厚生労働科学研究費補助金
がん臨床研究事業

治癒切除不能進行胃癌に対する減量手術の意義に関する研究

平成20～22年度　総合研究報告書

研究代表者　　辻仲 利政

平成23（2011）年3月

目　　次

別添３

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Ｉ総合研究報告書

治癒切除不能進行胃癌に対する減量手術の意義に関する研究

研究代表者　辻仲利政

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研究要旨

治癒切除不能胃癌を対象とした多施設共同ランダム化比較第Ⅲ相試験を行い、減量手術の意義を検証する。本試験の対象は肝転移（H1）、腹膜播種（P1）、#16a1/b2 大動脈周囲リンパ節転移（M1）の非治癒因子のうち１つのみを有する場合とし、JCOG 初の国際共同試験として、JCOG 胃がん外科グループの 39 施設と韓国胃癌学会の主要１５施設によって実施された。本試験の予定登録症例は 330 名、症例登録期間は４年、追跡期間２年。総研究期間：６年である。

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A. 研究目的

治癒切除不能な進行胃がんに対して、減量手術が選択されるとしては、胃原発巣は化学療法が比較的奏効しにくい部位であること、胃切除により原発巣に起因する狭窄や出血などを回避できることである。しかし、減量手術を行うことにより、各種の術後合併症が発生する、術後化学療法の開始が遅

れる、化学療法の完遂率が低下する、などの可能性がある。胃切除により生存期間の延長が得られたとする報告が多いが、化学療法を行うか、胃切除を行うかの治療選択に際しては大きなバイアスがある。減量手術の意義は、最も科学的に信頼できるランダム化比較第Ⅲ相試験により検証する必要がある。

本研究は、減量手術の意義を検証する世界で始めてのランダム化比較第Ⅲ相試験であり、JCOG 初の国際共同試験として行われる。世界の胃癌の約60%は東アジアで発生しており、日本と韓国はともに世界の胃癌治療の先導する役割を担っている。

B. 研究方法

JCOGプロトコール（JCOG0705）に記載された方法に従って研究は行われる。

組織学的に胃癌と証明され、あらかじめ定められた適格規準をすべて満たす患者を登録適格患者とする。

登録・割付に関して、日本の施設は登録適格性確認票を JCOG データセンターに電話連絡または FAX 送信にて、韓国の施設は国立ソウル大学病院データセンターに Web 送信にて、登録を行う。登録にあたって治療群は日韓それぞれのデータセンターでランダムに割りつける。ランダム割り付けに際しては、国（日本/韓国）を層別因子とし、施設、リンパ節転移(N0-1/N2-3)、非治癒因子（H1/P1/ M1）を調整因子とする最小化法を用いる。

治療計画として、化学療法単独群（A群）では登録後 14 日以内に S-1+CDDP による化学療法、減量手術群（B 群）では登録後 21 日以内にプロトコール治療を減量手術および S-1+CDDP による術後化学療法を開始する。両群における化学療法は、中止規準に該当しない限り継続する。B 群で行う減量手術は、開腹による胃切除および D1 郭清を原則とし、完全な D2 郭清や他臓器の合併切除は許容しない。

エンドポイントと必要症例数に関しては、本試験の主要評価項目は生存期間、副次評価項目は無増悪生存期間および有害事象発生割合とした。本試験の A 群における 2 年生存割合は 20～25%程度と予想し、B 群においては A 群に対して 2 年生存割合で 10%の上乗せ効果を期待し、α=0.05（片側）、検出力 80%、登録期間 4 年、追跡期間 2 年とし、必要症例数は両群合計 330 名とした。

（倫理面での配慮）

本試験では、試験の参加に際しては同意説明文を用いた説明と文書での同意を前提とし、研究参加に関して各施設の倫理審査委員会の承認を受ける。研究は、JCOG 効果安全評価基準に基づいて行わる。データの取り扱いに際

しては、患者氏名等直接個人が識別できる情報を用いず、かつデータベースのセキュリティを確保し、個人情報（プライバシー）保護を厳守する。倫理面での配慮は十分保障されている。急送報告を必要とする有害事象に関しては、リエゾン事務局を通じて両国での情報交換を行うシステムを構築している。

C. 研究成果

平成19年12月にJCOGプロトコール審査委員会での承認が得られ、平成20年1月に日本においてキックオフ会議を行い、その後各施設のIRBの承認を得て試験を開始した。日本での平成23年3月における登録症例数は58症例である。韓国では、現在15施設においてIRBの承認が得られ、平成23年3月における登録症例数は50症例である。本年度、両国から定期モニタリングレポートが提出され、相互検討を行い、研究の同質性を担保している。本年度末までに11回の日韓研究者会議を開催した。韓国側のデータセンター（ソウル大学）とJCOGデータセンターの相互訪問と意見交換を継続して行っている。両国におけるデータ管理の均質性を保つよう努力した。

本研究の意義、とくに胃癌手術に関する初の国際共同試験の意義について、ACOS（アジア臨床腫瘍学会：岐阜、2010.8月）において口演発表した。

日韓研究者会議のたびに、症例集積状況が予定よりも大幅に遅れている現状について検討した。両国において、適格症例数、同意および不同意数、研究説明の施行数をサーベイランスして動機付けを高めている。適格例に対する研究説明施行率を上げること、未登録施設からの登録を積極的に促すことを同意した。適格条件を拡大して症例集積を促進する可能性について検討を行った。さらに、登録促進のために、運営委員を両国で1名ずつ増加した。日韓会議での合意事項に関して、日本の各施設担当者に通知した。

急送報告の対象となる予期されないプロトコール治療中の死亡がいままで2件あり、JCOG効果安全評価委員会に急送報告を行い、possibleと判定された。日本の参加施設には班会議時に報告し、韓国へは英訳した報告書を送り日韓会議にて報告した。

新たに、シンガポール国立大学外科から当研究への参加希望があり、プロトコールを英訳して送付した。それに基づいてIRB申請され、許可された。2011.4月から登録可能となる予定である。

D. 考察

本試験の結果、減量手術群の優越性が示された場合には、現在の標準治療である化学療法単独治療に延命効果で優る新しい標準治療が確立されるこ

とになる。減量手術群の優越性が示されなかったとしても、これまで十分なエビデンスがないまま広く行われていた治癒切除不能進行胃癌に対する化学療法施行前の胃切除術に対して歯止めをかけ、化学療法単独治療が標準治療であるという確固たるエビデンスを示す意義がある。また、本研究を日韓国際共同研究として行うことで、迅速な症例登録が得られるだけではなく、両国における結果の再現性が確認され、得られた結果の国際的インパクトも非常に大きい。

両国でのサーベイランスの結果から、本研究の対象となる患者数は、胃がん発生の多い両国においても比較的少ないことが判明した。症例数を確保する点でも、国際共同試験として本試験を計画したことは妥当であった。また、従来 JCOG 胃がん外科グループの第3相試験においても、登録終了までに予定よりも約2倍の期間を有してきている。外科試験は登録に時間がかかるが、研究者主導でしか行えないこと、類似した試験が行われていないことなどから、時間がかかっても得られた結果のもつ意義は大きく、科学的重要性も高い。

研究開始から3年経過して、国際共同研究体制が整ってきた。登録促進のために取るべき方法として、未登録施設の解消、適格症例の見逃しの防止、研究説明症例施行率の向上を繰り返し日韓会議と班会議において説明してきたが、非常に適格性が得られにくい研究であること、同意取得率に限界があることから、大きな改善は得られていない。

しかしながら、定期交流を重ねることにより、研究推進への共同意識が形成され、質の高い研究となるための基盤出来てきている。リエゾン事務局を介した相互情報交換も機能してきており、国際共同研究に対する経験が蓄積されてきた。

進行胃がんに対する治療開発が、日韓国際共同研究として行われていることはアジアおよび欧米において認知されてきている。現在の共同研究体制は、新たな共同研究の基盤形成に役だっている。

E. 結論

国際共同研究の基盤が固まり、症例集積が両国で開始された。対象症例が限られているため、研究の遅れはあるが着実に集積が進んでおり、最終結果が得られる可能性が高い。

F. 健康危険情報

両国において、健康危険事象が発生した場合の対応システムを確立している。現在までに、前述したように治療に関連した重篤な健康危険事象が計2例発生した。高度進行胃がんが対象であり、治療関連死亡がある程度予想さ

れる。急送報告を JCOG 効果安全性評価委員会に提出し、回答を得た。回答を日本の研究者には班会議にて周知し、韓国研究者にはリエゾン事務局を通じて、各 IRB に報告してもらった。

G.研究結果

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H. 知的財産の出願・登録状況

なし

研究成果の刊行に関する一覧表

辻仲利政

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Randomized Controlled Trial Comparing Gastrectomy Plus Chemotherapy with Chemotherapy Alone in Advanced Gastric Cancer with A Single Non-curable Factor: Japan Clinical Oncology Group Study JCOG 0705 and Korea Gastric Cancer Association Study KGCA01

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Received March 15, 2008; accepted June 10, 2008; published online July 9, 2008

A randomized controlled trial has started in both Japan and Korea to evaluate the role of gastrectomy in the management of incurable advanced gastric cancer (AGC). Patients with AGC diagnosed as having a single non-curable factor are randomized to gastrectomy plus chemotherapy or chemotherapy alone. Surgeons at 33 specialized centers in Japan and at 15 high-volume hospitals in Korea will recruit 330 patients. Primary end-point is overall survival, and secondary end-points are progression-free survival and adverse events associated with either gastrectomy or chemotherapy.

Key words: gastrectomy – chemotherapy – advanced gastric cancer – non-curable factor – randomized controlled trial

INTRODUCTION

The prognosis of advanced gastric cancer (AGC) patients with non-curable factors, such as hepatic and peritoneal metastases, is poor and most of them die within 1 year. For these patients, the role of gastrectomy remains controversial. However, gastrectomy is the preferred procedure for these patients, even in the absence of any symptoms such as bleeding and stenosis, based on the results of retrospective studies showing that the procedure confers a survival benefit. In the literature (1–9), overall survival of 8.0–12.2 months is reported with gastrectomy compared with 2.4–6.7 months without gastrectomy, and the survival benefit of gastrectomy is obtained only in patients with a single non-curable factor. Obviously, there should be enormous selection bias in these data, generally speaking in favor of surgical patients. Furthermore, chemotherapy alone has recently shown, for the first time, a median survival time over 1 year in AGC deemed incurable (10). These situations warrant a prospective randomized controlled trial designed to investigate the role of gastrectomy in AGC with a single non-curable factor. The Clinical Trial Review Committee of the Japan Clinical Oncology Group (JCOG) approved the following protocol on 18 December 2007, and the study was activated on 4 February 2008.

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PROTOCOL DIGEST OF THE JCOG0705/ KGCA01

Purpose

The purpose of this trial was to investigate the superiority of gastrectomy followed by chemotherapy to chemotherapy alone in clinically stage IV AGC with a single non-curable factor, in terms of survival benefit and safety associated with gastrectomy or chemotherapy.

Study Setting

The study was a multi-institutional (33 specialized centers in Japan and 15 high-volume hospitals in Korea) randomized controlled trial.

Resources

Grants-in-Aid for Cancer Research (17S-3, 17S-5), from the Ministry of Health, Labor and Welfare, Japan. Grants for Cancer Research, from the Korean Gastric Cancer Association, Korea.

End-Points

The primary end-point is overall survival. The secondary end-points are progression-free survival and adverse events associated with gastrectomy or chemotherapy.

Eligibility Criteria

Tumors are staged according to the Japanese Classification of Gastric Carcinoma (11).

Inclusion Criteria

Patients are included in the trial if they meet all of the following criteria: (i) histologically proven primary gastric adenocarcinoma, (ii) presence of only one of the following patterns of metastasis, which is confirmed by both computed tomography (CT) scan and staging laparoscopy (or open laparotomy): (a) hepatic metastasis (H1) (2–4 lesions, maximum diameter <5 cm), (b) peritoneal dissemination (P1) without massive ascites or intestinal obstruction or (c) extensive para-aortic lymph node metastasis (No. 16a1 and/or b2), (iii) clinical T1-3, (iv) no evidence of para-aortic and/or retropancreatic lymph node metastasis (i.e. N0–2) in the cases of hepatic or peritoneal metastasis, (v) no evidence of other distant metastasis than H1, P1 or LN 16a1/b2, (vi) no apparent pleural effusion, (vii) length of esophageal invasion 3 cm or less with no need of thoracotomy for resection, (viii) not stump carcinoma, (ix) aged 20–75 year old, (x) performance status (PS) of 0 or 1 on Eastern Cooperative Oncology Group (ECOG) scale, (xi) sufficient oral intake without active bleeding from the gastric tumor, (xii) no prior treatment of chemotherapy or radiation therapy against any other malignancies, and no prior treatment for gastric cancer except EMR (endoscopic mucosal resection), (xiii) adequate organ functions defined as indicated below: (a) WBC $\geq 3000/mm^3$, WBC $\leq 12\ 000/mm^3$, (b) Hb ≥ 8.0 g/dl without any transfusion 2 weeks before enrollment, (c) Plt $\geq 100\ 000/mm^3$, (d) AST ≤ 100 IU/l, (e) ALT ≤ 100 IU/l, (f) T.Bil ≤ 2.0 mg/dl, (g) Cr ≤ 1.2 mg/dl, (h) Ccr ≥ 60 ml/min/body and (xiv) written informed consent.

Exclusion Criteria

Patients are excluded if they meet any of the following criteria: (i) active double cancer (synchronous double cancer and metachronous double cancer within five disease-free years), excluding carcinoma *in situ* (lesions equal to intraepithelial or intramucosal cancer), (ii) pregnant or breast-feeding women, (iii) severe mental disorder, (iv) systemic administration of corticosteroids, (v) medication of furucytocin, fenytoin or warfarin, (vi) active bacterial infection or mycosis, affecting systemic condition, (vii) unstable angina or myocardial infarction within 6 months of the trial, (viii) unstable hypertension, (ix) diabetes mellitus, uncontrolled or controlled with insulin, (x) severe respiratory disease requiring continuous oxygen therapy.

Randomization

After confirmation of the above criteria, registration is made by telephone call or fax to the JCOG Data Center in Japan, and by web system to Seoul National University Hospital (SNUH) Data Center in Korea. Patients are randomized in each country by a minimization method of balancing the arms according to institution, nodal status (N0–1/N2–3) and non-curable factor (hepatic/peritoneal/para-aortic metastasis).

Treatment Methods

Gastrectomy Plus Chemotherapy

Either a total, distal or proximal gastrectomy with D1 lymph node dissection is performed depending on the tumor location with the metastatic lesions untouched. Neither complete D2 lymphadenectomy nor combined resection of adjacent organs except for gallbladder, mesocolon and diaphragm is acceptable. Within 8 weeks after surgery, the patient is placed on a chemotherapy regimen, S-1 + CDDP. Oral S-1 is administered at a dose of 80 mg/m^2/day for 3 consecutive weeks followed by a 2-week rest. Cisplatin is delivered on Day 8 at a dose of 60 mg/m^2. This regimen is repeated every 5 weeks until disease progression.

Chemotherapy Alone

Patients receive the same chemotherapy as described above without any operation until disease progression.

Follow-up

Patients are assessed every months to detect any adverse events with verbal interview, physical examination and blood tests, including a complete blood cell count and measurements of liver and renal function, until progressive disease. Abdominal CT scan and measurements of CEA and CA19-9 are carried out every 3 months.

Study Design and Statistical Methods

This trial is designed to evaluate the superiority of gastrectomy followed by chemotherapy to chemotherapy alone in terms of overall survival. The hypothesis to be tested is that 2-year overall survival on gastrectomy followed by chemotherapy is greater than that (20–25%) obtained by chemotherapy alone by 10%. If a 10% improvement in a 2-year overall survival rate is demonstrated, gastrectomy followed by chemotherapy will be the preferred treatment. The planned sample size is 330, 165 cases per arm, with 2 years follow-up after 4 years of accrual. This will provide an 80% power with a one-sided alpha of 5%.

Interim Analysis, Monitoring and Audit

Two interim analyses are planned, with adjustments for repeated comparisons taken into account by the Lan and DeMets method. We use the O'Brien–Fleming-type alpha spending function. The Data and Safety Monitoring Committee (DSMC) of the JCOG independently reviews the interim analysis report and will consider stopping the trial early, in agreement with SNUH Data Center. Central monitoring is performed by the respective Data Center in each country to ensure data submission, patient eligibility, protocol compliance, safety and on-schedule study progress. The monitoring reports are submitted to and reviewed by the respective Data Center independently every 6 months. The monitoring summary is exchanged between the two countries semiannually. Audits of the participating facilities are also carried out independently in each country, and brief summaries are exchanged.

PARTICIPATING INSTITUTIONS

Japan: Iwate Medical University, Sendai National Hospital, Miyagi Cancer Center, Yamagata Prefectural Central Hospital, National Defense Medical College, Saitama Cancer Center, National Cancer Center Hospital East, National Cancer Center Hospital, Tokyo Metropolitan Komagome Hospital, Tokyo Medical and Dental University, Cancer Institute Hospital, Tokyo Metropolitan Bokutoh Hospital, Kanagawa Cancer Center, Niigata Cancer Center Hospital, Nagaoka Chuo General Hospital, Tsubame Rosai Hospital, Toyama Prefectural Central Hospital, Gifu Municipal Hospital, Shizuoka Prefectural General Hospital, Aichi Cancer Center, Fujita Health University, Kyoto 2nd Red Cross Hospital, Kinki University, Osaka Medical Center for Cancer and Cardiovascular Diseases, National Osaka Medical Center, Osaka Medical College, Toyonaka Municipal Hospital, Sakai Municipal Hospital, Itami City Hospital, Wakayama Medical University, Hiroshima City Hospital, National Shikoku Cancer Center, Oita University.

Korea: Ajou University Hospital, Chonnam University Hwasun Hospital, Dong-A University Hospital, Hanyang University Hospital, Kangnam St Mary's Hospital, Korea Cancer Center Hospital, Korea University Guro Hospital, Kosin University Hospital, Kyungpook University Hospital, National Cancer Center, Samsung Medical Center, Seoul National University Hospital, Seoul National University Bundang Hospital, Yonsei University Severance Hospital, Yonsei University Youngdong Hospital.

Conflict of interest statement

Mitsuru Sasako states that he has received honoraria from Taiho Pharmaceutical Company for giving educational lectures in 2007.

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ANTICANCER RESEARCH *28*: 2379-2384 (2008)

The Significance of Gastrectomy in Advanced Gastric Cancer Patients with Non-curative Factors

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Abstract. *Background: The role of gastrectomy in the treatment of advanced gastric cancer patients with non-curative factors remains controversial. We investigated prognostic factors and evaluated the role of gastrectomy in such patients. Patients and Methods: Eighty-eight advanced gastric cancer patients with non-curative factors were prospectively studied. The patients were categorized into the following two groups: Group A: 52 patients who underwent gastrectomy and subsequently received chemotherapy, Group B: 36 patients who received chemotherapy alone. Results: The median survival times of group A and B patients were 351 and 182 days, respectively (p=0.008). Multivariate analysis showed that gastrectomy was the only positive independent prognostic factor, with no effect on the results of chemotherapy. There was no significant difference in the duration of hospital stay between patients of the two groups, while significantly longer maintenance of oral intake was observed for group A. Conclusion: In advanced gastric cancer patients with non-curative factors, gastrectomy was beneficial for survival with longer maintenance of oral intake.*

The prognosis of advanced gastric cancer (AGC) patients with non-curative factors, such as hepatic and peritoneal metastases, is poor and most of them die within one year. For these patients, opinion is divided on the role of gastrectomy while leaving metastatic lesions. However, gastrectomy is the preferred procedure for AGC, even in the absence of any symptoms such as bleeding and stenosis, based on the results of retrospective studies showing that the procedure confers a survival benefit (1, 2).

On the other hand, despite the potential survival benefit of gastrectomy, patient quality of life (QOL), such as duration of hospital stay and oral intake, may be negatively influenced by gastrectomy because of postoperative morbidities. In addition, gastrectomy may reduce the efficacy and safety of chemotherapy, which is considered to be an integral part of the treatment for AGC patients, due to delayed commencement of postoperative chemotherapy or reduced compliance with chemotherapy.

The present study was conducted to investigate whether gastrectomy followed by chemotherapy was more beneficial than chemotherapy alone in AGC patients with non-curative factors.

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Key Words: Gastrectomy, non-curative factor, prognostic factor, advanced gastric cancer.

Patients and Methods

Patient characteristics. This study was conducted on 88 patients diagnosed with AGC having non-curative factors at Osaka National Hospital between Jan 1, 1999 and Dec 31, 2004. These patients were categorized into the two groups shown in Table I. A total of 52 patients in group A, 38 males and 14 females with a median age of 69 (range: 43-87) years, underwent gastrectomy with subsequent chemotherapy. Thirty-six patients in group B, 27 males and 9 females with a median age of 66 (range: 19-80) years, received chemotherapy alone without gastrectomy. All of the patients had a performance status (PS) of 2 or less on the Eastern Cooperative Oncology Group (ECOG) scale at initial diagnosis and none had received prior chemotherapy or radiation therapy. Most patients had advanced cancer of T3 or deeper, with positive lymph node metastases. Histologically, around one-third of patients had intestinal-type adenocarcinoma and two-thirds had diffuse-type adenocarcinoma. The patients had a range of non-curative factors. If a tumor showed infiltration to adjacent organs (T4) and was deemed radically unresectable, such a T4 tumor was regarded as a non-curative factor. Para-aortic lymph node metastasis (N3) was also considered to be a non-curative factor. In addition, hepatic metastasis (H), peritoneal metastasis (P), positive cytology of abdominal lavage (CY) and distant metastasis (M) were all regarded as non-curative factors. The classifications of T-stage, N-stage and non-curative factors were made in accordance with the guidelines of the Japanese Gastric Cancer Association (3). As for the number of non-curative factors, 38 patients in group A had a single non-curative factor while 14 patients had two or more; 15 patients in group B had a single factor and 21 patients had two or more.

Various chemotherapeutic agents were administered to the patients in both groups. More than half the patients received an oral fluoropyrimidine derivative, such as S-1 (4), UFT (a combination

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Table I. *Patient characteristics.*

	Group A	Group B	*p*-value
Number of patients	52	36	
Male/female	38/14	27/9	NS
Median age, years (range)	69 (43-87)	66 (19-80)	NS
PS 0/1/2	28/19/5	14/17/5	NS
T stage: 2/3/4	4/28/20	1/23/12	NS
N stage: 0/1/2/3	2/17/23/10	3/13/5/15	**0.010**
Histological type:			
intestinal/diffuse	19/33	11/25	NS
Noncurative factor:			
T4/N3/H/PCY/M	2/10/15/37/4	12/15/16/18/8	**0.005**
Number of noncurative factors:			
1/2≤	38/14	15/21	**0.004**
Chemotherapeutic agents:			NS
S-1/UFT/5'-DFUR	39	27	
Cisplatin	12	15	
Irinotecan	16	14	
Paclitaxel	20	11	

Group A consisted of 52 patients undergoing gastrectomy and subsequent chemotherapy; Group B comprised 36 patients receiving chemotherapy alone without chemotherapy. PS: performance status, T4: tumor infiltrating to adjacent organs, N3: para-aortic lymph node metastasis, H: hepatic metastasis, P: peritoneal metastasis, CY: positive cytology of abdominal lavage, M: distant metastasis. UFT: uracil-tegafur, 5'DFUR: 5'-deoxy-5-fluorouridine, NS: not significant. *P*-values were calculated by χ^2 test.

of uracil and tegafur at a molar ratio of 4 to 1) and 5'-DFUR (5'-deoxy-5-fluorouridine). Intravenous agents such as cisplatin, irinotecan and paclitaxel were also administered to fewer than half the patients, as shown in Table I.

Analyses of prognostic factors. The therapeutic course of each patient was followed until death or until Dec 31st 2006. Seven patients in group A were alive on Dec 31st 2006 and treated as censored observations for survival analysis. The survival time was defined as the duration from the date of starting therapy, gastrectomy or chemotherapy, to death or Dec 31st 2006.

A univariate analysis was used to assess the association between each clinicopathological factor and overall survival. A multivariate analysis was performed to identify variables independently associated with survival.

QOL assessment. Duration of hospital stay and oral intake in each patient were estimated and used to assess the patient's QOL. The following indices were set: hospitalization index, the duration of hospital stay as a proportion of the overall survival period; and ingestion index, the duration of the period in which oral intake was maintained as a proportion of the overall survival period. These were used to make comparisons between the two groups.

Efficacy and safety of chemotherapy. Response to chemotherapy in each patient was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) (5) whenever possible. Toxicities of chemotherapy in all patients were scored according to the Common Terminology Criteria for Adverse Events version 3.0 (CTCAE) (6).

Statistical analysis. Stat View software Version 5.0 (SAS Institute Inc. Cary, NC, USA.) was used for all statistical analyses and a *p*-value of less than 0.05 was considered significant. The χ^2 test was employed to evaluate differences in proportions, and the differential significances of age, hospitalization index and ingestion index were determined by the Mann-Whitney test. The survival rates were calculated according to the Kaplan-Meier method and difference was evaluated by the log rank test. Cox's proportional hazards regression model was used to identify prognostic factors for survival.

Results

Overall survival and prognostic factors. Overall survival time was compared between the two groups. The median survival time (MST) of group A was 351 days, while that of group B was 182 days, with a significant difference between the two groups (p=0.008), as shown in Figure 1. Actual survival rates of 48.1% at 1 year and 20.2% at 2 years were obtained in group A, while Group B had rates of 16.7% at 1 year and 0% at 2 years. The results of univariate analysis of various clinicopathological factors for overall survival are summarized in Table II. Absence of gastrectomy (hazard ratio: 2.165, p=0.001), existence of T4 factor (hazard ratio: 2.190, p=0.0108), existence of N3 factor (hazard ratio: 1.897, p=0.0096), and presence of multiple non-curative factors (hazard ratio: 2.056, p=0.0020) were identified as significantly negative prognostic factors for overall survival. Multivariate analysis showed that only absence of gastrectomy was an independent negative prognostic factor (relative risk 1.745, p=0.0282), as shown in Table III.

Hospitalization Index and Ingestion Index. As shown in Table IV, the Hospitalization Index was not different between the two groups. On the other hand, the Ingestion Index was significantly higher in group A than in group B.

Influence of gastrectomy on efficacy and safety of chemotherapy. As shown in Table V, 43 patients (82.7%) in group A received chemotherapy after gastrectomy with the exception of 9 patients who had postoperative morbidities. The average interval between gastrectomy and commencement of chemotherapy was 44 days in group A. Twenty-five patients in group A had only P/CY factors, which were not evaluable on RECIST. In group B, all the patients received chemotherapy and had evaluable lesions, though 13 patients underwent the following surgical interventions prior to chemotherapy: exploratory laparotomy in 6, gastroenteroanastomosis in 4, jejunostomy in 1, and insertion of metallic stent into pyloric stenosis in 2. The best response to chemotherapy demonstrated in the entire therapeutic period in each patient is shown in Table V; response rates of around 25% were obtained in both groups with no significant difference (p=0.7515). Hematological and nonhematological

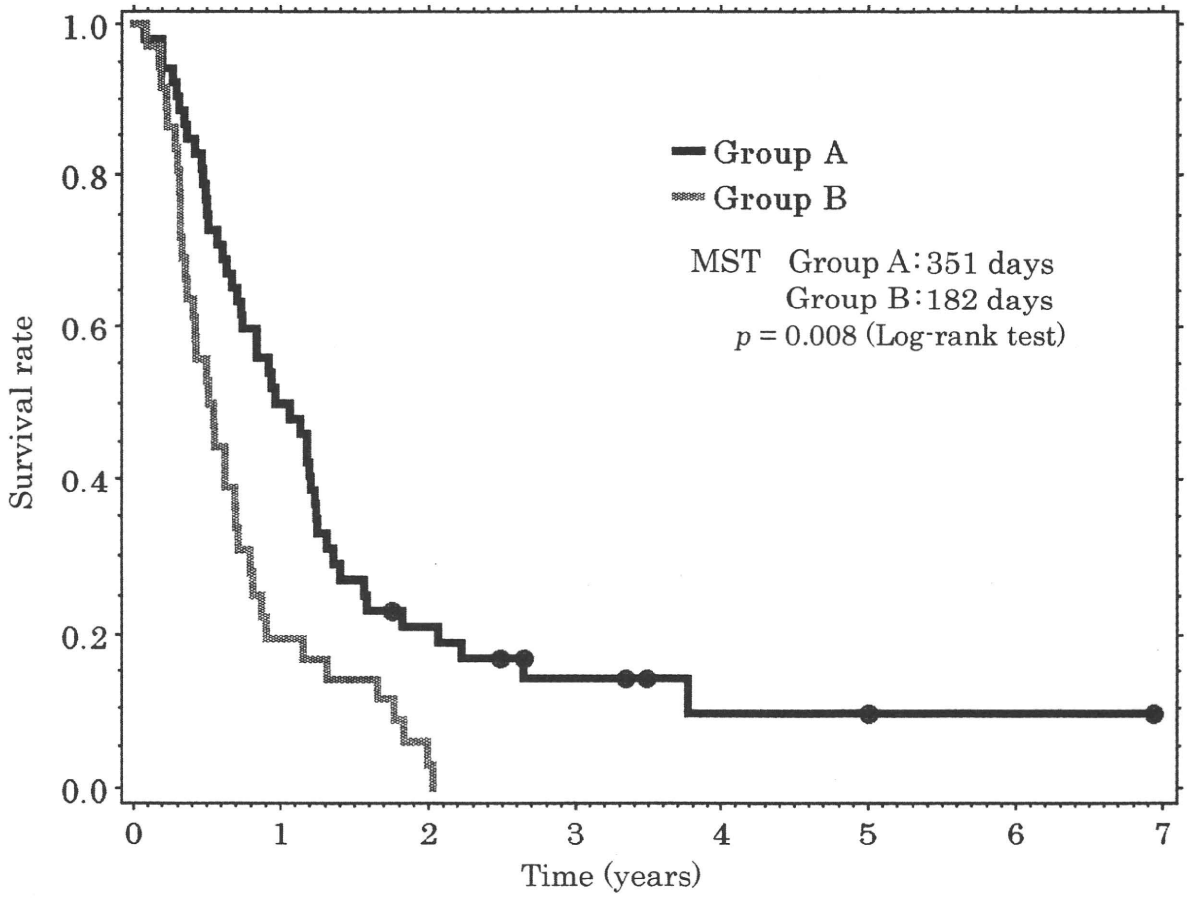

Figure 1. *Survival curves of the patients in Group A and B.*

adverse events during the entire chemotherapeutic period in both groups are shown in Table VI. There was no significant difference between the two groups, with no chemotherapy-related deaths in either group.

Discussion

An average of 15-30% of patients with newly diagnosed advanced gastric cancer (AGC) have non-curative factors that are detected initially at surgical staging by laparoscopy or laparotomy (7-11). When the disease is deemed incurable, treatment of AGC remains investigational in terms of prognosis and QOL.

Regarding the prognosis of patients with incurable AGC, some reports have shown the survival benefit of gastrectomy (1, 2, 10, 12-16). An MST of 8.0-12.2 months was reported with gastrectomy, compared to 2.4-6.7 months without gastrectomy. In addition, the survival benefit of gastrectomy was obtained only in patients with a single non-curative factor (1, 10, 12, 13, 16). In accordance with these findings, our patients showed an MST of 351 days with gastrectomy and 182 days without gastrectomy, a significant difference (p=0.008). In addition, the presence of a single non-curative factor was identified as a prognostic factor by univariate analysis as shown in Table II, and multivariate analysis showed that only the presence of gastrectomy was independently correlated with better prognosis (relative risk 0.573, p=0.0282) in Table III.

With regard to the safety of gastrectomy in AGC patients with non-curative factors, morbidity rates of 30-40% (11-13, 17, 18) and mortality rates of around 10% (11-14, 17-19) have been reported. Our patients had an operative morbidity of 21.2% and mortality of 3.8% (data not shown). These are good figures and might have partly contributed to the better survival of our patients with gastrectomy.

Satisfactory palliation of symptoms and QOL are two other principal objectives in the care of patients with non-curative gastric cancer. There have been few reports on the objective assessment of QOL in these patients. However, Ouchi *et al.* assessed hospital-free survival as a indicator of QOL and reported that total gastrectomy performed in patients with local

Table II. *Univariate analysis of various prognostic factors.*

	Hazard ratio	95% CI	*p*-value
Gastrectomy			
Absent	2.165	1.368-3.425	**0.0010**
Gender			
Female	0.826	0.500-1.366	0.4569
Age			
≥70	1.241	0.792-1.946	0.3461
Perfomance Status			
0	1.000		0.5727
1	0.389	0.119-1.278	
2	0.287	0.082-1.000	
Macroscopic type of tumor			
3&4	1.068	0.637-1.795	0.8016
Histology			
Diffuse type	0.890	0.559-1.417	0.6242
T stage			
2	1.000		0.5216
3	1.634	0.582-4.588	
4	1.838	0.637-5.305	
N stage			
0	1.000		0.2457
1	1.730	0.601-4.983	
2	1.958	0.664-5.774	
3	2.646	0.902-7.760	
T4 factor			
Present	2.190	1.199-4.000	**0.0108**
N3 factor			
Present	1.897	1.168-3.081	**0.0096**
H factor			
Present	1.160	0.734-1.832	0.5255
P/CY factor			
Present	0.825	0.726-1.293	0.4008
M factor			
Present	1.468	0.791-2.724	0.2300
No. of non-curative factors			
≥2	2.056	1.302-3.244	**0.0020**

P-values were calculated by the Cox's proportional hazards regression model.

Table III. *Multivariate analysis of prognostics factors.*

	Hazard ratio	95% CI	*p*-value
Gastrectomy			
Absent	1.745	1.061-2.871	0.0282
No. of non-curative factors			
≥2	1.464	0.752-2.851	0.2623
T4 factor			
Present	1.342	0.650-2.768	0.4265
N3 factor			
Present	1.228	0.638-2.364	0.5386

Table IV. *Hospitalization index and ingestion index.*

	Group A	Group B	*p*-value
Hospitalization index	0.311	0.406	0.066
Ingestion index	0.871	0.798	0.003

Hospitalization Index: the duration of hospital stay relative to the overall survival period. Ingestion Index: the duration of the period in which oral intake was maintained relative to the overall survival period. *P*-values were calculated by the Mann-Whitney test.

Table V. *Best response to chemotherapy.*

	Group A	Group B
CR	3	1
PR	1	9
SD	6	14
PD	8	12
NE	25	0
RR	22.2%	27.8%

RR: response rate, CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease, NE: not evaluable.

or no peritoneal metastasis and distal gastrectomy showed a better outcome for hospital-free survival than total gastrectomy performed with extensive peritoneal metastasis (2). Hoya *et al.* adopted hospitalization, the average volume of oral intake and variation in body weight for assessing QOL (20). They reported that in patients who underwent total gastrectomy, hospitalization was longer, the average volume of oral intake was less and the variation in body weight was greater than in patients with unresectable tumors. We evaluated the length of hospital stay after initiation of treatment and the period for which oral intake was maintained as objective indicators of QOL. In Table IV, it can be seen that gastrectomy was useful for maintaining a longer period of oral intake, while there was no significant difference between total gastrectomy and distal gastrectomy (data not shown).

Although chemotherapy is an integral part of the treatment of AGC, it may be affected by surgery due to delayed commencement of postoperative chemotherapy or reduced compliance with chemotherapy after surgery. However, in our patients, gastrectomy had no effect on either efficacy or safety of chemotherapy, as shown in Tables V and VI. There are few reports that address the question of whether gastrectomy performed in patients with non-curative factors is beneficial in terms of efficacy, safety and compliance with chemotherapy in a course of adjuvant chemotherapy.

In conclusion, gastrectomy was shown to be beneficial for survival with oral intake maintained for a longer period and it did not affect the results of chemotherapy in AGC patients with non-curative factors. These results warrant a prospective

Table VI. *The number of patients experiencing adverse events suspected of being related to chemotherapy.*

Grade	Group A	Group B
Leukopenia		
1	3	1
2	7	4
3	5	5
4	2	2
3/4	16.3%	19.4%
Anemia		
1	1	3
2	1	1
3	0	2
4	1	0
3/4	2.3%	5.6%
Thrombocytopenia		
1	1	0
2	0	1
3	1	1
4	0	0
3/4	2.3%	2.8%
Elevation of AST/ALT/Bilirubin		
1	5	4
2	5	3
3	1	1
4	0	0
3/4	2.3%	2.8%
Anorexia		
1	1	0
2	1	0
3	2	2
4	0	0
3/4	4.7%	5.6%
Diarrhea		
1	3	1
2	1	2
3	0	0
4	0	0
3/4	0.0%	0.0%
Stomatitis		
1	2	3
2	1	0
3	0	0
4	0	0
3/4	0.0%	0.0%
Nausea		
1	1	2
2	5	2
3	0	0
4	0	0
3/4	0.0%	0.0%

Group A consisted of 43 patients undergoing gastrectomy and subsequent chemotherapy, while Group B comprised 36 patients receiving chemotherapy alone.

randomized controlled trial designed to investigate the significance of gastrectomy in AGC patients with non-curative factors.

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Received February 11, 2008
Revised April 8, 2008
Accepted May 2, 2008

Int J Clin Oncol (2008) 13:117–120
DOI 10.1007/s10147-007-0743-1

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Current status of chemoradiotherapy for gastric cancer in Japan

Received: November 5, 2007

Abstract Chemoradiotherapy (CRT) is the latest modality to be explored as a treatment for gastric cancer. Advances have been made in the United States with CRT as preoperative or postoperative adjuvant treatment. The rationale for preoperative or postoperative adjuvant CRT is to increase the curability of surgery or to prevent local recurrence, because standard surgery (D0 or D1) is not sufficient to control local relapse and improve survival where disease has become advanced. D2 is standard in Japan and D2 gastrectomy plus postoperative adjuvant chemotherapy with S-1 is currently standard for stage II and III cancer. Predominant recurrence patterns associated with these advanced disease stages are peritoneal dissemination and hematogenous metastasis. Local relapse or regional nodal recurrence is infrequent. CRT has been provided at only a limited number of institutions in Japan. The response to and safety of CRT for gastric cancer, in combination with various chemotherapeutic agents, are currently being studied in patients with unresectable or recurrent disease. Considering the high response rate, CRT seems to be an attractive option. In the near future, an examination will be made to ascertain whether neoadjuvant CRT in combination with extensive surgery has survival benefits in the treatment of locally advanced disease. Prior to this, a phase I/II study should be conducted in patients with unresectable or recurrent disease.

Key words Gastric cancer · Chemoradiotherapy · Adjuvant therapy · Unresectable/Recurrent cancer · Surgery · Lymphadenectomy

Introduction

Chemoradiotherapy (CRT) is the latest modality to be explored as a treatment for gastric cancer. A report from Japanese Society for Therapeutic Radiation and Oncology (JASTRO) in 2005 showed that, in common malignancies, radiation therapy (RT) was used in breast cancers (20%), lung cancers (20%), urological cancers (12%), head and neck cancers (11%), esophageal cancers (7%), and malignancies of the central nervous system and gynecological cancers (6%). Abdominal malignancies, with the exception of pancreatic and biliary malignancies, are rarely candidates for RT in Japan. The limited numbers of personnel available for carrying out RT, such as radiation oncologists, medical physicists, and radiation technologists, may be a primary reason for this. Thus, because we are unfamiliar with the use of RT for abdominal organs, no standardization of the irradiation field and technique has been established. CRT as treatment for gastric cancer has been tried in the West. In the 1970s, phase III trials for advanced tumors were conducted to demonstrate the superiority of CRT over chemotherapy (CT) or RT.[1,2] In the 1990s, postoperative CRT became established, and a well-known phase III trial[3] showed that postoperative CRT in conjunction with CT improved survival over surgery alone, though the quality of surgery in the study was criticized. Since the 2000s, high pathologic response and curative resection rates have been reported for neoadjuvant CRT.[4–6] The rationale for neoadjuvant CRT is to increase the curability of surgery and to prevent local recurrence, because surgery alone is considered insufficient to prevent local relapse, the rate of which has been reported to be 38%–93%.[7] In contrast, only one phase III trial of the use of RT for gastric cancer has been conducted in Japan. This trial compared intraoperative RT for advanced disease with surgery alone, and showed that intraoperative RT may have a potential benefit.[8] RT/CRT has been employed for the palliation of symptoms, such as gastric or biliary obstruction, pain due to bone or lymph node metastasis, and bleeding. Among these conditions, pain control seemed to be the main reason for using RT/CRT in gastric cancer. Since the 2000s, case reports and the results of a phase II study of CRT for unresectable/recurrent tumor have been published.[9] Japan lags well behind the West in the use of RT/CRT for gastric cancer.

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