months)
Mean value	354.2 ± 122.0	11.7 ± 7.2
median	300	12
range	200–600	1–24

Group B : patients that received UFT postoperatively as adjuvant chemotherapy

Survival rates

The five-year survival rate of patients in group B was significantly better than that in group A (36.4% vs. 57.0%). The ten-year survival rate of group B was also significantly better than that of group A (12.1% vs. 50.6% P = 0.0079, Fig. 1).

Table 3 shows the results of univariate and multivariate analyses of the survival rates of the all cases. A univariate analysis proved that there were significant difference in the extent of lymph nodes metastasis and stage (P = 0.0117 and P = 0.0001, respectively) as well as UFT administration. Similarly, the multivariate analysis proved the extent of lymph node metastasis, stage and the postoperative administration of UFT to be independent factors for the prolongation of survival time (P = 0.0143, P = 0.0002 and P = 0.0096, respectively).

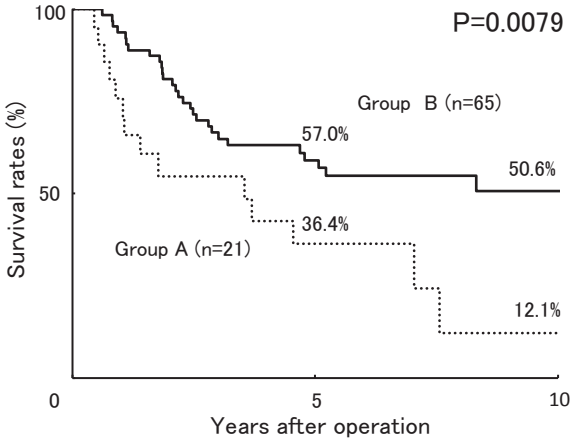

Fig. 1 Survival curves for the current patients. The dotted line represents Group A (n = 21) and the bold line indicates Group B (n = 65), respectively. The ten-year survival rates of Group B was significantly better than that of the surgery alone group (P = 0.0079).
Group A indicates patients with surgery alone with no oral anti-cancer agents, while Group B patients were prescribed UFT postoperatively as adjuvant chemotherapy.

Table 3 Univariate and multivariate analyses of the prognostic factors for all the cases

Analysis of the prognostic factors	Univariate analysis	Multivariate analysis		
Factors	p value	p value	Hazard ratio	95% CI
age				
(less than 65 vs. 65 over)	0.1599	0.1568	1.5533	0.8439-2.8662
sex				
(male vs. female)	0.8032	0.8030	0.9227	0.4905-1.7358
depth of tumor invasion				
(t1, 2 vs. t3, 4)	0.0694	0.0738	1.9623	0.9373-4.1038
lymph node metastasis				
(n0, 1 vs. n2, 3)	0.0117	0.0143	2.4348	1.1946-4.9623
histological type				
(undifferentiated vs. Differentiated)	0.2805	0.2803	0.7050	0.3738-1.3297
stage				
(stage II, IIIA Vs. IIIB, IV)	0.0001	0.0002	3.3976	1.7922-6.4412
adjuvant chemotherapy				
(Group A vs. Group B)	0.0079	0.0096	0.4260	0.2233-0.8127

CI : confidence interval
Group A : the patients with surgery alone with no oral anti-cancer agents
Group B : the patients that received UFT postoperatively as adjuvant chemotherapy.

Discussion

The outcome of gastric cancer after curative surgery is closely related to the incidence of both local recurrence and distant metastases[13]. The role of adjuvant chemotherapy is to eradicate such residual cancer cells probably left in the peritoneal cavity after surgery or other occult metastatic sites such as lung, brain and bones. Since there are no clinically sufficient techniques for detecting such micro metastasis remaining in the body, adjuvant chemotherapy is thus essential for patients with gastric cancer who undergo a potentially curative operation except for those at the early stage of disease[14].

A diagnosis of curability B[12] is actually regulated by the degree of cancer development and the extent of surgical resection. Curability B surgery indicates resection with the intent of potential cure. Therefore, it is reasonable to consider that curability B cases have a higher possibility of residual cancer cells left in the peritoneal cavity or micro distant metastases to other organs. There is general agreement that the mechanisms of the therapeutic effects of adjuvant chemotherapy depend on better perfusion of blood with access of the drug to small tumor cells, or a better sensitivity to anti-cancer drugs in rapidly proliferating cells in small tumors[15][16]. The current study found a significant prolongation of the ten-year survival rate as well as five-year survival rate by postoperative administration of UFT, which was probably due to the cytotoxicity of 5-FU on occult cancer cells in such curability B cases[17]. These findings suggest that curability B cases were good candidates for adjuvant chemotherapy.

There are a few reports of a correlation between long-term survival following curative resection and postoperative adjuvant chemotherapy. Abe et al.[18] showed that postoperative adjuvant chemotherapy did not have a significant effect on the ten-year survival of patients with T1, T2 disease. Di Costanzo et al.[19] observed no effect of intravenous adjuvant chemotherapy containing cisplatin on the long-term survival in curatively resected cases, either. However, the current univariate and multivariate analyses demonstrated the administration of UFT to be an independent prognostic factor influencing the long-term survival in such cases, as was the extent of lymph node metastasis and stage of disease.

S-1 has been the standard first-line postoperative adjuvant chemotherapy for gastric cancer patients following curative resection[20][21]. However, UFT might be an alternative to S-1 especially in older patients or in those with other strong adverse reactions to S-1, because this drug has milder adverse reactions in comparison to S-1.

In conclusion, this study demonstrated that administration of UFT as postoperative adjuvant chemotherapy might therefore result in a better prognosis for the long-term survival for curability B category gastric cancer patients in comparison to surgery alone patients according to the findings of multivariate analyses.

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Competing interests

None declared

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（和文抄録）

術後補助化学療法を施行した根治度 B 切除胃癌症例の十年生存率
―単変量，多変量解析―

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【目的】胃癌切除症例において，経口抗癌剤による術後補助化学療法の有効性が示されてきた．今回，根治度 B 切除症例における同治療法の十年生存率に及ぼす効果を解析した．
【対象と方法】福岡市民病院外科において 1989–2005 年に切除術を施行され，根治度 B と診断された胃癌 86 例を対象とし，手術単独群（group A）21 例と術後に経口フッ化ピリミジン製剤を投与した群（group B）65 例の臨床病理学的因子および 10 年生存率を retrospective に比較した．
【結果】⑴ group A は group B に比較し高齢者の割合が多かったが（p=0.0002），他の背景因子に差はなかった．⑵経口フッ化ピリミジン製剤の平均投与量は 354.2mg，平均投与期間は 11.7 カ月であった．⑵ group A の 5 年生存率，10 年生存率は各 36.4%，12.1% であったのに対し group B では同 57.0%，50.6% であり，後者においていずれも有意に良好であった（p=0.0079）．⑶多変量解析において，リンパ節転移，stage に加え，術後補助化学療法が独立した予後因子であることが判明した（p=0.0096）．
【結論】根治度 B 胃癌切除症例に対し，経口抗癌剤による術後補助化学療法を行うことにより 10 年生存率が向上した．本治療が，同症例の長期予後の改善に寄与する可能性が示された．