厚生労働科学研究費補助金

がん臨床研究事業

# 進行胃がんの生存率を向上させる標準的治療法の開発に関する研究

## 平成21年度 総括研究報告書

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腹腔鏡検査を含めた臨床ステージングで遠隔転移が無く、完全切除可能と考えられる大型3型・4型胃がんに対して、D2手術およびTS-1による術後補助化学療法1年投与を対照とし、試験治療であるTS-1＋CDDP療法2コース後に同様な手術と補助化学療法を施行する新規治療の優越性を検定するランダム化比較試験を実施している。登録ペースが遅く、洗浄細胞診陽性例も適格とする試験計画の変更が承認され、今年度は1年間で59例の登録が行われ、予定の登録ペースに達するようになった。予定登録数は316例に対して22年3月末で142例の登録を認めている。幸い治療関連死は発生しておらず、順調に試験は進んでいる。

研究分担者

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## A．研究目的

全体では70%近い治癒率を達成した胃がんにおいて、依然10%程度の5年生存率にとどまっているスキルス胃がん、あるいはそれに準ずる大きな3型胃がんの予後改善が本研究の目的である。スキルス胃がんは20代の若年者にも多く発生し、数多くの悲劇を生んできた。就労期の患者が多数を占める同疾患の予後改善の必要性は高く、その社会的な意義も極めて大きい。がん対策基本法にうたわれた75才以下のがん生存率の改善にこの研究は極めて重要である。

## B．研究方法

【研究形式】多施設共同の第Ⅲ相ランダム化比較試験（優越性試験）：標準治療を対照としたランダム化比較試験で、プライマリーエンドポイントは全生存期間。

【研究対象】腹腔鏡検査を含めた臨床的検索で遠隔転移を伴わない(ただし洗浄細胞診陽性は可)、治癒切除可能な8cm以上の大型3型・4型胃がん症例を対象とした。術前の画像診断で食道浸潤が3cm以

下であり、登録時の年齢が 20 歳以上 75 歳以下、PS0,1、充分な経口摂取ができ、諸臓器の機能が良好で、患者本人の自由意志に基づく文書による同意を得ていること。

【症例登録とランダム割付】腹腔検査の結果を含めて適格性を満たし、同意が得られた患者を JCOG データセンターで中央登録する。施設、肉眼型、壁深達度、リンパ節転移程度を割付調整因子として最小化法にて割り付ける。

【治療内容】試験治療：術前TS-1(3週投与1週休薬)＋CDDP(day8)による化学療法を2コース行う。治癒切除可能症例ではD2以上の郭清を伴う根治手術を行い、術後6週以内よりTS-1単独による化学療法を手術後1年を目安に実施する。対照群：割付後早期に試験群と同様な内容の手術を行い、術後は試験治療と同じTS-1単剤による化学療法を1年を目安に実施する。

【解析方法】全生存期間を用いた中間解析は、予定登録数の半数が登録された後の最初の定期モニタリング時及び全症例が登録を完了して治療が終了する時期の2度予定する。中間解析は適切な方法で多重性を考慮して行う。最終解析は、全例登録後3年経過時点で行う。

【予定症例数】予定登録数は登録再開後両群併せて300例とし、すでに登録した16例と併せて全予定登録数は316例となった。

【実施施設】JCOG 胃がん外科グループに所属する消化器がんの基幹施設 38 施設で実施する。

**(倫理面への配慮)**

本第Ⅲ相試験は、臨床試験評価委員会では手術単独を対照群とした試験として承認され、開始されたが、ACTS-GC 試験（術後 TS-1 単独療法による補助化学療法を評価するランダム化比較試験）の結果をふまえて標準治療が変わった。倫理的観点から、それが判明した時点で即刻登録を中止した。約半年の作業でプロトコールを改訂し、改訂プロトコールは平成 19 年 2 月に JCOG 効果安全性評価委員会で承認された。各参加施設では倫理審査委員会で変更点に関する審査を受け、再登録を再開した。本人に口答及び文章による説明を行い、文章による同意を得る。説明内容には、試験参加の自由、同意後の撤回の自由、質問の自由、個人情報の扱いなどが含まれ、試験の同意取得は、ヘルシンキ宣言、個人情報保護法、臨床研究に関する倫理指針の総ての要件を満たして行われる。

## C．研究結果

本試験は 2005 年に手術単独と術前化学療法＋手術を比較する試験として開始されたが、2006 年に我が国の 1000 例を超す大規模試験で術後補助化学療法の有用性が証明され、我が国のステージ 2 以上の進行胃がんに対する標準治療は D2 手術＋術後 TS-1 の 1 年間投与に変更となった。この影響で試験の登録を一時中止して、両群ともに術後補助化学療法を加えた内容に治療を変更して 2007 年に再開した。2010 年 3 月末までに 142 例を登録した。21 年度 1 年間では 59 例を登録した。これまでに手術合併症による死亡はなく、順調に試験は進行している。

## D．考察

治癒切除可能進行胃がんに対する標準治療は 3 極化しており、米国では治癒切除後に術後放射線化学療法、欧州では術前術後補助化学療法、我が国は治癒切除後（D2）に術後化学療法単独となっている。術前化学療法は高いコンプライアンスが特徴で、微小転移のコントロールに

期待が寄せられている。一方で無効症例での手術の遅れ、臨床的ステージングの間違いにより必ず一定頻度でその様な治療が不要な患者にまで負担をかけることなどの問題もある。また、我が国では術後補助化学療法単独でもかなり良好な治療成績を得ること、欧米に比して症例数が5倍以上多く、進行胃がんの全例に入院治療を要する術前化学療法を行う社会的な負担(医療経済)および入退院マネージメントの煩雑さから、現時点では広く進行胃がんを対象とするには時期尚早と考えられている。本試験でかかる治療の有効性が明確となれば、ステージ3胃がんでもより予後の良い対象にも術前化学療法を適応しようとする流れが予想できる。一方で、現在、進行再発胃がん症例を対象に、TS-1にOxaliplatinを併用する治療が現在の標準であるTS-1+CDDPに対して非劣性であるかどうかの試験が進行中であり、それが証明されれば外来での術前化学療法が可能となることも考えられる。

## E．結論

予後不良な大型3型・4型胃がんに対してTS-1＋CDDPによる術前化学療法を2コース行う治療は安全に施行でき、今後の生存解析の結果が注目される。

## F．健康危険情報

現在まで登録された症例では該当なし。

## G．研究発表

### 1．論文発表

(1)Kinoshita, T., Sasako, M., Sano, T., Katai, H., Furukawa, H., Tsuburaya, A., Miyashiro, I., Kaji, M., Ninomiya, M. (on behalf of the Gastric Cancer Surgery Study Group of the Japan Clinical Oncology Group): Phase II trial of S-1 for neoadjuvant chemotherapy against scirrhous gastric cancer (JCOG0002). Gstric Cancer, 12: 37-42, 2009.

(2)Sasako, M., Kurokawa, Y.: Challenges in performing surgical randomized controlled trials in Japan. Surgery, 145:598-602, 2009.

(3)Nashimoto, A., Yabusaki, H., Nakagawa, S., Takii, Y., Tsuchiya, Y., Otsuo, T.: Preoperative Chemotherapy with S-I and Cisplatin for Highly Advanced Gastric Cancer. Anticancer research, 29:4689-4696, 2009.

(4)Yoshikawa, T., Sasako, M., Yamamoto, S, Sano, Imamura, H.,Fujitani, K., Oshita, H., Ito, S., Kawashima, Y., Fukushima, N.: Phase II study of neoadjuvant chemotherapy and extended surgery for locally advanced gastric cancer. Br J Surg., 96:1015-1022, 2009.

(5) Kodera, Y., Ito, S., Mochizuki, Y., Kondo, K., Koshikawa, K., Suzuki, N., Kojima, H., Kojima, T., Matasui, T., Takase, T., Tsuboi, K., Fujiwara, M., Nakao, A.: A phase II study of radical surgery followed by postoperative chemotherapy with S-1 for gastric carcinoma with free cancer cells in the peritoneal cavity (CCOG0301 study). Eur J Surg Oncol, 35: 1158-1163, 2009.

(6)松井恒志、梨本篤、藪崎裕、中川悟、野村達也、瀧井康公、土屋嘉昭、田中乙雄：進行胃癌術後補助化学療法としてS-1の投与方法についての検討．癌と化学療法 36(6):953-957, 2009.

(7)梨本篤、藪崎裕、中川悟：胃癌の適切なフォローアップ計画．癌と化学療

法　36(9):1402-1407, 2009.

## 2. 学会発表

(1)Sasako,M.:Working Report-Gastric Cancer: Surgical Treatment and Adjuvant Therapy for Curable Advanced Gastric Cancer. 20th Asia Pacific Cancer Conference, Tsukuba, Nov. 12-14, 2009.

(2)Nashimoto A. : Intraperitoneal infusion of Docetaxel with S-1 for metastatic or recurrent gastric cancer with peritoneal metastasis. 43rd World Congress of the International Society of Surgery, Adelaide, Australia, Sep.8, 2009.

(3)Isobe, Y., Nashimoto, A.:Gastric cancer treatment in Japan: annual report of the JGCA nationwide registration program 2008. 8th International Gastric Cancer Congress, Krakow, Porland, Jun. 11, 2009.

(4)Iwasaki, Y., Ohashi, M., Iwanaga, T., Takahashi, T.: Neoadjuvant chemotherapy for patients with advanced gastric cancer. 8th International Gastric Cancer Congress, Krakow, Porland, Jun. 11, 2009.

(5)Imakita, T., Miyatani, T., Iwasaki, Y., Ohashi M., Nishikiori, T., Iwanaga, T.: A case of type 4 gastric cancer underwent curative gastrectomy followed by S-1 plus cisplatin as neoadjuvant chemotherapy. 8th International Gastric Cancer Congress, Krakow, Porland, Jun. 11, 2009.

(6)Nishikiori, T., Iwasaki, Y., Ohashi, M., Iwanaga, T.: Prognostic significance in patients of advanced gastric cancer with positive peritoneal cytology and no macroscopic peritoneal metastases. 8th International Gastric Cancer Congress, Krakow, Porland, Jun. 11, 2009.

(7)Kurokawa, Y., Sasako, M., Sano, T., Iwasaki, Y., Tsuburaya, A., Fukuda, H.: Validity of response criteria in neoadjuvant chemotherapy against gastric cancer. 8th International Gastric Cancer Congress, Krakow, Porland, Jun. 11, 2009.

(8)Okumura, Y., Iwasaki Y., Ohashi, M., Iwanaga, T.: A successfully treated case of stage IV gastric cancer with outlet stenosis undergoing curative gastrectomy after pre-operative S-1 plus cisplatin following laparoscopic assisted gastrojejunostomy. 8th International Gastric Cancer Congress, Krakow, Porland, Jun. 11, 2009.

(9)Miyatani, T., Iwasaki, Y., Ohashi, M., Iwanaga, T.: Significance of surgery after chemotherapy using new generation anticancer drugs for patients with stage IV gastric cancer. 8th International Gastric Cancer Congress, Krakow, Porland, Jun. 11, 2009.

(10)梨本篤:胃がん全国登録データからみた胃がん治療の現況と問題点について. 第109回日本外科学会総会、福岡、2009年4月.

(11)石川卓、梨本篤:高度進行胃癌に対する術前分割DCS療法. 第82回日本胃癌学会総会、新潟、2010年3月.

(12)伊藤誠二、梨本篤:高度リンパ節転移を伴う進行胃がんに対する術前化学療法+外科切除の治療開発-JCOG臨床試験を通じた標準治療の確立-. 第109回日本外科学会総会、福岡、2009年4月.

(13)藪崎裕、梨本篤: Staging

laparoscopy (SL) による腹膜転移陽性胃癌に対する治療戦略. 第 109 回日本外科学会総会、福岡、2009 年 4 月.
(14)加治正英, 萩野茂太、宮永章平、山口　紫、庄司秦弘、尾嶋英介、橋本伊佐也、寺田逸郎, 山本精一, 前田基一, 藪下和久, 清水康一：当科におけるスキルス胃癌症例の検討と治療戦略について. 第 71 回日本臨床外科学会総会、京都、2009 年 11 月.
(15)肥田圭介、高橋正統、藤原久貴、千葉丈広、木村祐輔、西塚哲、岩谷岳、野田芳範、木村聡元、柏葉匡寛、新田浩幸、大塚幸喜、水野　大、佐々木章、池田健一郎、若林　剛: 初発進行胃癌に対する TS-1/CDDP 併用化学療法後根治手術の有用性. 第 109 回日本外科学会、福岡市、2009 年 4 月.
(16)錦織達人、大橋　学、岩崎善毅、岩永知大、中野大輔、山口達郎、松本　寛、高橋慶一：他に非治癒因子のない POCY1 胃癌の治療成績. 第 64 回日本消化器外科学会総会、大阪、2009 年 7 月.
(17)岩崎善毅、大橋　学、岩永知大、高橋慶一、山口達郎、松本　寛、中野大輔：切除可能胃癌に対する Neoadjuvant 療法. 第 64 回日本消化器外科学会総会、大阪、2009 年 7 月.
(18)宮谷知彦、岩崎善毅、大橋　学、岩永知大、中野大輔、松本　寛、山口達郎、高橋慶一：StageⅣ胃癌に対する新規抗癌剤治療後の胃切除術の意義. 第 64 回日本消化器外科学会総会、大阪、2009 年 7 月.
(19)岩崎善毅：胃癌術前化学療法の現状と将来展望. 第 13 回よこはま外科癌フォーラム、横浜、2009 年 8 月.
(20)岩崎善毅、大橋　学、岩永知大、大日向玲紀、高橋慶一、山口達郎、松本寛、中野大輔：臨床的に根治切除可能な進行胃癌に対する術前化学療法の意義. 第 71 回日本臨床外科学会総会、京都、2009 年 11 月.
(21)伊藤誠二、笹子三津留、円谷 彰、古河 洋、福島紀雅、藤谷和正、種村廣巳、川島吉之、佐野 武、田中洋一、梨本 篤、中村健一 、山本精一郎 、福田治彦：高度リンパ節転移を伴う進行胃がんに対する術前化学療法+外科切除の治療開発　-JCOG 臨床試験を通じた標準治療の確立-. 第 109 回日本外科学会定期学術集会、福岡、2009 年 4 月.

## H. 知的財産権の出願・登録状況
## (予定を含む)

**1. 特許取得**

該当するもの無し

**2. 実用新案登録**

該当するもの無し

**3. その他**

該当するもの無し

研究成果の刊行に関する一覧表

雑誌

| 発表者氏名 | 論文タイトル名 | 発表誌名 | 巻号 | ページ | 出版年 |
|---|---|---|---|---|---|
| Kinoshita, T., Sasako, M., Tsuburaya, A., Kaji, M.,et al. | Phase II trial of S-1 for neoadjuvant chemotherapy against scirrhous gastric cancer (JCOG0002). | Gstric Cancer | 12 | 37-42 | 2009 |
| Sasako, M., Kurokawa, Y. | Challenges in performing surgical randomized controlled trials in Japan. | Surgery | 145 | 598-602 | 2009 |
| Nashimoto, A., Yabusaki, H., et al. | Preoperative Chemotherapy with S-I and Cisplatin for Highly Advanced Gastric Cancer. | Anticancer research | 29 | 4689-4696 | 2009 |
| Yoshikawa, T., Sasako, M., Ito, S., Fukushima, N. et al. | Phase II study of neoadjuvant chemotherapy and extended surgery for locally advanced gastric cancer. | Br J Surg | 96 | 1015-1022 | 2009 |
| Kodera, Y., Ito, S.,et al | A phase II study of radical surgery followed by postoperative chemotherapy with S-1 for gastric carcinoma with free cancer cells in the peritoneal cavity (CCOG0301 study). | Eur J Surg Oncol | 35 | 1158-1163 | 2009 |
| 松井恒志、梨本篤、他 | 進行胃癌術後補助化学療法としてS-1の投与方法についての検討 | 癌と化学療法 | 36(6) | 953-957 | 2009 |
| 梨本篤、藪崎裕、中川悟 | 胃癌の適切なフォローアップ計画 | 癌と化学療法 | 36(9) | 1402-1407 | 2009 |

# Ⅲ. 研究成果の刊行物・別刷

「がん臨床研究事業」

研究代表者　笹子　三津留

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*Original article*

# Phase II trial of S-1 for neoadjuvant chemotherapy against scirrhous gastric cancer (JCOG 0002)

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**Abstract**

***Background.*** **The prognosis of scirrhous gastric cancer remains poor despite extended surgery or adjuvant or neoadjuvant chemotherapy. A pilot study of S-1 (TS-1; Taiho Pharmaceutical, Tokyo, Japan), an oral 5-fluorouracil derivative, for neoadjuvant chemotherapy unexpectedly showed good response and a promising effect on survival. Therefore, the Japan Clinical Oncology Group conducted a phase II trial to confirm the efficacy of S-1 for neoadjuvant chemotherapy against resectable scirrhous gastric cancer.**

***Methods.*** **Patients were eligible if they had typical scirrhous gastric cancer invading more than half of the stomach, and resectable disease confirmed by laparoscopic staging. The treatment schedule consisted of two courses (each, 4-week administration and 2-week withdrawal) of S-1 (100–120 mg/body per day), followed by radical surgery.**

***Results.*** **Fifty-five eligible patients were registered. Three completed only one course of the neoadjuvant chemotherapy, whereas 52 completed two courses. Toxicity was acceptable, with a few grade 3 (5.5%) events, but no grade 4 adverse events. The response rate was 32.6% in 43 evaluable patients. Of the 55 patients, 2 refused operation, 1 developed lung metastasis, and 52 underwent laparotomy. The curative resection rate was 80.8%, with acceptable morbidity and no mortality. The survival curve at 2 years' follow up showed a better survival rate than that of the historical controls, but did not reach the expected survival rate.**

***Conclusion.*** **S-1 neoadjuvant chemotherapy appeared feasible and showed positive effects against scirrhous gastric cancer; however, the survival rate with S-1 did not reach the expected rate required when selecting an agent for a phase III trial to confirm the effectiveness of neoadjuvant chemotherapy against scirrhous gastric cancer.**

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**Key words** Scirrhous gastric cancer · Neoadjuvant chemotherapy · S-1

## Introduction

Scirrhous gastric cancer, also known as linitis plastica or Borrmann type 4, is a special type of stomach cancer known for its very poor prognosis. It is very difficult to identify this cancer in its early stage, and even aggressive surgical procedures and adjuvant chemotherapies have not considerably improved the survival rate in patients with this neoplasia. Owing to its low incidence, only a few drug trials against this neoplasia have been conducted thus far. On the other hand, several studies of neoadjuvant chemotherapy against scirrhous gastric cancer have suggested the efficacy of such treatment [1–4]. However, all these studies involved a small sample size and they usually did not determine the survival benefits of such treatment. Furthermore, a phase II trial of sequential high-dose methotrexate and fluorouracil combined with doxorubicin (FAMTX) for neoadjuvant chemotherapy has shown moderate toxicity and no survival benefits [5]. Interestingly, S-1, which is a dihydropyrimidine dehydrogenase (DPD)-inhibitory fluoropyrimidine, has shown the highest response rate among many oral anticancer agents against unresectable advanced gastric cancer in early and late phase II trials [6–8]. In these late phase II trials, S-1 showed a 33% response rate against scirrhous gastric cancer. Because of the reported promising effects of S-1 for neoadjuvant chemotherapy against scirrhous gastric cancer in a previous pilot study [9], the Japan Clinical Oncology Group

(JCOG) decided to conduct a phase II trial to determine survival benefits of S-1 treatment.

## Patients, materials and methods

### *Patient eligibility*

Patient eligibility required the fulfillment of the following criteria: histologically confirmed gastric adenocarcinoma; potentially resectable laparoscopy-confirmed typical scirrhous gastric cancer (without definitive ulceration) that invaded more than half of the stomach; received no prior treatment; 70 years or younger; Eastern Cooperative Oncology Group performance status of 0 or 1; and oral intake possible. Patients also had to have adequate organ functions (creatinine clearance, ≥50 ml/min; blood urea creatinine, within the institutional limit; GOT and GPT, within twice the institutional limit; leukocytes, 3500/mm$^3$≤ leukocyte <12000/mm$^3$; hemoglobin, ≥9.0 g/dl; thrombocytes, ≥1000000/mm$^3$; total bilirubin, within twice the institutional limit; and normal electrocardiogram).

Diagnostic and staging procedures included physical examination, barium gastrography, endoscopy, chest X-ray, abdominal computed tomography (CT) scan, and laparoscopy with cytological examination of peritoneal washing of the Douglas pouch. Patients with positive cytology on peritoneal washing and potentially resectable disease without visible peritoneal dissemination were also included in the study.

This study was approved by the Institutional Review Board, and written informed consent was obtained from all patients.

### *Treatment schedule*

Chemotherapy consisted of two courses (4-week administration and 2-week withdrawal) of S-1 at 100–120 mg/body per day. After two courses of neoadjuvant chemotherapy, patients were reevaluated for the presence of potentially resectable disease and those who were positive underwent laparotomy. Because two patients underwent endoscopic examination after one course of chemotherapy and stopped chemotherapy due to progressive disease, the treatment protocol was revised such that the evaluation of the effect of neoadjuvant chemotherapy should be carried out only after two courses and only by fluoroscopic examination. If indicated, patients received curative or palliative resection or exploratory laparotomy within 14 days after completing the second course of adjuvant chemotherapy. Patients with curative resection were followed up without any adjuvant chemotherapy every 3 months until cancer relapse.

### *Evaluation of response and toxicity*

Potentially resectable scirrhous gastric cancer usually shows no measurable lesions, except for primary foci. We decided to evaluate the response of only primary foci following chemotherapy. Because it is very difficult to evaluate the response of the primary foci using the Response Evaluation Criteria in Solid Tumors criteria, we used a National Institutes of Health (NIH) image to calculate the barium-filling area or whole stomach on a double-contrast fluoroscopic examination study, as well as to compare the area before and after chemotherapy. Responses were classified as partial response (PR), more than 50% increase in the area after chemotherapy; stable disease (SD), 0 to less than 50% increase in the area; and progressive disease (PD), any decrease in the area and the appearance of new lesions. National Cancer Institute Common Toxicity Criteria ver2.0 were employed for determining chemotherapy toxicity.

Pathological assessment was performed to evaluate disease extent, resection margins, and response to chemotherapy as evidenced by the presence of necrotic and cancer cells. The pathological response to chemotherapy was classified according to the following criteria provided by the Japanese Gastric Cancer Association [10]: grade 0, absence of necrosis or degeneration; grade 1a, necrosis or degeneration is observed in less than one-third of the tumor; grade 1b, less than two-thirds and more than one-third of the tumor show necrosis or degeneration; grade 2, more than two-thirds of the tumor shows necrosis or degeneration; grade 3, all tumors show necrosis or degeneration.

### *Historical controls*

Because we applied laparoscopic staging to exclude patients with visible peritoneal dissemination, it was very difficult to find good historical controls. Laparoscopic staging had gained popularity at the commencement of this trial; however, we had no identical historical controls. The historical controls consisted of 241 patients who had the same lesions as those described in the eligibility criteria for this study, and who had no visible peritoneal dissemination at laparotomy without laparoscopic staging, and had been treated at the participating institution during 1991–1993. Data for the historical controls were as follows: 2-year survival rate, 45%; curative resection rate, 90.3%; 30-day operative mortality rate, 1.2%; and in-hospital mortality rate, 3.5%.

### *Statistical considerations*

The primary endpoint of this study was the 2-year survival rate. Fifty-five patients were required to be registered on the basis of the expectation that the 2-year survival rate of those receiving this neoadjuvant chemo-

therapy would be 60% (15% higher than that of the historical controls), allowing 10% of ineligible patients. Survival time was calculated from the initial date of the initiation of neoadjuvant chemotherapy to the date of death or the last follow-up date. Survival data were analyzed according to the method of Kaplan and Meier and then compared with the data of the historical controls.

## Results

### *Patient accrual*

From March 14, 2001, to February 4, 2003, 55 patients were enrolled in the study from 15 institutions. The mean age was 56 years (range, 31–70 years).

### *Neoadjuvant chemotherapy*

The patients were composed of 26 male and 29 female patients. The scheduled two courses of neoadjuvant chemotherapy were performed in 52 patients. The remaining 3 patients received one course, because 2 of the 3 patients were judged to have PD by endoscopic evaluation after one course before the revision of the protocol, and 1 patient was found to have advanced bile duct carcinoma after one course of chemotherapy. These 3 patients received curative resection after one course of neoadjuvant chemotherapy. There was no chemotherapy-induced grade 4 adverse reaction in the cohort. Only 3 patients developed grade 3 adverse reactions (Table 1).

As mentioned earlier, the effect of adjuvant chemotherapy was evaluated from the change in the barium-filling area before and after the chemotherapy, as calculated from the NIH images. Among the 43 patients whose fluoroscopic films could be evaluated, 14 patients (32.6%) showed more than 1.5 times enlargement of the stomach (PR); 13 patients showed SD (30.2%), and 16 patients showed PD (37.2%).

**Table 1.** Adverse reactions

| | Grade | | | | % | |
|---|---|---|---|---|---|---|
| | 0 | 1–2 | 3 | 4 | Grade 4 | Total |
| T. Bil | 32 | 23 | 0 | 0 | 0 | 55 |
| WBC | 42 | 13 | 0 | 0 | 0 | 55 |
| Neutrophils | 42 | 12 | 1 | 0 | 0 | 55 |
| ALT | 43 | 11 | 2 | 0 | 0 | 55 |
| AST | 45 | 9 | 0 | 0 | 0 | 55 |
| Hb | 48 | 7 | 0 | 0 | 0 | 55 |
| Nausea/vomiting | 36 | 19 | 0 | 0 | 0 | 55 |
| Pigmentation | 44 | 11 | 0 | 0 | 0 | 55 |
| Anorexia | 45 | 10 | 0 | 0 | 0 | 55 |
| Diarrhea | 45 | 10 | 0 | 0 | 0 | 55 |
| Stomatitis | 45 | 10 | 0 | 0 | 0 | 55 |
| General fatigue | 46 | 9 | 0 | 0 | 0 | 55 |

Only three patients developed grade 3 adverse reactions, and they recovered by withdrawal of S-1

T. Bil, serum total bilirubin; WBC, white blood cell count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Hb, hemoglobin

### *Operation*

Among the 55 patients, 3 did not undergo operation, because of the refusal of 2 and because the other patient was found to have pulmonary metastases. Fifty-two patients underwent laparotomy, including the 3 patients who received one course of the neoadjuvant chemotherapy. Among the 52 patients, 6 patients did not undergo resection (5, peritoneal dissemination; 1, unresectable invasion of the duodenum and pancreatic head). Ten patients underwent palliative resection of the main tumor (2, peritoneal dissemination; 6, positive cytological examination of abdominal washing; 1, unresectable tumor with severe invasion to the retroperitoneum; 1, widespread lymph node metastases). The other 36 patients underwent curative total gastrectomy with various combined organ resections (25, spleen; 1, distal pancreas + spleen; 5, gallbladder; 2, left adrenal gland; 2, transverse colon; 1, pancreatic head and duodenum). Among the 36 patients, only 1 had D1 lymph node dissection and the remaining 35 had D2 or more lymph node dissection.

The mean operation time for curative resection was 214 min (range, 130–460 min) and that for noncurative resection was 295 min (range, 150–401 min). The mean blood loss for curative resection was 586 ml (range, 30–1815 ml) and that for noncurative resection was 872 ml (range, 230–2100 ml).

Among the 46 patients who underwent resection, postoperative complications were observed in 11 patients (23.9%). Overall, there was no mortality and there were no serious complications. The actual complications were as follows: wound infection, deep vein thrombosis, pancreatic fistula, anastomotic ulcer, pneumonia, pulmonary embolism, sepsis, abdominal abscess, liver function disorder, and mycotic uveitis.

Changes in the T, P, and CY (cytological examination of the abdominal washing) factors before and after neoadjuvant chemotherapy are shown in Tables 2 and 3. With regard to the T factor, a response was observed in 14 patients; however, cancer progression was observed in 8 patients. In regard to the P and CY factors, a response (PR) was observed in only 2 patients; however, 10 showed progressive disease (PD). The other 40 patients showed stable disease (SD).

The pathological therapeutic effects of neoadjuvant chemotherapy were evaluated according the grading described by the Japanese classification of gastric carci-

noma [10] general rules for gastric cancer study: grade 0, 12 patients (26.1%); grade 1a, 19 patients (41.3%); grade 1b, 4 patients (8.7%), and grade 2, 11 patients (23.9%).

At the time of the scheduled analyses (March 2005), 10 patients were still alive without recurrence, 13 were alive with recurrence, and 32 had already passed away. The modes of recurrence were as follows: peritoneal, 17 patients; retroperitoneal, 2 patients; local, 1 patient; lymph node, 1 patient.

**Table 2.** Changes in T factors before and after chemotherapy

| Laparoscopic T | | Pathological T |
|---|---|---|
| T2:7 | | T2:11 |
| T3:39 | Chemotherapy | T3:37 |
| T4:5 | | T4:4 |
| Tx:1 | | |

Progression, 8 patients; downstage, 14 patients
Tx, T unknown

**Table 3.** Changes in P and CY factors before and after chemotherapy

| | |
|---|---|
| No change or progression (SD and PD) | |
| P0, CY0→P0,CY0 | 37 (SD) |
| P0, CY0→P0, CY1 | 2 (PD) |
| P0, CY1→P0, CY1 | 3 (SD) |
| P0, CY0→P1 | 4 (PD) |
| P0, CY1→P1 | 4 (PD) |
| Downstage (PR) | |
| P0, CY1→P0, CY0 | 2 (PR) |

The survival curves of all patients ($n$ = 55) and the historical controls are shown in Fig. 1. The survival curve of the study arm was better than that of the historical controls; however, the survival rate did not reach the expected rate (2-year survival rate: 59% vs 60%).

With regard to the secondary endpoints, the response rate to the neoadjuvant chemotherapy was 32.6%. The rate of postoperative complications was 23.9%, as against 25.7% in the historical controls. The in-hospital mortality rate was 0% as against 3.5% in the historical controls. The curative resection rate was 80.8%, as against 90.3% in the historical controls.

## Discussion

Despite recent advances in chemotherapy and extended surgery, the treatment outcomes of scirrhous gastric cancer, also known as diffuse gastric cancer, linitis plastica, or Borrmann type 4 in the West, have remained very poor because of the aggressive biological behavior of this tumor. Because of failure to improve survival even with aggressive postoperative chemotherapy, neoadjuvant chemotherapy has been applied to patients with resectable or unresectable scirrhous gastric cancer.

To date, the efficacy of neoadjuvant chemotherapy against scirrhous gastric cancer remains to be established because of the lack of well-validated phase II and phase III studies. The first phase II neoadjuvant chemotherapy trial was reported by Takahashi et al., using FAMTX [5]. In their trial, neoadjuvant chemotherapy was shown to be seemingly feasible against scirrhous

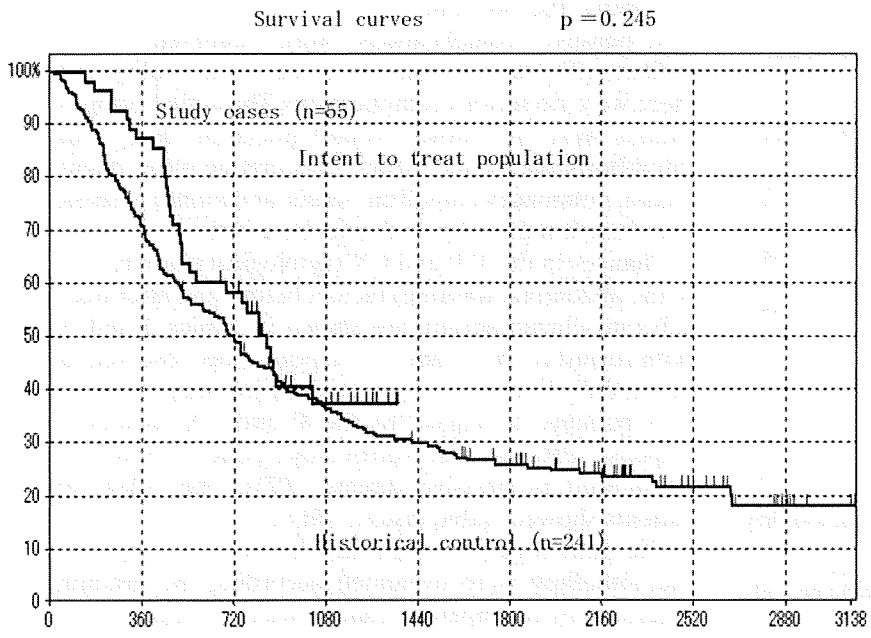


**Fig. 1.** Survival curves of all patients ($n$ = 55) and the historical controls ($n$ = 241)

gastric cancer, producing a higher resectability rate without any increase in morbidity rate. However, an interim analysis of the 2-year survival rate in 20 patients enrolled in the trial showed no improvement over the survival rate of the historical controls. Myelosuppression was the major cytotoxic effect of the FAMTX regimen, and grade 3 or 4 neutropenia was observed in 14 out of the 20 patients (70%). Eleven of these 14 patients required granulocyte colony-stimulating factor support. The overall response rate was 15% (3 PRs in 20 patients). Eighteen resected specimens showed only marginal histological effects (grades 0-Ib). For these reasons, Takahashi and co-workers discontinued the trial.

Because S-1 showed promising effects when used for neoadjuvant chemotherapy against scirrhous gastric cancer in a pilot study [9], we decided to conduct a phase II trial of S-1 to determine its beneficial effects on survival. Because of the difficulty in excluding patients with peritoneal dissemination by conventional diagnostic imaging procedures such as CT scan and the use of barium enema, we performed laparoscopic examination to identify and exclude patients with peritoneal dissemination.

At the time of starting the phase II trial, laparoscopic examination for cancer staging was still not a common procedure. Thus, we need to standardize this technique using a video for the quality control of the procedure. Regarding the historical controls, it was not possible to submit patients without peritoneal dissemination to laparoscopic examination, for the same reason. Data for previous patients with the same eligibility criteria and without peritoneal dissemination, confirmed by laparotomy, were collected from the participating institutions. Thus, in the present study, the control group was not identical to the study group.

Neoadjuvant chemotherapy using S-1 was safe and feasible when compared with other toxic combination chemotherapies. Only a few grade 3 and no grade 4 adverse reactions resulting from cytotoxicity were observed, and no specific morbidity and no increases in morbidity and mortality rates were seen when compared with the data in the historical controls.

Patients with positive cytological examination results were included in this phase II trial. This is the reason why we expected the S-1 neoadjuvant chemotherapy to produce negative cytological examination results. However, the results of the trial, in terms of cytological findings, were not very promising. Without considering the cytological examination results, it can be observed that although there was no significant difference in the curative resection rate between the study group and the historical control group, the curative resection rate in the study group was lower than the expected rate.

From the viewpoint of the pathological therapeutic effects of chemotherapy, S-1 neoadjuvant chemotherapy showed a much better therapeutic effect than FAMTX.

The survival rate of our study group showed a better curve than that of the historical controls; however, it did not reach the expected rate ($P = 0.245$). On the other hand, combination chemotherapy using S-1 and cisplatin (CDDP) showed a markedly high response rate (76%) in a phase II trial. Therefore, this combination can be considered more promising than S-1 monotherapy for neoadjuvant chemotherapy against scirrhous gastric cancer. The JCOG has also completed the accrual of patients evaluated in the phase II trial of neoadjuvant chemotherapy using the above S-1 and CDDP regimen for resectable scirrhous and more-than-8-cm giant type 3 gastric cancer. Because of the superiority of this regimen over S-1 monotherapy in terms of the response rate and pathological therapeutic effects, the JCOG group has already started a phase III trial to confirm the effectiveness of neoadjuvant chemotherapy using S-1 + CDDP as against extended surgery in patients with scirrhous or large type 3 gastric cancer.

In summary, neoadjuvant chemotherapy using S-1 against potentially resectable scirrhous gastric cancer appears feasible and effective; however, in the present phase II trial, the survival rate of the patients did not reach the expected rate. On the other hand, an S-1 + CDDP regimen is now being tested in a phase III trial by the JCOG group as a more promising neoadjuvant regimen.

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## References

1. Mai M, Ogino T, Ueda H, Ooi A, Takahashi Y, Sawaguchi K, et al. Study on neoadjuvant chemotherapy of Borrmann 4 type carcinoma of the stomach and its clinical significance. Nippon Gan Chiryo Gakkai Shi (J Jpn Soc Cancer Ther) 1990;25:586–97.
2. Maeda O, Iwase H, Mamiya N, Nakamura M, Mizuno T, Nishio Y, et al. A case of scirrhous cancer of the stomach which survived for more than 5 years after neoadjuvant chemotherapy with UFT (uracil and tegafur) and cisplatin. Intern Med 2000;9:239–44.
3. Eriguchi M, Osada I, Fujii Y, Takeda Y, Yoshizaki I, Akiyama N, et al. Pilot study for preoperative administration of 1-OHP to patients with advanced scirrhous type gastric cancer. Biomed Pharmacother 1997;51:217–22.
4. Suga S, Iwase H, Shimada M, Nishio Y, Ichihara T, Ichihara S, et al. Neoadjuvant chemotherapy in scirrhous cancer of the stomach using uracil, tegafur and cisplatin. Intern Med 1996;35:930–6.
5. Takahashi S, Kinoshita T, Konishi M, Nakagohri T, Inoue K, Ono M, et al. Phase II study of sequential high-dose methotrexate and fluorouracil combined with doxorubicin as a neoadjuvant chemo-

therapy for scirrhous gastric cancer. Gastric Cancer 2001;4; 192–7.
6. Sugimachi K, Maehara Y, Horikoshi N, Shimada Y, Sakata Y, Miyachi Y et al. An early phase II study of oral S-1, a newly developed 5-fluorouracil derivation for advanced and recurrent gastrointestinal cancers. Oncology 1999;57:202–10.
7. Sakata Y, Ohtsu A, Horikoshi N, Sugimachi K, Mitachi Y, Taguchi T. Late phase II study of novel oral fluoropyrimidine anticancer drug S-1 (1 M tegafur-04 M gimestat-1 M otastat potassium) in advanced gastric cancer patients. Eur J Cancer 1998; 34:1715–20.
8. Koizumi W, Kurihara M, Nakano S, Hasegawa K. Phase II study of S-1, a novel oral derivative of 5-fluorouracil, in advanced gastric cancer. Oncology 2000;58:191–7.
9. Kinoshita T, Konishi M, Nakagohri T, Inoue K, Oda T, Takahashi S, et al. Neoadjuvant chemotherapy with S-1 for scirrhous gastric cancer. A pilot study. Gastric Cancer 2003;6:40–4.
10. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma—second English edition—. Gastric Cancer 1998;1:10–24.

# CHALLENGES IN PERFORMING SURGICAL RANDOMIZED CONTROLLED TRIALS IN JAPAN

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SURGICAL TRIALS IN ONCOLOGY have gradually become more popular since the late 1980s. They remain a challenge, however, because of the large number of cases needed to provide adequate statistical power and the difficulty in maintaining quality control when treatment is provided by numerous participating surgeons.[1] The smaller the number of surgeons involved, the easier it is to ensure that high surgical standards are applied. However, as the number of surgeons decreases, the accrual period increases and the results become less generalizable. The optimum approach to such trials would be to use a group of surgeons with similar standards of safety and efficacy. The first section of this article lists the pitfalls of surgical trials based on the experience of the Dutch Gastric Cancer Study (DGCS), whereas the second section outlines the challenges faced by the Japan Clinical Oncology Group (JCOG) in its studies of gastric cancer and provides suggestions to surgeons who plan to carry out similar clinical trials.

## LESSONS FROM THE DGCS

The author (M.S.) was asked to take on the role of instructor in the DGCS in 1989.[2] This study was one of the first multicenter randomized controlled trials (RCT) to evaluate 2 surgical procedures for cancer. Extended lymphadenectomy (D2) was compared with limited lymphadenectomy (D1) as treatments of curable gastric cancer. This study elucidated several critical problems in running surgical trials related to cancer treatment. Most of these issues have been pointed out in other articles.[3-6]

**When to proceed to phase 3: ensuring patient safety.** Specific training is required to perform any surgical procedure, which may be particularly the case with those aimed at cancer treatment.[7] Before starting the DGCS, only 1 of the Dutch surgeons had experience performing a D2 gastrectomy. Even in Japan, where both hospital and surgeon volumes are high, this procedure carries some risk of potentially fatal complications.[8] Retrospectively, a feasibility study to confirm the safety of this procedure when performed by Dutch surgeons on Dutch patients should have been carried out. Because prior to this study, no prospective phase 2 study had been conducted to evaluate the risk and safety of D2 dissection if performed by surgeons of little experience, we did not properly estimate the risk of 1 of the treatment arms and thus began a phase 3 trial without testing feasibility. Consequently, the hospital mortality of the D2 arm was 10%, which was more than double that of the D1 arm at 4%.[2] Similar or even worse postoperative mortality (14%) was observed in the Medical Research Council trials that compared D1 with D2, which was also carried out by surgeons with little experience in United Kingdom. These results are also the highest mortality rate reported in recent years among all cancer surgeries in high-volume hospitals, including esophageal and pancreatic cancers, which usually require more aggressive operative therapy than D2 gastrectomy.[9,10]

**Defining procedural details.** In this study, the details of both procedures were decided by a few surgeons, including the author (M.S.). The author had never observed operative performance of Dutch surgeons and, therefore, was unfamiliar with the standard techniques used for upper abdominal surgery in the Netherlands. Moreover, Dutch surgeons had no experience with D2 surgery. Thus, routine use of splenectomy and pancreatectomy in the D2 procedure was adopted in this trial, but in retrospect it was not the proper choice.[11] In multicenter trials on surgical procedures, a clear, detailed definition of each procedure is mandatory. The choice of a procedure must be based on the actual experience of the participants. Training via an instructional video or textbook is obviously insufficient. Ideally, all participating surgeons should engage in the process of defining the details of the procedure to be studied.

**Quality control of treatment.** If the quality of the operation is substandard, then the results should be carefully interpreted. In the words of U. Guller, "Garbage in, garbage out."[12] The greater the number of hospitals and surgeons involved in a trial, the wider the range of quality in surgical treatment that can be expected. This point is not an important issue in medical treatment, but it is a critical issue both in radiotherapy and in operative therapy. Quality control for radiotherapy may be easier than for surgical procedures. In the SWOG9008/INT0116 trial to evaluate postoperative chemoradiotherapy as adjuvant treatment for curable gastric cancer, a central review of the irradiation plan was carried out, and modification of the initial plan was performed in more than 30% of cases.[13] By managing quality control at a central level, trial leaders could minimize morbidity and anticipate the effect of radiotherapy. This trial proved the usefulness of postoperative adjuvant chemoradiotherapy, which is now the standard of care in the United States. This kind of quality control/assurance is not possible in an operation. As mentioned, only 1 of the participating

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surgeons in the DGCS had ever carried out D2 gastrectomy before the study began. To provide a standard level of D2 dissection, 80 participating hospitals were divided into 8 regions where 1 or 2 specialists responsible for quality control always participated in D2 surgeries. The author (M.S.) remained in the Netherlands for the first 4 months of the study period to provide hands-on training to these individuals, who had had no prior experience with D2 surgery. Considering the complex nature of the procedure, this time frame was too short to afford adequate instruction, because only 33 patients were available for instruction of D2 surgery during this period. This allowed us to provide at maximum only 3 mentored exposures to D2 dissection for each quality controller. This example does emphasize the importance of quality control in surgical trials.[14]

In this trial, retrieved lymph nodes were examined in detail according to the protocol.[4] This method is useful in assessing the accuracy of lymphadenectomy. Although this method could improve the quality of operative therapy in hospitals where all dissected nodes are examined, thorough pathologic assessment of lymph nodes was seldom regarded as important in Dutch hospitals. In fact, the mean number of examined nodes from the specimens dissected by the author (M.S.) was counted as 31 if nodes were retrieved by Dutch pathologists and as 60 in other specimens from which all nodes were retrieved by the author (M.S.) himself.[15]

**Regular monitoring and termination rules.** As mentioned in the first section of this article, DGCS was started without any phase 2 studies to confirm feasibility, and no selection criteria limited hospital participation. Given this situation, rather strict termination rules should have been included in the protocol, based on hospital mortality rates, because of the uncertain safety of D2 gastrectomy performed by Dutch surgeons. A regular monitoring committee met to discuss problems in the trial, but much attention was not given to mortality issues. If an independent data and safety monitoring committee had existed, it could have recommended or ordered a temporary cease of accrual and could have changed the basic structure of the trial and minimized avoidable patient deaths. From an ethical point of view, more than double the risk of hospital mortality without certainty of an accompanying survival benefit is not acceptable in a randomized surgical study. If patients had been informed of the interim safety results, then it is doubtful that many would have accepted randomization.

**Data handling and restriction of data access.** An independent data center was implemented, but all data were accessible to investigators, and survival comparisons could have been carried out numerous times throughout the study period. In this study, there was no concept of multiplicity data analysis, and no planned interim analysis was required within the protocol. Survival analyses were carried out more than several times, the results of 2 of which were published without referring to the consumption of alpha error. Applying common sense with regard to statistical approaches should have prevented the problems in data analysis experienced in this study.

**Postoperative care.** The DGCS had many critical problems, as mentioned above, but it was still an important first step in this field. In particular, the heavy attention devoted to the quality control of an operation strongly affected studies planned afterward. However, no attention was given to the quality control of postoperative care in these patients; this issue that proved unexpectedly to be significantly related to the high hospital mortality rates that were observed. D2 surgery, which includes pancreaticosplenectomy, was expected to have high morbidity, but such high mortality after major complications was not anticipated. Hospital mortality after an anastomotic leak was greater than 40%, and that after pancreatic fistula with intra-abdominal abscess was 21%, whereas mortality rates after these events in a Japanese series in the 1980s were 14% and 3%, respectively.[16] Accumulation of experience was necessary to avoid postoperative hospital deaths after major complications. In the DGCS, the average number of D2 dissections per year was less than 2 per hospital; thus, gaining the postoperative management experience to avoid treatment related deaths was almost impossible. It has been suggested that Dutch patients might be much more fragile than those from Japan and that the high mortality rates observed might be caused by their underlying physical weakness. However, another RCT on the surgical treatment of esophagogastric junctional tumor (EGJT) performed by 2 specialized Dutch hospitals demonstrated much lower hospital mortality with a much higher incidence of potentially fatal major complications.[17] The only possible explanation is that the DGCS was carried out in 80 hospitals, which include peripheral general hospitals whose patient volume was low, whereas the EGJT study was performed in only 2 specialized centers. In the latter trial, each hospital had high volumes; thus, the requisite experience to manage potentially fatal complications and avoid treatment-related deaths was available.

## CHALLENGES IN THE JCOG

**Advantage of a cooperative group.** In Japan, several cooperative groups exist, and the JCOG was the first and is the best organized of these. This organization has a strictly independent data center and 14 organ-specific groups. It also has a steering committee (headquarters) and several other functioning committees, such as an audit committee, data and safety monitoring committee, and protocol review committee. All aspects of a trial, especially safety aspects, are strictly monitored by several committees. Peer review by statisticians, medical oncologists, surgeons, or clinical research coordinators in various fields allows protocols to be clear, scientific, and ethical. All the data are controlled by the data center, and data sets cannot be accessed by researchers individually. Most trials include planned interim analyses, which are performed by statisticians that do not belong to the specific group conducting the trial. Survival results are shown only to the independent data and safety monitoring committee, which does not include any of the group's own researchers or statisticians. A lack of this type of organization was one of the many weak points of the DGCS.

**Setting up phase 3 trials in the JCOG.** In the JCOG, the first step in setting up a trial is to write a protocol concept. When the researchers in an organ-specific group agree to undertake a clinical trial, one of them writes a protocol concept to explain the background, methods, and feasibility of the study. With the help of the group's associated statistician, statistical aspects such as alpha, beta, and sample size are also discussed. A committee, which is composed of statisticians, medical oncologists, surgeons, and clinical research coordinators, peer reviews the protocol and then reports their evaluation along with any questions they might have. This report is discussed by the steering committee, and a vote is held to decide whether the study is worth performing in the JCOG. Any lack of safety information or lacking of experience of the participants involved in the study is usually pointed out, and the review committee sometimes recommends that the researchers carry out a feasibility study or a phase 2 study instead of proceeding immediately to phase 3. Especially in cases of surgical trials, hospital mortality should be maintained below 5% even with multidisciplinary treatment such as extended operative therapy after neoadjuvant chemotherapy. At the moment, a mortality rate higher than 5% is no longer acceptable in Japan for any cancer operation.

After approval by the steering committee, a full protocol is written by researchers together with coordinating physicians who are specialists at compiling protocols for clinical studies. This process takes a rather long time, especially in surgical trials, because the details of each surgical technique used in the study must be defined clearly and agreed on by all trial participants so as to minimize the variation in procedural implementation. Occasionally, selection of the participants is debated, especially in studies that require learning of new techniques, such as laparoscopic cancer surgery. The nature of the surgical technique also influences the decision of how to evaluate the results of the procedure performed in each case.

**Actual trials in the Gastric Cancer Surgical Study Group (GCSSG) of the JCOG.** In the GCSSG of the JCOG, 5 surgical trials have been conducted since 1995. The first trial, JCOG9501, was a phase 3 trial among 24 Japanese hospitals that compared D2 gastrectomy with superextended D3 gastrectomy, which is a D2 gastrectomy plus para-aortic nodal dissection, for T2b-T4 gastric cancer. Between July 1995 and April 2001, we randomized 523 patients intraoperatively to either the D2 arm (263 patients) or the D3 arm (260 patients). No adjuvant therapy was permitted until recurrence. The primary endpoint was overall survival. We paid careful attention to this initial surgical trial because of the experience of DGCS as previously mentioned. This trial selected surgeons who had experience with more than 100 gastrectomies with D2 dissection, or hospitals with an annual gastrectomy volume of more than 80 cases. During the study planning stages, all participating surgeons agreed to the technical details of both types of operations. In addition to reviewing the semiannual monitoring report, several participating surgeons presented videos of 1 or both procedures of arbitral patients to ensure uniformity of treatment and the procedures' technical details were discussed. To assess compliance with the specified type of lymphadenectomy, node retrieval in all regional nodal stations and number of dissected nodes in the para-aortic area were recorded on case report forms, which were also monitored. As a result, both surgical arms showed permissible complication rates and low hospital mortalities (0.8% in each arm).[8] Unexpectedly, no significant difference was observed in either overall survival or recurrence-free survival between the 2 groups. In conclusion, this first JCOG surgical phase 3 trial demonstrated that superextended D3 gastrectomy should not be used to treat this target population.[18]

In parallel with JCOG9501, another phase 3 trial was conducted to compare the effects of a left thoracoabdominal (LTA) approach with a abdominal-transhiatal (TH) approach in the treatment of gastric cancers with an esophageal invasion of 3 cm or less (corresponding mainly to tumors classified as Siewert type 2 or 3). Following a similar quality control procedure as JCOG9501, the JCOG9502 trial selected 27 specialized hospitals for participation. Only 3 patients died in hospital after LTA and none after TH. Morbidity was less favorable after LTA than after TH. Nevertheless, the survival of the LTA arm was diminished compared with the TH arm at the first interim analysis.[19] We therefore closed the accrual and opened the results according to the recommendation of the independent data and safety monitoring committee. Thus, the JCOG9501 and JCOG9502 trials demonstrated the ineffectiveness of more extensive surgeries and led to the establishment of standard surgeries in the field of gastric cancer.

Through the experience of these initial trials, other surgical trials were planned and are now ongoing in the GCSSG of the JCOG. JCOG0110 is a trial to evaluate the role of splenectomy in total gastrectomy for proximal gastric cancer in terms of survival benefit and postoperative morbidity.[20] Because this trial was designed in a noninferiority fashion, we have managed quality control more strictly than in previous trials, using a superiority-based approach so as not to affect the final results inappropriately. For example, the details of the planned surgical procedures were specified and described more clearly in the trial protocol before the study began. The number of dissected nodes in all stations was recorded on case report forms to be used for assessing the quality of operative therapy. We made a termination rule regarding hospital mortality in advance. If the number of deaths caused by surgical complications reached 10, the accrual would be stopped temporarily to wait for a judgment from the data and safety monitoring committee. The randomization to either gastrectomy with or without splenectomy was performed during operation after intraoperative confirmation of the eligibility criteria. Recruitment of the planned sample of 500 patients was accomplished in March 2009, after which all patients will be followed for 5 years.

We have also conducted a phase 2 trial of laparoscopy-assisted distal gastrectomy (LADG). Recently, this laparoscopic surgery technique has been established in specialized institutions. Although the technical difficulties of LADG have been solved gradually, some retrospective studies have reported that LADG is associated with a higher risk of surgical morbidities, such as anastomotic leak, stenosis, and pancreatic fistula, compared with open gastrectomy. The aim of the JCOG0703 trial is to evaluate the safety of LADG in clinical stage I gastric cancer. The primary endpoints are incidence of anastomotic leak and pancreatic fistula. If the incidence of these 2 postoperative complications is as low as expected (3% in total), then a subsequent phase 3 trial will be started to evaluate noninferiority of LADG compared with open gastrectomy in terms of long-term survival. Only surgeons with experience of more than 30 LADG and 30 open distal gastrectomies were allowed to participate in this trial. In addition to monitoring the number of dissected nodes in all stations with a case report form, we performed a central review of the surgical procedure by photographs of all patients and by videotaping of arbitrarily selected patients. This trial would have stopped accrual if treatment related deaths or life-threatening complications had reached 6.[21]

The latest JCOG phase 3 trial has just started with the international collaboration of the Korean Gastric Cancer Association. The prognosis of patients who suffer from incurable gastric cancer with hepatic or peritoneal metastases is poor. To investigate the role of gastrectomy in advanced gastric cancer with a single noncurable factor, 43 specialized hospitals (33 Japanese and 10 Korean) are conducting this REGATTA (JCOG0705) trial. Patients are randomized to either gastrectomy plus chemotherapy or to chemotherapy alone. The primary endpoint is overall survival, and the planned sample size is 330 with 2 years of follow-up after 4 years of accrual. The JCOG data and safety monitoring committee will independently perform the interim analysis and will consider stopping the trial early on behalf of both countries. 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 2 countries semiannually. Audits of the participating facilities are also carried out independently in each country, and brief summaries are exchanged. In this trial, if the number of treatment-related deaths reaches 9 in the chemotherapy-alone arm or 14 in the gastrectomy-plus-chemotherapy arm, the accrual will be stopped temporarily. Prior to its initiation, we had all expected significant difficulties in starting this international trial because of the many differences in medical culture and customs, as well as language, between Japan and Korea. Furthermore, most surgical trials are initiated by investigators without industrial sponsors, which requires them to obtain governmental or other competitive grants. Fortunately, the above challenges have been overcome, and the trial has been launched thanks to all the investigators' sincere efforts. Thus, the key to success in conducting high-quality surgical clinical trials is the investigators' enthusiasm and commitment to providing the best possible treatment to all future patients worldwide.

In conclusion, many issues in surgical oncology clinical trials are not relevant to medical oncology trials. If the treatment provided in surgical trials is not marked by the high quality afforded by specialists, the resulting benefits will not be appreciated by either patients or their providers. Establishing a cooperative group of specialists whose technical variance is minimal is therefore of paramount importance in performing meaningful clinical trials in surgical oncology.

## REFERENCES

1. McCulloch P, Taylor I, Sasako M, Lovett B, Griffin M. Randomised trials in surgery: problems and possible solutions. Br Med J 2002;324:1448-51.
2. Bonenkamp JJ, Hermans J, Sasako M, van de Velde CJ, Welvaart K, Songun I, et al. Extended lymph node dissection for gastric cancer. N Engl J Med 1999;340:908-14.
3. Sasako M. Clinical trials of surgical treatment of malignant diseases. Int J Oncol 2005;10:165-70.
4. Bunt AM, Hermans J, Boon MC, van de Velde CJ, Sasako M, Fleuren GJ, et al. Evaluation of the extent of lymphadenectomy in a randomized trial of Western- versus Japanese-type surgery in gastric cancer. J Clin Oncol 1994;12:417-22.
5. Brennan MF. Lymph-node dissection for gastric cancer. N Engl J Med 1999;340:956-7.
6. Hundahl SA. Surgical quality control in gastric cancer trials. Surg Oncol Clin N Am 2002;11:445-58.
7. Parikh D, Johnson M, Chagla L, Lowe D, McCulloch P. D2 gastrectomy: lessons from a prospective audit of the learning curve. Br J Surg 1996;83:1595-9.
8. Sano T, Sasako M, Yamamoto S, Nashimoto A, Kurita A, Hiratsuka M, et al. Gastric cancer surgery: morbidity and mortality results from a prospective randomized controlled trial comparing D2 and extended para-aortic lymphadenectomy–Japan Clinical Oncology Group study 9501. J Clin Oncol 2004;22:2767-73.
9. Van Lanschot JJ, Hulscher JB, Buskens CJ, Tilanus HW, ten Kate FJ, Obertop H. Hospital volume and hospital mortality for esophagectomy. Cancer 2001;91:1574-8.
10. Gordon TA, Bowman HM, Tielsch JM, Bass EB, Burley GP, Cameron JL. Statewide regionalization of pancreaticoduodenectomy and its effect on in-hospital mortality. Ann Surg 1998;228:71-8.
11. Sasako M. Risk factors for surgical treatment in the Dutch gastric cancer trial. Br J Surg 1997;84:1567-71.
12. Guller U. Caveats in the interpretation of the surgical literature. Br J Surg 2008;95:541-6.
13. Macdonald JS, Smalley SR, Benedetti J, Hundahl SA, Estes NC, Stemmerman GN, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med 2001;345:725-30.
14. Bonenkamp JJ, Hermans J, Sasako M, van de Velde CJH. Quality control of lumph node dissection in the Dutch

randomized trial of D1 and D2 lymph node dissection for gastric cancer. Gastric Cancer 1998;1:152-9.
15. Bunt AMG, Hermans J, Boon MC, van de Velde CJH, Sasako M, Hoefsloot FAM, et al. Lymph node retrieval in a ramdomized trial on Western-type versus Japanese-type surgery in gastric cancer. J Clin Oncol 1996;14:2289-94.
16. Sasako M, Saka M, Fukagawa T, Katai H, Sano T. Surgical treatment of advanced gastric cancer: Japanese perspective. Dig Surg 2007;24:101-7.
17. Hulscher JBF, van Sandick JW, de Boer AGEM, Wijnhoven BPL, Tijssen JGP, Fockens P, et al. Extended transthoracic resection compared with limited transhiatal resection for for adenocarcinoma of the esophagus. N Engl J Med 2002;347:1662-9.
18. Sasako M, Sano T, Yamamoto S, Kurokawa Y, Nashimoto A, Kurita A, et al. D2 lymphadenectomy alone or with para-aortic nodal dissection for gastric cancer. N Engl J Med 2008;359:453-62.
19. Sasako M, Sano T, Yamamoto S, Sairenji M, Arai K, Kinoshita T, et al. Left thoracoabdominal approach versus abdominal-transhiatal approach for gastric cancer of the cardia or subcardia: a randomised controlled trial. Lancet Oncol 2006;7:644-51.
20. Sano T, Yamamoto S, Sasako M. Randomized controlled trial to evaluate splenectomy for proximal gastric carcinoma: Japan Clinical Oncology Group Study JCOG0110-MF. Jpn J Clin Oncol 2002;32:363-4.
21. Kurokawa Y, Katai H, Fukuda H, Sasako M. Phase II study of laparoscopy-assisted distal gastrectomy with nodal dissection for clinical stage I gastric cancer: Japan Clinical Oncology Group Study JCOG 0703. Jpn J Clin Oncol 2008; 38:501-3.

# INVESTIGATIONS USING CLINICAL DATA REGISTRIES: OBSERVATIONAL STUDIES AND RISK ADJUSTMENT

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OUTCOMES RESEARCH has progressed a great deal in the past several years with the increasing availability of population-based data sources as well as other types of data registries. Also, the increasingly powerful and menu-driven statistical packages have made analyses of such data sets common, place, and have contributed to the increasing numbers of such publications. In this regard, however, there are a number of issues that an investigator needs to understand and address when performing such analyses. This article will review the following approaches to observational studies, with particular comments relevant to the use of clinical registry data:

- No risk adjustment
- Cohort study
- Case-control study
- Stratified study
- Regression-based risk adjustment
- Matching
- Propensity scores
- Instrumental variables

Following these observations, a few additional topics that are critical to the most common approaches will be briefly discussed:

- Sensitivity analysis
- Adjusting for exogenous and endogenous factors
- Regression to the mean
- Average treatment effect versus treatment effect on the treated
- The use of administrative data for risk adjustment

## BACKGROUND: RANDOMIZED CONTROLLED TRIALS VERSUS OBSERVATIONAL STUDIES

The experiment is a critical element of the scientific method:

*In the scientific method, an experiment (Latin: ex periri "of (or from) trying") is a set of observations performed in the context of solving a particular problem or question, to retain or falsify a hypothesis or research concerning phenomena. The experiment is a cornerstone in the empirical approach to acquiring deeper knowledge about the physical world.*[1]

There are some critical and desirable features in the design of experiments. First, only one factor or treatment, referred to as the *experimental, treatment* or *independent variable,* should vary systematically across the experiment's groups. When this is true, the experiment is considered a *controlled experiment.* In controlled experiments, other factors that might also affect the outcome being studied do not vary systematically between groups. This method enables strong conclusions about the isolated effect of the experimental variable. A second major desirable feature in the design of experiments is for the outcome being studied (the *dependent variable*) to actually reflect an influence of the independent variable and for the measurement of that outcome to be possible without error or with describable error.

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