

Original

A Study of Conversion Surgery in Curatively Unresectable Advanced Gastric Cancer

Akiyoshi SESHIMO, Kunitomo MIYAKE, Kunihiko AMANO,
Toru NARITA, Yoshiko BAMBA, Tomoichiro HIROSAWA,
Shimpei OGAWA, Michio ITABASHI and Shingo KAMEOKA

Department of Surgery II, Tokyo Women's Medical University
(Accepted August 27, 2014)

Background: With advancements in chemotherapy, outcomes have improved even in recurrent and curatively unresectable advanced gastric cancer patients, and resection has become possible in cases of shrinkage. This procedure is called conversion surgery, which is the concept of performing surgery to further increase the effect of chemotherapy. Given this concept, such patients in our department were analyzed in order to investigate factors associated with benefit from conversion surgery. **Subjects:** In our department, chemotherapy was performed first in patients judged as curatively unresectable stage IV; 29 of these cases from 2002 through 2013 in which the primary lesion was resected after chemotherapy were the subjects of this study. **Results:** Combined administration of S-1 with other drugs was performed in 26 cases. The response rate was 55%. Surgery results were curability B in 20 cases and C in 9 cases. The median survival time was 35.7 months, and the 5-year survival rate was 30%.

When multivariate analysis was performed to identify prognostic factors, only curability was found to be a significant factor. Drug therapy continues to advance. Although appropriate indications and definitions have not been established, conversion surgery appears to be a therapeutic method that should be investigated.

Key Words: gastric cancer, chemotherapy, converting surgery, adjuvant surgery

Introduction

Advancements in chemotherapy are expected to bring beneficial effects for patients with gastrointestinal cancer. Outcomes have improved even in recurrent and advanced curatively unresectable gastric cancers. At present, the median survival time exceeds 11 months, and the tumor shrinkage effect is also good¹⁾²⁾. There have been reports of long-surviving patients and cases of resection becoming possible due to tumor shrinkage. Such surgery is also called conversion surgery³⁾⁴⁾ (adjuvant surgery). The concept is to perform surgery to further increase the effect of chemotherapy. Conventional preoperative chemotherapy has been performed in anticipation of greater effect in resectable cases; however, that is the opposite idea. Studies on the indications and significance of conversion sur-

gery have recently been initiated. In our department, chemotherapy was introduced in cases judged to be curatively unresectable, and surgery was performed in patients with severe symptoms or a shrinkage effect. These patients were analyzed in order to investigate factors associated with benefit from conversion surgery.

Subjects

In our department, 111 patients were diagnosed with preoperative stage IV cancer from January 2002 through July 2013. Gastrectomy was performed as the initial therapy in 41 of these cases, and gastrojejunostomy was performed in another 5 patients. The remaining 65 cases were judged to be curatively unresectable, and chemotherapy was started, and in 29 of these cases, the primary lesion was resected after chemotherapy (CS group). These

Table 1 Background (13th edition) of the 29 cases of the CS group Stage IV factor

M:F	18:11
Median age, years (range)	66 (46-83)
Histological type	
Differentiated/undifferentiated	11/18
Stage IV factor	
Si/P/N/H/M	21/5/15/1/4 (bone 3, lung 1)
Numbers of stage IV factors (Single/multiple)	18/11 cases
Staging laparoscopy	5 cases
Mean time to surgery, months (range)	4 (3-48)

Cases were classified according to the Japanese Classification of Gastric Carcinoma, 13th edition. Si, tumor invasion of adjacent structures; P, peritoneal metastases; N, metastasis to group 3 or 4 lymph nodes; H, liver metastases; M, distant metastases.

29 patients were the subjects of this study. The terminology in this report conforms to the Japanese Classification of Gastric Carcinoma, 13th edition⁵⁾. JMP version 10.0.2 was used for all statistical analyses.

Results

The background characteristics of the 29 subjects are shown in Table 1. The CS group consisted of 18 men and 11 women aged 46 to 83 years (median age, 66 years). Stage IV factors were T4 (tumor invasion of adjacent structure) in 21 cases, P(peritoneal metastases) in five, N (metastasis to Group 3 or 4 lymph nodes) in 15, H (liver metastases) in one, and M (distant metastases) in four cases, with 16 subjects having a single factor and 13 subjects having multiple factors. Staging laparoscopy was also performed in five patients.

The drugs administered were S-1 + CDDP in 16 cases, S-1 + paclitaxel in 7 cases, 5FU + CDDP in 3 cases, and docetaxel + CDDP + S-1 in 3 cases. The therapeutic effect on imaging was partial response (PR) in 16 cases and no change (NC) in 13 cases, with a response rate of 55%.

Surgical results were curability A&B in 20 cases and C in nine cases. Eight cases were P1 or peritoneal washing cytology-positive. The histologic effect of chemotherapy was 1a in 15 cases and greater than 1b in 10 cases.

In terms of prognosis, the median survival time (MST) was 35.7 months, and the 5-year survival rate was 30% in the CS group (Fig. 1). The prognoses of

the other stage IV groups are also shown in the diagram for reference. Because of different background factors, they should not simply be compared with each other.

Next, regarding the prognosis of the CS group by factor in terms of MST (Fig. 2), MST (in months) by histologic type was 45.2 for differentiated and 25.1 for undifferentiated ($p = 0.03$); by number of stage 4 factors, it was 36.9 for single and 10.4 for multiple ($p = 0.06$); by effect on imaging, it was 31.5 for PR and 25 for NC ($p = 0.01$); by histologic effect, it was 37.4 for effective and 30.6 for non-effective (0.03); by curability, it was 45.2 for B, 10.4 for C ($p = 0.0001$), 37.4 for P (-), and 12.9 for P (+) ($p = 0.02$). When multivariate analysis was performed using the factors showing a significant difference, namely histologic type, effect on imaging, peritoneal metastasis, and curability (Table 2), a significant difference was seen only for curability (Fig. 2).

Discussion

Starting with S-1, there have been remarkable advancements in chemotherapy as of the year 2000, and MST of 10 months with a single drug was reported for recurrent and unresectable advanced gastric cancers¹⁾. With the survival time of the conventional best supportive care being reported at three to four months^{6,7)}, chemotherapy had become definitively better. There were even some cases in which radical surgery had become possible due to shrinkage of the primary lesion and metastases. Chemotherapy is the mainstay of therapy in such

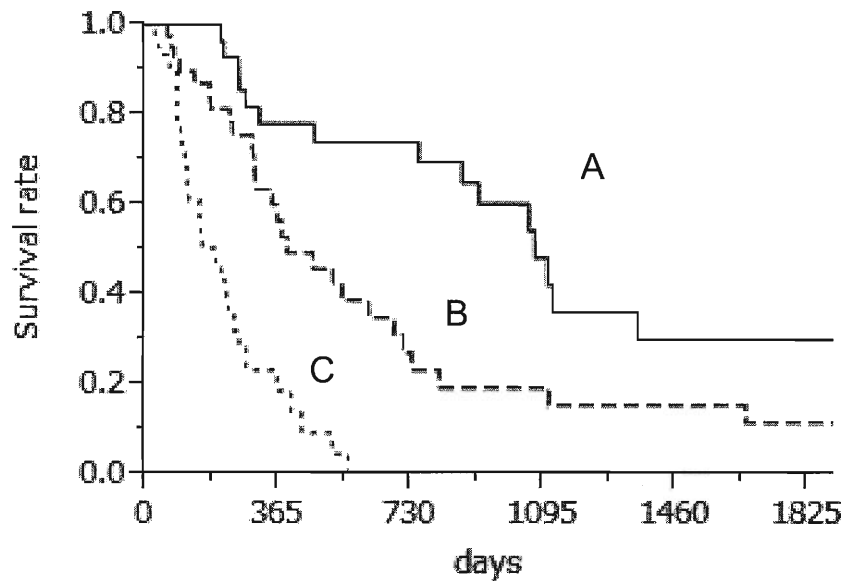


Fig. 1 Survival of stage 4 gastric cancer patients after treatment

A) CS group: MST 35.7 months.

B) 41 cases in which gastrectomy was performed as the initial therapy: MST 13.0 months.

C) 36 cases who were treated with chemotherapy alone: MST 6.3 months.

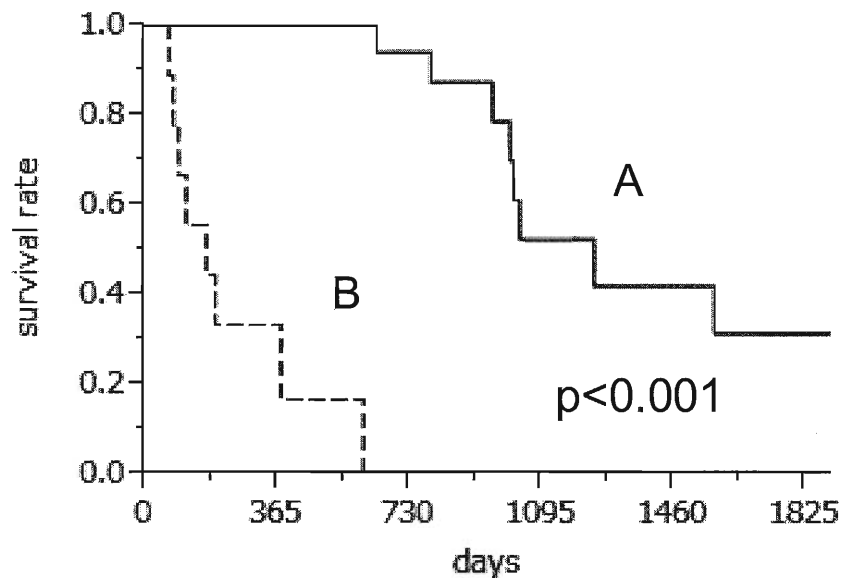


Fig. 2 Survival by curability

A) curability A&B: MST 40.0 months.

B) curability C: MST 5.6 months.

advanced cases, but surgery has been increasingly performed to further improve its effect. Consequently, research is now being conducted on the significance of this type of surgery, advocated as adjuvant surgery³⁴⁾. With the concept of conversion therapy, physicians are now performing chemotherapy on unresectable liver metastasis followed by radical surgery in colon cancer patients. A panel

discussion on conversion surgery was held at the 2014 conference of the Japanese Gastric Cancer Association; however, the definition, indications, and efficacy of this surgery have not yet been established. Taomoto et al⁸⁾ reported performing S-1 + docetaxel therapy in 103 cases of unresectable advanced gastric cancer, followed by resection in 20 of those cases. Their MST was 855 days, and it was re-

Table 2 Multivariate analysis of prognostic factors

Factor	Category	Relative Risk	p value
Histological Type	Diff.	1	0.07
	Un-dif.	3.09	
Clinical Effect	PR	1	0.91
	NC	1.09	
Peritoneal Metastasis	-	1	0.82
	+	1.17	
Curability	A&B	1	0.002
	C	27.8	

Dif, differentiated type; Un-dif, undifferentiated type; PR, partial response; CR, complete response.

ported that long-term survival can be expected in cases of macroscopic radical resection. Looking at recent results of clinical studies on chemotherapy in unresectable cases, the MST of the standard therapy group using S-1 was from 10 to 11.4 months¹⁾²⁾. Leaving aside differences in background factors, the results are considered good. However, further prospective clinical studies are necessary to confirm the efficacy, cancer staging is ambiguous due to imaging being the primary method, and there are a number of points yet to be studied, such as chemotherapy regimen, duration, and suitability of conversion surgery. Reports with small sample sizes are starting to accumulate, and we are now at the stage of performing comprehensive studies.

MST was 35.7 months in the present study, but resectability was judged by imaging before surgery, and it is very possible that some early-stage patients were included among those judged unresectable. However, there was also a subject in whom prominent cancerous peritonitis was confirmed by screening laparoscopy, and one year later, surgery was performed after complete response was confirmed by another screening laparoscopy. Although this was a study of a small number of cases, it was found that chemotherapy was therapeutically effective in differentiated cases,

and the prognosis of patients with no peritoneal metastasis after surgery was good. If the results of surgery are curability B in such cases, a relatively good prognosis can be expected.

Conclusion

Drug therapy continues to advance, and molecular-targeted drugs are now in development. Furthermore, the number of cases for which surgery is considered is expected to increase. Although appropriate indications and definitions have not been established, we believe that conversion surgery is a therapeutic method that should be investigated.

The authors indicated no conflicts of interest.

References

- 1) **Boku N, Yamamoto S, Fukuda H et al:** Gastrointestinal Oncology Study Group of the Japan Clinical Oncology Group: Fluorouracil versus combination of irinotecan plus cisplatin versus S-1 in metastatic gastric cancer: A randomized phase 3 study. *Lancet Oncol* **10**: 1063–1069, 2009
- 2) **Koizumi W, Narahara H, Hara T et al:** S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. *Lancet Oncol* **9** (3): 215–221, 2008
- 3) **Yoshida K, Yamaguchi K, Suzuki T et al:** The roles of surgical oncologist in the new era. Minimally invasive surgery for early gastric cancer and adjuvant surgery for metastatic gastric cancer. *Pathobiology* **78**: 343–352, 2011
- 4) **Suzuki T, Tanabe K, Ohdan H et al:** Preliminary trial of adjuvant surgery for advanced gastric cancer. *Oncol Lett* **1**: 743–747, 2010
- 5) *Japanese Classification of Gastric Cancer, 13th ed.* Japanese Research Society for Gastric Cancer (2010)
- 6) **Murad AM, Santiago FF, Petroianu A et al:** Modified therapy with 5-fluorouracil, doxorubicin, and methotrexate in advanced gastric cancer. *Cancer* **72** (1): 37–41, 1993
- 7) **Glimelius B, Hoffman K, Haglund U et al:** Initial or delayed chemotherapy with best supportive care in advanced gastric cancer. *Ann Oncol* **5** (2): 189–190, 1994
- 8) **Taomoto J, Tanabe K, Suzuki T et al:** Adjuvant surgery for advanced gastric cancer. *Jpn J Cancer Chemotherapy* **37**: 263–266, 2010

根治切除不能進行胃癌における conversion surgery の検討

東京女子医科大学医学部外科学（第2）講座

セシモ	アキヨシ	ミヤケ	クニトモ	アマノクニヒコ
瀬下	明良	三宅	那智	天野久仁彦
ナリタ	トオル	バンバ	ヨシコ	ヒロサワトモイチロウ
成田	徹	番場	嘉子	廣澤知一郎
オガワ	シンペイ	イタバシ	ミチオ	カメオカ シンゴ
小川	真平	板橋	道朗	亀岡 信悟

〔背景〕化学療法が進歩し、胃癌でも再発例や根治切除不能な進行例の成績も向上し、縮小例では切除も可能となってきた。このような手術は conversion surgery とよばれ、化学療法の効果をより高めるために、手術を行うという概念である。当科では、根治手術不能と判断して化学療法を導入し、症状の強い症例や縮小効果を認めた症例では手術を行ってきた。どのような症例で予後の改善が得られるか、これらの症例について検討し、conversion surgery について考察した。〔対象〕2002年1月から2013年7月までに、根治手術不能のステージIVと判断し化学療法を行い、その後に原発巣を切除した29例を対象とした。〔結果〕投与薬剤は26例でS-1と他の薬剤の複合投与が行われた。画像上の治療効果はno change (NC)/partial response (PR)が13/16例で、奏効例が55%であった。手術結果では、根治度A&B/Cは20/9例となった。化学療法の組織学的効果は、1a/above 1b:15/10であった。Median survival time (MST)は35.7ヵ月、5年生存率は30%であった。予後を組織型、画像上効果、腹膜播種、根治度で多変量解析を行うと、根治度に有意差を認めた。〔まとめ〕分子標的薬をはじめとして、薬物療法はさらに進歩を遂げつつあり、切除が可能となる根治切除不能進行胃癌が増えてきている。適応、定義等も確立していないが、conversion surgery は検討すべき治療手段として考えられる。