厚生労働科学研究費補助金

がん臨床研究事業

高度進行胃がんの治療に関する研究

平成１６年度～１８年度　総合研究報告書

主任研究者　　笹子　三津留

平成１９年（２００７）年４月

目　　次

厚生労働科学研究費補助金（がん臨床研究事業）
総合研究報告書

高度進行胃がんの治療に関する研究

主任研究者　笹子　三津留　国立がんセンター中央病院副院長

研究要旨
予後が極めて不良なスキルス胃がん（4型胃がん）及びそれに準ずる8cm以上の大型3型胃がんを対象に治療成績の改善を目指して術前化学療法実施後に根治手術を行う治療法の開発を試みた。第1段階では新しい治療法としてのTS-1＋CDDP療法を術前に2コース行い、その後にD2　以上の根治手術を行う治療のfeasibilityを検証する第Ⅱ相試験を行った。この段階では腹腔鏡検査は必須とせず、臨床的に根治可能な大型3型・4型胃がんを対象に、TS-1+CDDP療法を2コースの実施可能性・有害事象、その後のD2以上の手術における根治切除達成率と合併症の発生率を評価した。
前記第Ⅱ相試験で実施可能性と有効性が見込まれたことから、第Ⅲ相試験を計画し、実施している。第Ⅲ相試験では、腹腔鏡検査で播種を含めた遠隔転移がないことが確認された大型3型・4型胃がんに対して、手術単独群を対照とし、試験アームはTS-1＋CDDP療法を2コース行う術前化学療法を施行後に根治手術を行う試験として2005年10月より開始した。2006年7月初め、16例を登録した時点で、本研究にとって極めて重大な影響のある市販後臨床試験、ACTS-GC試験が第1回中間解析で有効中止となったという情報が入った。その結果、今後わが国では、ステージII以上の胃がんでは、TS-1の術後補助化学療法が標準治療となると考えられ、この時点で試験への登録を緊急に中止した。ACTS-GCの結果の詳細を確認後、本第Ⅲ相試験のプロトコール改訂作業に入った。対照群の治療を手術単独から術後TS-1による補助化学療法とし、試験治療群にも同じ補助化学療法を追加し、TS-1+CDDPによる術前化学療法の上乗せ効果を見る試験として、改訂した。2007年2月にJCOG効果・安全性評価委員会で改訂が承認され、登録が再開された。

分担研究者
荒井　邦佳　*1東京都立駒込病院　部長
岩崎　善毅　*2東京都立駒込病院　医長
木下　平　*2国立がんセンター東病院　部長
栗田　啓　*3独立行政法人国立病院機構四国がんセンター　部長
小西　孝司　*4富山県立中央病院　院長
小林　理　*5神奈川県立がんセンター　部長
斎藤　和好　*3岩手医科大学第一外科　教授
塩崎　均　*3近畿大学医学部外科　教授
清水　武昭　*1新潟県厚生連長岡中央綜合病院　副院長
高金　明典　*5岩手医科大学附属病院外科学第一外科　講師
田中　洋一　*2埼玉県立がんセンター　部長
種村　廣巳　*1岐阜市民病院　副院長
塚原　康生　*2豊中市立豊中病院　中央診療局次長兼外科部長兼内視鏡部部長
辻仲　利政　*2独立行政法人国立病院機構大阪医療センター　がんセンター診療部長・外科科長
円谷　彰　*2神奈川県立がんセンター　部長
梨本　篤　*6新潟県立がんセンター新潟病院　部長
二宮　基樹　*1広島市立広島市民病院　部長

福島　紀雅　*6山形県がん・生活習慣病センター　副部長、山形県立中央病院　医長
古河　洋　*6堺市立堺病院　院長
宮下　薫　*5燕労災病院　副院長
宮代　勲　*4地方独立行政法人大阪府立病院機構大阪府立成人病センター　副部長
山村　義孝　*7愛知県がんセンター中央病院　部長

*1　平成16年4月1日～18年3月31日
*2　平成18年4月1日～19年3月31日
*3　平成16年4月1日～17年3月31日
*4　平成17年4月1日～19年3月31日
*5　平成17年4月1日～18年3月31日
*6　平成16年4月1日～19年3月31日
*7　平成16年4月1日～17年3月31日
　　平成18年4月1日～19年3月31日

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歳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】１）多施設共同の第Ⅱ相試験：新規治療での治療完遂率（化学療法が2コース安全に施行され、根治切除が行われた症例の割合）と治療関連死率を評価する。２）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】第Ⅱ相試験では実施可能性が問題であり、腹膜播種のある症例を必ずしも除外する必要がなかったため、早期の治療完遂と第Ⅲ相試験への移行を目指した、腹腔鏡検査を行わず、臨床的に根治切除可能と判断できる大型3型・4型胃がんが対象。第Ⅲ相試験では、生存率を比較するため、腹腔鏡検査を含めた臨床的検索で遠隔転移を伴わない、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。適格性を判断するために行う検査は総て日常臨床で通常行う検査であり、それらにより適格となった場合に、本試験に関する説明を行う。

【症例登録とランダム割付】第Ⅱ相試験、第Ⅲ相試験とも、JCOGデータセンターで中央登録する。第Ⅲ相試験では、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。対照群は手術単独であったが、術後補助化学療法に関する新しいエビデンスに基づき、プロトコール改訂後は手術＋術後TS-1による補助化学療法と変更された。それに伴い、試験治療もTS-1+CDDPによる術前化学療法2コース＋根治手術＋TS-1による術後補助化学療法と変更された。

【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およ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約30施設で実施する。

（倫理面への配慮）

本研究における第Ⅱ相試験はJCOGのプロトコール審査委員会、臨床試験評価委員会の承認を得た後に、各参加施設の倫理審査委員会で承認を受け、実施された。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ことから、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、再登録を再開する。いずれの試験も、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

1）術前化学療法のfeasibility試験である第Ⅱ相試（JCOG0210）では、50例が登録され、49例が適格例であった。44例で術前化学療法は完遂された。途中毒性中止例を含めて48例で手術が実施され、治療完遂とされるR0/1手術は36例（73%）で達成でき、この治療完遂率は期待値、閾値とも大幅に上回っていた。治療関連死は治療開始間もなくの原発巣からの出血死1例であり、安全性にも問題はなかった。Grade3/4の毒性は好中球減少14%と食欲不振14%が最も頻度が高いものであり、現在進行胃がん治療として行われる他の治療に比して極めて安全性の高い治療と考えられた。また、術後合併症も膵液瘻の8%で最も頻度の高かった合併症で、他の手術の臨床試験と比較しても、術後合併症という面でも、安全な治療と言える結果であった。また、本試験の生存結果も得られ、3年生存率は26%（95% CI：14.9-38.6%）であり、有効性の閾値15%もほぼ却下できるものであった。

2）17年11月より手術単独を対照群とする第Ⅲ相ランダム化試験（JCOG0501）を開始した。倫理審査委員会の承認を得られた施設数が増え、ようやく月間4例の登録がコンスタントとなり始めた18年7月に、TS-1の術後補助化学療法の有用性が証明されたことがわかった。この結果今後本邦では、ステージⅡ以上の胃がん治癒切除後はTS-1による補助化学療法を行うことが標準となる。我々の試験には、その時点ですでに16例が登録されていたが、倫理的に手術単独を対照とすることはできないため、プロトコールの大改訂を目的に、7月25日にて登録を一時中止した。

改訂では、治療群では術前化学療法+根治手術+術後補助化学療法として、対照群は根治手術+術後補助化学療法と変更することになり、平成19年2月に改訂プロトコールは承認された。その後1例の登録があり、平成19年3月末では計17例が登録されたことになる。本改訂では、改訂前の症例数が少なかったこと、治療内容が手術単独とかなり異なることから新たに300例の集積を上乗せ、計316例の登録予定数とし、登録期間も6年半と延長した。

D．考察

本試験治療法（TS-1+CDDP＋根治手術）は第Ⅱ相試験での評価において、第Ⅲ相試験の試験アームにふさわしいと考えられた。第Ⅱ相試験では、主たる目的がfeasibilityの確認であったことから、適格性を臨床・画像検査のみで決めたが、本第Ⅲ相試験では診断的腹腔鏡検査を実施した上で、腹膜播種が無く、洗浄細胞診陰性の症例のみを対象として実施している。この第Ⅲ相試験の対象は前記第Ⅱ相臨床試験と同じ大型3型・4型胃がんで、手術単独群を対照治療として開始されたが、既に述べたように、わが国の大規模試験の結果を受けて、標準治療が代わり、TS-1術後補助化学療法1年間の投与を両群に行うこととなった。

倫理審査が終了して、登録参加施設が増えるにつれて、月間登録数が予定数に近くなった時期に、登録中止に追い込まれたことは痛手であった。しかし、この改訂により、両群に化学療法が入ることになったため、予後不良の対象に手術単独をコントロール群としていた元々のプロトコールよりは、登録の同意が患者さんから得られやすい可能性が高い。今後はあらゆる方法で参加施設を鼓舞しながら、積極的な試験への参加を呼びかけていく。年間60例を見込んでおり、月間5例であることから、今後は施設毎に対象症例数、その内の試験登録数と非登録例における非登録理由の把握を実施していく予定である。

また、JCOG胃がん外科グループでは、同じレジメンを用いて高度リンパ節転移を有する局所進行胃がん症例に対する術前化学療法の第Ⅱ相試験も実施中であり、安全性情報等は共有していく。両試験を通じて、今までのところ治療関連死亡は経験していない。

E．結論

TS-1+CDDP療法は安全性と治療効果に優れ、遠隔転移のない予後不良進行胃がん症例に対する新しい治療法となりうるポテンシャルを持ち、第Ⅲ相試験を施行中である。

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)Sasako, M.: Role of surgery in multidisciplinary treatment for solid cancers. Int J Clin Oncol, 9: 346-351, 2004.

(2)Sasako, M.: Clinical trials of surgical treatment of malignant diseases. Int J Clin Oncol, 10:

165-170, 2005.
(3)Kodera, Y., Sasako, M., Yamamoto, S., Sano, T., Nashimoto, A., Kurita, A. on behalf of the Gastric Cancer Surgery Study Group of Japan Clinical Oncology Group: Identification of risk factors for the development of complications following extended and superextended lymphadenectomies for gastric cancer. British Journal of Surgey, 92: 1103-1109, 2005.
(4)Ohtsu, A. and Sasako, M.: Overview of adjuvant therapy for resected gastric cancer: Differences in Japan and the United States. Seminars in Oncology, 32(suppl 9): S101-S104, 2005.
(5)阪眞、笹子三津留：特集：臨床腫瘍学の現状と展望 V. がん薬物療法の実際 4. 消化器癌 2) 胃癌 b) 進行胃癌のアジュバント療法.Progress in Medicine、25(8): 2073-2078、2005.
(6)吉川貴己、円谷彰、小林理：腹膜転移を有する初発胃癌の治療戦略．癌と化学療法、32: 1398-1403、2005.
(7)種村廣巳、他：大型3型/4型/Bulky N2進行胃癌に対するTS-1+CDDPを用いた術前化学療法の経験．癌と化学療法、32: 2079-2085、2005.
(8)Miyashiro, I., Takachi, K., Doki, Y., Ishikawa, O., Ohigashi, H., Murata, K., Sasaki, Y., Imaoka, S., Nakaizumi, A., Takenaka, A., Furukawa, H., Hiratsuka, M.: When is curative gastrectomy justified for gastric cancers with positive peritoneal lavage cytology but negative macroscopic peritoneal implant? W.J. Surg., 29: 1131-1134, 2005.
(9) Yoshikawa, T., Sasako, M., Sano, T., Nashimoto, A., Kurita, A., Tsujinaka, T., Tanigawa, N., Yamamoto, S., for the Gastric Cancer Surgical Study Group of the Japan Clinical Oncology Group: Stage migration caused by D2 dissection with para-aortic lymphadenectomy for gastric cancer from the results of a prospective randomized controlled trial. British Journal of Surgery, 93: 1526-1529, 2006.
(10)Makino, T., Tsujinaka, T., et al.: An icteric tyow hepatocellular carcinoma with no detectable tumor in the liver: Report of a case. Surg Today, 36: 633-637, 2006.
(11)土屋康紀、梨本篤：TS-1+CDDP療法1コースにてCRとなった進行胃癌の1例．癌と化学療法 33: 807-809、2006.
(12)山口健太郎、梨本篤：Paclitaxel+Low dose FP術前化学療法が奏効し原発巣が消失した進行胃癌の1例．癌と化学療法 33: 1163-1166、2006.
(13)伊藤誠二、小寺泰弘、望月能成、山村義孝：スキルス胃癌非切除の方針は妥当か？外科治療、95: 73-74、2006.

２．学会発表
(1)伊藤誠二、山村義孝、他：スキルス胃癌治療成績の変化-非切除の方針は妥当か一．第104回日本外科学会定期学術集会、大阪、平成16年4月
(2)片井均、笹子三津留、佐野武、古河洋、藤谷恒明、福島紀雅、田中洋一、山村義孝、種村廣巳、辻仲利政（日本臨床腫瘍外科グループ(JCOG)胃がん外科グループ）：高度リンパ節転移を伴う進行胃がんに対する術前CPT11+CDDP療法+外科切除の第Ⅱ相臨床試験．第59回日本消化器外科学会定期学術総会、鹿児島、平成16年7月
(3)嶋田善久、荒井邦佳、岩崎善毅、片柳創、高橋慶一、山口達郎、松本寛、宮本英典：高度進行胃癌に対する術前化学療法としてのTS-1/CDDP併用療法の検討．第66回日本臨床外科学会総会、盛岡、平成16年10月
(4)平成人、栗田啓、野崎功雄、小森栄作、久保義郎、棚田稔、高嶋成光：切除可能高度進行胃癌に対する術前TS-1, CDDP併用療法に関する検討．第42回日本癌治療学会総会学術集会、京都、平成16年10月
(5)佐々木寛、二宮基樹、原野雅生、青木秀樹、小野田正、塩崎滋弘、大野聡、桧垣健二、高倉範尚：当院における高度進行胃癌に対する術前化学療法の経験．第42回日本癌治療学会総会、京都、平成16年10月
(6)Taira, N., Kurita, A., Okita, A., Nozaki, I., Komori, E., Kubo, Y., Tanada, M., Takashima, S.: Evaluation of TS-1 combined with cisplatin for neoadjuvant chemotherapy in patients with advanced gastric cancer. 19th World Congress of International Society for Digestive Surgery, Yokohama, Japan, 2004. 12.
(7)Nashimoto, A.: Evaluation of S-1 and Cisplatin combination chemotherapy as neoadjuvant chemotherapy for patients with advanced gastric cancer.19th World Congress of InternationalSociety for Digestive Surgery, Yokohama, Japan, 2004. 12.
(8)Tsuburaya, A., Sasako, M.,

Furukawa, H., Fukushima, N., Fujitani, T., Tanemura, H., Yamamoto, S., Gastric Cancer Surgical Study Group of JCOG: Preoperative adjuvant chemotherapy with irinotecan and cisplatin for gastric cancer with extensive lymph node metastasis: A multicenter phase IIstudy by Japan Clinical Oncology Group (JCOG0001). 2005 Gastrointestinal Cancers Symposium: Multidisciplinary Approaches to Gastrointestinal Malignancies and Premalignancies, Hollywood, Florida, U.S.A, 2005. 1.

(9)Sasako, M.: Attractive regimen for neo-adjuvant chemotherapy of gastric cancer. 6th International Gastric Cancer Congress, Yokohama, Japan, 2005. 5.

(10)Sasako, M., Iwasaki, Y., Sano, T., Tsuburaya, A., Furukawa, H., Tanaka, Y., Yamamura, Y., Tsujinaka, T., Yamamoto, S.: Preoperative adjuvant chemotherapy with irinotecan and cisplatin for gastric cancer with extensive lymph node metastasis: Results of JCOG0001 study. 6th International Gastric Cancer Congress, Yokohama, Japan, 2005. 5.

(11)Kinoshita, T., Sasako, M., Sano, T., Katai, H., Furukawa, H., Kobayashi, O.: Results of a phase II trials of neoadjuvant chemotherapy by S-1 for scirrhous gastric cancer. JCOG0002. 6th International Gastric Cancer Congress, Yokohama, Japan, 2005. 5.

(12)Kinoshita, T., Miyashiro, I., Furukawa, H., Sasako, M., Yamamoto, S., Nashimoto, A., Nakajima, T., Kobayashi, O., Arai, K., Kitamura, M.: Results of a RCT of adjuvant chemotherapy with CDDP+UFT in serosa-positive gastric cancer. 6th International Gastric Cancer Congress, Yokohama, Japan, 2005. 5.

(13)Kobayashi, O., Murakami, H., Yoshida, T., Osaragi, T., Yoshikawa, T., Tsuburaya, A., Sairenji, M.: Efficacy of Neo-adjuvant Chemotherapy Using S-1+CDDP in Patients with Advanced Large Gastric Cancer (ALGC). 6th International Gastric Cancer Congress, Yokohama, Japan, 2005. 5.

(14)Fujiwara, H., Takagane, A., Abe, K., Irinoda, T., Yonezawa, H., Nakaya, T., Oyama, K., Takahashi, M., Terashima, M., Saito, K.: A combination chemotherapy with intra-peritoneal infusion of CDDP and TS-1 for gastric cancer with peritoneal metastasis or positive peritoneal cytology. 6th International Gastric Cancer Congress, Yokohama, Japan, 2005. 5.

(15)Nashimoto, A.: Evaluation of S-1 and Cisplatin combination chemotherapy as neoadjuvant chemotherapy as neoadjuvant chemotherapy for advanced gastric cancer. 6th International Gastric Cancer Congress, Yokohama, Japan, 2005. 5.

(16)Kosugi, S., Nashimoto, A.: Evaluation of staging laparoscopy (SL) for advanced gastric cancer, 6th International Gastric Cancer Congress, Yokohama, Japan, 2005. 5.

(17)Ninomiya, M., Sasaki, H., Takakura, N.: Significance of neoadjyuvant chemotherapy for highly advanced gastric cancer. 6th International Gastric Cancer Congress, Yokohama, Japan, 2005. 5.

(18)村上仁志、吉田達也、大佛智彦、円谷彰、小林理、西連寺意勲：進行胃癌に対する術前補助化学療法-当科における経験-. 第77回日本胃癌学会総会、横浜、平成17年5月

(19)岩崎善毅、笹子三津留、佐野武、荒井邦佳、福島紀雅、小林理、梨本篤、種村廣巳、辻仲利政、古河洋、木下平：進行胃癌に対するneo-adjuvant chemotherapy: JCOG胃がん外科グループの挑戦. 第77回日本胃癌学会総会、横浜、平成17年5月

(20)二宮基樹、佐々木寛 、矢野修也、児島亨、原野雅生、青木秀樹、小野田正、塩崎滋弘、大野聡、高倉範尚：高度進行胃癌に対する術前化学療法の意義. 第77回日本胃癌学会総会、横浜、平成17年5月

(21) 種村廣巳、他：大型3型/4型/Bulky N2進行胃癌に対するTS-1+CDDPを用いた術前化学療法の成績. 第78回日本胃癌学会総会、大阪、平成18年3月

(22)藪崎裕、梨本篤：診断的腹腔鏡検査(SL)を用いた4型胃癌に対する治療戦略. 第60回日本消化器外科学会総会 、東京、平成17年7月

(23)Sasako, M., Sano, T., Katai, H., Fukagawa, T., Saka, M.: Surgical treatment of advanced gastric cancers with poor prognosis. 18th Asia Pacific Cancer Conference, Seoul, Korea, 2005. 7.

(24)岩崎善毅、笹子三津留、佐野武、荒井邦佳、木下平、梨本篤：大型3型、4

型胃癌に対する新しい治療戦略．第60回日本消化器外科学会、東京、平成17年7月
(25)矢野修也、二宮基樹、佐々木寛、丁田泰宏、原野雅生、青木秀樹、小野田正、塩崎滋弘、大野聡、高倉範尚：スキルス胃癌の治療戦略の検討．第60回日本消化器外科学会総会、東京、平成17年7月
(26) 高金明典、藤原久貴、大山健一、高橋正統、千葉丈広、阿部薫、中屋勉、米澤仁志：TS-1/CDDP併用療法が著効し根治切除となった胃癌高度リンパ節転移の一例．第43回日本癌治療学会総会、名古屋、平成17年10月
(27)Sasako, M., Saka, M., Fukagawa, T., Katai, H., Sano, T.: Is the extended lymphadenectomy standard procedure? International Surgical Week 2005 / 41st World Congress of Surgery of ISS/SIC, Durban, South Africa, 2005. 8.
(28)Iwasaki, Y., Sasako, M., Sano, T., Yamamoto, S., Sato, A., Tsujinaka, T., Fukushima, N., Nashimoto, A., Arai, K., Kinoshita, T.: Phase II study of preoperative S-1 and cisplatin in patients with clinically respectable type 4 and large type 3 gastric cancer: Japan Clinical Oncology Group Study (JCOG 0210). 2006 Gastrointestinal Cancers Symposium: Multidisciplinary Aproaches to the Prevention, Diagnosis, and Therapy of GI Cancers (ASCO), San Francisco, U.S.A., 2006. 1.
(29)岩崎善毅、笹子三津留、佐野武、荒井邦佳、小林理、梨本篤、木下平：進行胃癌に対するneo-adjuvant chemotherapy：JCOG胃がん外科グループの臨床試験．第78回日本胃癌学会総会、大阪、平成18年3月
(30)Sasako M., Sano, T. (Gastric Cancer Surgical Study Group (GCSSG) of the Japan Clinical Oncology Group(JCOG)): Clinical phase III studies in surgery for gastric cancer. 第78回日本胃癌学会総会、大阪、平成18年3月
(31)笹子三津留、佐野武、片井均、深川剛生、阪眞：高度リンパ節転移を有する胃癌症例に対する術前化学療法後の拡大根治手術．第106回日本外科学会定期学術集会、東京、平成18年3月
(32)Yoshikawa, T., Sasako, M., Sano, T., Nashimoto, A., Kurita, A., Tsujinaka, T., Tanigawa, N., Yamamoto, S.: Stage migration caused by D2 + para-aortic lymphadenectomy for gastric cancer: Analyses from a prospective randomized controlled trial (JCOG 9501) comparing D2 and D2+para-aortic lymphadenectomy. 2006 Gastrointestinal Cancers Symposium: Multidisciplinary Aproaches to the Prevention, Diagnosis, and Therapy of GI Cancers (ASCO), San Francisco, U.S.A., 2006. 1.
(33)黒川幸典、笹子三津留、木下平、吉村健一、山本精一郎、佐藤暁洋、福田治彦：胃癌取扱い規約における腫瘍縮小効果判定基準の問題点．第78回日本胃癌学会総会、大阪、平成18年3月
(34)笹子三津留、佐野武、片井均、深川剛生、阪眞：高度リンパ節転移を有する胃癌症例に対する術前化学療法後の拡大根治手術．第106回日本外科学会定期学術集会、東京、平成18年3月
(35)岩崎善毅、笹子三津留、佐野武、荒井邦佳、小林理、梨本篤、木下平：進行胃癌に対するneo-adjuvant chemotherapy：JCOG胃がん外科グループの臨床試験．第78回日本胃癌学会総会、大阪、平成18年3月
(36)梨本篤：高度進行胃癌に対するTS-1+CDDP併用療法後の拡大手術．第78回日本胃癌学会総会、大阪、平成18年3月
(37)Nashimoto, A.: Phase II study of neoadjuvant chemotherapy (NAC) with S-1 and cisplatin (CDDP) for patients (pts) with highly advanced gastric cancer (GC). 42nd American Society of Clinical Oncology, Atlanta, U.S.A., 2006. 6.
(38)笹子三津留：消化器癌に対するネオアジュバント治療の功罪　胃癌治療にネオアジュバント治療は有効か（基調講演）．第61回日本消化器外科学会定期学術総会、横浜、平成18年7月
(39)宮代勲、岸健太郎、高地耕、矢野雅彦、山田晃正、大植雅之、大東弘明、佐々木洋、石川治、今岡真義：スキルス胃癌の治療戦略における腹腔鏡ステージングの役割．第61回日本消化器外科学会定期学術総会、横浜、平成18年7月
(40)宮代勲、岸健太郎、高地耕、矢野雅彦、江口英利、能浦真吾、山田晃正、大植雅之、大東弘明、佐々木洋、石川治、今岡真義：4型胃癌および大型3型胃癌に対して診断的腹腔鏡を行うべきか？第44回日本癌治療総会、東京、平成18年10月
(41)岩崎善毅、笹子三津留、佐野武、荒井邦佳、福島紀雅、小林理、梨本篤、種村廣巳、辻仲利政、古河洋、木下平：大型3型、4型胃癌に対するneo-adjuvant chemotherapy：JCOG胃がん外科グループの臨床試験．第68回日本臨床外科学

会総会、広島、平成18年11月
(42)梨本篤：高度進行胃癌に対する術前TS-1+CDDP療法のphase II study. 第44回日本癌治療学会総会、横浜、平成18年11月
(43)梨本篤：高度進行胃癌に対する術前化学療法によるCY陰性化の意義. 第68回日本臨床外科学会総会、広島、平成18年11月
(44)藪崎裕、梨本篤：4型胃癌に対する術前化学療法(NAC)としてのTS-1/CDP併用療法（第Ⅱ相試験）の評価と問題点. 第68回日本臨床外科学会総会、広島、平成18年11月
(45)Yoshikawa, T., Sasako, M., Sano, T., Yoshimura, K., Fujiya, T., Fukushima, N., Tanaka, Y., Yamamura, Y., Tanemura, H., Furukawa, H., The Gastric Cancer Surgical Study Group of JCOG, Tokyo, Japan: A phase II study of preoperative chemotherapy with irinotecan and cisplatin followed by gastrectomy with D3 dissection for gastric cancer with extensive lymph node metastasis: Final results of JCOG0001. 2007 Gastrointestinal Cancers Symposium (ASCO-GI) / Multidisciplinary Approaches to the Prevention, Diagnosis, and Therapy of GI Cancers, Orlando, U.S.A., 2007. 1.
(46)笹子三津留：わが国の胃がん術後補助療法に放射線治療は必要か. 第79回日本胃癌学会総会、名古屋、平成19年3月

H．知的財産権の出願・登録状況
該当なし。

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
Sasako, M.	Role of surgery in multidisciplinary treatment for solid cancers	Int J Clin Oncol	9	346-351	2004
Sasako, M.	Clinical trials of surgical treatment of malignant diseases	Int J Clin Oncol	10	165-170	2005
Kodera, Y., Sasako, M., et al.	Identification of risk factors for the development of complications following extended and superextended lymphadenectomies for gastric cancer	British Journal of Surgey	92	1103-1109	2005
Ohtsu, A., Sasako, M.	Overview of adjuvant therapy for resected gastric cancer: Differences in Japan and the United States	Seminars in Oncology	32 (suppl 9)	S101-S104	2005
阪眞、笹子三津留	特集：臨床腫瘍学の現状と展望　V．がん薬物療法の実際　4．消化器癌　2）胃癌　b）進行胃癌のアジュバント療法	Progress in Medicine	25	2073-2078	2005
吉川貴己、小林理、他	腹膜転移を有する初発胃癌の治療戦略	癌と化学療法	32	1398-1403	2005
種村廣巳、他	大型3型/4型/Bulky N2進行胃癌に対するTS-1+CDDPを用いた術前化学療法の経験	癌と化学療法	32	2079-2085	2005
Miyashiro, I., et al.	When is curative gastrectomy justified for gastric cancers with positive peritoneal lavage cytology but negative macroscopic peritoneal implant?	W J Surg	29	1131-1134	2005

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Yoshikawa, T., Sasako, M., et al.	Stage migration caused by D2 dissection with para-aortic lymphadenectomy for gastric cancer from the results of a prospective randomized controlled trial	British Journal of Surgery	93	1526-1529	2006
Makino, T., Tsujinaka, T., et al.	An icteric tyow hepat ocellular carcinoma with no detectable tumor in the liver: Report of a case	Surg Today	36	633-637	2006
土屋康紀、梨本篤、他	TS-1+CDDP療法１コースにてCRとなった進行胃癌の1例	癌と化学療法	33	807-809	2006
山口健太郎、梨本篤、他	Paclitaxel+Low dose FP術前化学療法が奏効し原発巣が消失した進行胃癌の1例	癌と化学療法	33	1163-1166	2006
伊藤誠二、小寺泰弘、望月能成、山村義孝	スキルス胃癌非切除の方針は妥当か？	外科治療	95	73-74	2006

III. 研究成果の刊行物・別刷

「高度進行胃がんの治療に関する研究」

主任研究者　　笹子　三津留

Int J Clin Oncol (2004) 9:346–351
DOI 10.1007/s10147-004-0429-x

FROM THE ASCO-JSCO JOINT SYMPOSIUM

Mitsuru Sasako

Role of surgery in multidisciplinary treatment for solid cancers

Received: June 7, 2004

Abstract In the evolution of solid cancer, there are four steps: noninvasive tumor, local invasive cancer without metastasis, local invasive cancer with lymph node metastasis, and eventually systemic disease. For the first three phases, local treatment, including lymph node dissection, may cure the disease. The choice of local treatment depends on the tumor characteristics, but surgery remains important in many of these cancers. Gastric cancer is one of the typical tumors which remain locally invasive, with or without nodal metastasis, but without systemic metastasis for a rather long period. Metastasis to lymph nodes occurs, frequently even in T1 tumors, but seldom to other sites until the late stage. Thus, the target of local control is the regional lymph nodes. The Intergroup study IT-0116 proved the effect of chemoradiotherapy (CRT) for curable gastric cancer, and thus proved the insufficiency of limited surgery (D0/1). The conventional method of local control for gastric cancer is surgery, including regional lymph node dissection (D2). However, the superiority of D2 has not been proven by randomized controlled trials (RCTs). But all RCTs so far have a crucial problem in the quality of treatment given in the D2 arm. D2 is not a dangerous procedure if done by specialists in large-volume hospitals. D0/1 plus CRT is better than D0/1 alone, but it may be worse than D2 alone. The survival benefit of CRT after D2 is an open question. Establishing standard adjuvant chemotherapy after D2 is a more urgent clinical issue, and there is no reason to abandon D2 gastrectomy for curable gastric cancer in Japan.

Key words Role of surgery · Gastric cancer · Chemoradiotherapy · Local control

M. Sasako (✉)
National Cancer Center Hospital, Tokyo, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan
Tel. +81-3-3542-2511; Fax +81-3-3543-9321
e-mail: msasako@gan2.ncc.go.jp

Presentation made at the ASCO-JSCO Joint Symposium in Sapporo, Japan, on October 22, 2003.

The role of surgery in multidisciplinary treatment for cancer

We believe that solid cancers evolve as follows: lesions without invasion, then locally invasive cancer, which will soon metastasize to regional lymph nodes and then to other organs as systemic disease. The initial lesion of cancer is sometimes noninvasive, and is therefore called dysplasia, in spite of cellular or structural atypia, in the West. There are many arguments about dysplasia and early noninvasive cancer between the West and Japan, including, recently, lung cancer. Due to the development of helical computed tomography (CT), very early cancers, i.e., possible noninvasive cancers, are now being diagnosed in many countries, including the United States and Japan. For a long time, in Japan, we have diagnosed these lesions (which are called dysplasia in the West) in the stomach or in the colon, as cancer. It is well known that many of these dysplastic lesions will invade in a rather short time, at which time they are locally invasive cancers (at this point, a diagnosis of cancer is made in the West). The lesions then start to show metastasis to the regional lymph nodes, and then finally, become systemic disease, with metastases in many distant organs. For noninvasive cancer or dysplasia, just observation or limited resection, such as endoscopic mucosal resection (EMR), is the best way to manage them. For locally invasive cancer, just a wide excision could be sufficient. However, as it is impossible to discriminate exactly between locally invasive lesions with and without regional lymph node metastasis, these lesions are often treated by a wide excision plus lymph node dissection. Recently, sentinel-node biopsy has been used to discriminate those lesions with or without nodal metastasis and to minimize the level of aggressive surgery for these tumors. If the tumor becomes systemic disease, local control plus systemic treatment is mandatory if we aim to cure the disease. As the weapon for local treatment, surgery is most frequently used, but radiation can also be used, depending on the tumor characteristics. Different cancers have different patterns of tumor development or evolution. For example, small-cell

lung cancer has a very short span of limited disease, and most of the lesions of this cancer are already local regional disease plus systemic metastasis when diagnosed. At the opposite extreme is gastric cancer. In Japan, more than half of newly diagnosed lesions are T1, early gastric cancers. Advanced lesions of gastric cancer still have only local invasion and regional lymph node metastasis, which can often be cured by surgery alone. Squamous cell cancer of the esophagus would be situated between these two extremes.

Focus on gastric cancer

Table 1 shows the pattern and incidence of metastasis from gastric cancer, according to the tumor depth.[1] Lymph nodes, liver, and peritoneum are the three frequently involved sites. Other sites in the body, such as lung, bone, brain or skin, may have metastasis from gastric cancer, but only at the end of the disease development, at the terminal stage in these patients.

Table 1. Biological behavior of gastric cancer: incidence of metastasis and 5-year survival

Depth	*n*	LN	Liver	Peritoneum	5-Year survival
pT1					
M	1063	3.3	0.0	0.0	93.3
SM	881	17.4	0.1	0.0	88.9
pT2					
MP	436	46.4	1.1	0.5	81.3
SS	325	63.7	3.4	2.2	65.8
pT3					
SE	1232	78.9	6.3	17.8	35.5
pT4					
SI	724	89.8	15.5	41.6	10.1
Overall	4683	47.8	4.5	11.5	60.3

Patients operated on between 1972 and 1991, at the National Cancer Center Hospital (NCCH), including those with exploratory laparotomy: there were 22 non-resected patients, in whom T was unknown

As shown in Table 1, metastasis occurs almost exclusively to lymph nodes until the primary tumor becomes T3. Liver metastasis occurs in just 6% of the patients with T3 tumor, and in 15.5% of those with T4 tumor. Peritoneal metastasis occurs only after the tumor has reached the serosa, becoming a T3 tumor; the incidence remains at less than 20% in T3 tumors. On the other hand, the incidence of lymph node metastasis is rather high, even in the early stage of disease evolution. Even T1 submucosal invasive tumors have nodal metastasis in nearly 20% of cases. If the tumor becomes T2, over 50% of patients have regional lymph node metastasis. If these nodal metastases were to be left behind after surgery, they would metastasize and eventually become systemic disease.

So, if the patients are treated by D2 or more extensive surgery, which is the standard treatment in Japan, local regional recurrence is not common, as shown in Table 2.[1] This means that D2 dissection can provide rather good local control. By far the commonest site of recurrence is the peritoneum, and systemic and hematogenous metastases are rare (just 7% of all treated patients). Therefore, in patients with gastric cancer, local control can lead to a fairly high success rate for cure. Only 28% of patients developed recurrence; thus, over 70% of patients survived without recurrence. If these tumors are treated by very limited surgery, local regional recurrence could be a big problem.

Dr. Gunderson[2] reported the pattern of failure after limited surgery with curative intent at his institute. Fifty-four percent of recurrences occurred only in the gastric bed, and recurrences reached nearly 90% if all those with local regional failure were included regardless of other type of recurrence. This shows the importance of local control for gastric cancer.

In gastric cancer, the lymph nodes are the most important metastatic site. Table 3 shows the topographical pN stage according to the tumor depth.[1] The deeper the tumor, the more frequently lymph nodes are metastatic and the more frequently distant regional nodes become metastatic. If the tumor becomes T3, three-fourths of patients have nodal metastasis. If the tumor remains as T1 or T2, we do not see distant regional lymph node metastasis very often.

Table 2. Primary site of recurrence after ≥D2

Depth	*n*	Recurrence	LN + RF	Peritoneum	Hematogenous (%)
pT1					
M	1063	2	0	0	2 (0.2)
SM	881	18	6	3	9 (1.0)
pT2					
MP	436	45	10	9	26 (5.9)
SS	325	74	15	28	31 (9.5)
pT3					
SE	1232	625	146	330	149 (12.1)
pT4					
SI	724	562	173	283	106 (14.6)
Overall	4683	1326 (28.3%)	330 (7.0%)	635 (13.6%)	323 (6.9%)

Patients operated on between 1972 and 1991, at the NCCH, including those with exploratory laparotomy

A large proportion of patients have N2 disease; even in T2 tumor, over 20% of patients have N2 disease, and in the T3 tumors, over 40% of patients have N2 disease. This means that main target of local control in gastric cancer is lymph node metastasis. There are several grounds for saying that good local control is essential to cure this cancer. First, Professor Siewert reported that R0 resection is by far the most important prognostic factor after curative operation.[3] Second, the results of the Intergroup study (IT-0116) showed that adding irradiation to adjuvant chemotherapy could improve the results of limited surgery alone, which could not be achieved by adjuvant chemotherapy alone.[4] Good local control by radiation, together with chemotherapy, could improve the results of treatment remarkably. The researchers of the Intergroup study also carefully analyzed the prognostic factors in the patients treated in that trial, and found that surgical under-treatment was an independent prognostic factor. This theory can be applied to some other solid cancers as well.

The preferred method of local control depends on the efficacy of treatment other than surgery. If we see a non-Hodgkin's lymphoma in the stomach, we do not operate on the patients now, and chemotherapy alone can often control both the primary site and the metastasis. Of course, chemoradiotherapy does work, too. Regarding squamous cell carcinoma of the esophagus, chemoradiotherapy can often control the primary tumor and the nodal metastasis, although the local recurrence rate is as high as 20%–30% after chemoradiotherapy. For gastric cancer, even chemoradiotherapy can seldom control an advanced primary tumor, but it may well control nodal disease. Based on the results of the IT-0116 study, if gastric cancer is treated by limited surgery plus chemoradiation (CRT), the primary lesion is controlled by the surgery, and micrometastases in lymph nodes are controlled by the chemoradiation. If gastric cancer is treated by D2 surgery, both the primary and these metastases are controlled by surgery.

Table 3. Lymph node metastasis according to the depth of tumor invasion

Depth	No.	pN+ (%)	pN0	pN1	pN2 (%)	pN3	pN4
T1							
M	619	14 (2)	605	9	5 (0.8)	0	0
SM	499	89 (18)	410	60	29 (5.8)	0	0
T2							
MP	276	126 (46)	150	74	47 (17)	5	0
SS	207	130 (63)	77	65	57 (28)	3	5
T3							
SE	646	484 (75)	162	171	266 (41)	28	19
T4							
SI	152	121 (80)	31	31	65 (43)	12	13
Total	2399	964 (40)	1435	410	469 (20)	48	37

In gastric cancer, the main target of local control is lymph node metastasis

Table 4 shows a comparison of two studies, the IT-0116 study, and the Japan Clinical Oncology Group (JCOG) 9501 study.[5] The JCOG 9501 study is a trial organized by the Gastric Surgery Division of JCOG to evaluate the role of paraaortic lymph node dissection, which is quite extensive surgery. There are remarkable differences between these two trials: in the IT-0116, surgery was rather limited (D0; very limited resection) in 54% of patients, and D1 surgery was done in 36%, while so-called Japanese-type surgery was done in only 10%. But in the JCOG 9501 study, half of the patients underwent D2 dissection, the standard surgery in Japan. The other half underwent much more extensive surgery (D3 dissection). Regarding adjuvant treatment, those allocated to the test arm in the IT-0116 study underwent 45-Gray radiotherapy together with chemotherapy (5-fluorouracil [5-FU] and leucovorin). In the JCOG 9501 trial, none of the patients underwent adjuvant treatment until they developed recurrence. There was no difference in tumor locations between these two trials, although researchers in the United States always say that they have more proximal tumors than antral tumors. Unlike the pattern of tumor location in the general population, a much larger proportion of patients in this American trial had antral tumors, while more tumors of the body were seen in the Japanese trial. Tumor depth is shown in Table 4: 14 T1, 74 T2, 175 T3, and 18 T4 in the IT-0116 study; and 23 T1, 257

Table 4. Comparison of the results of IT-0116 and JCOG 9501

	IT-0116	JCOG 9501
Surgery	D0/D1/D2-54%:36%:10%	D2/D3-50%:50%
Adjuvant	Radiation 45 Gy Chemotherapy 5-FU + LV	None
No of patients	281 (Test arm)	523
Tumor location	Antrum, 53%; corpus, 24%; cardia, 21%; multiple, 2%	Lower third, 41%; middle third 39%; upper third, 19%
pT stage (1:2:3:4)	14:74:175:18	23:257:230:13
Treatment-related deaths	3 (1.1%) + Postop.	4 (0.8%)
Survival	3-Year: 50% 5-Year: 42%	5-Year: 71.4 (66.5%–76.3%)

Table 5. Estimated 5-year survival of the IT-0116 patients if they would have undergone D2-3 surgery

IT-0116 patients	NCCH[a] 5-Year survival	Calculated survival proportion	CIH[b] 5-Year survival	Calculated survival proportion
T1, 14	92.2	12.9	96.6	13.5
T2, 74	77.5	57.4	80.6	59.6
T3, 175	47.1	82.4	40.2	70.4
T4, 18	29.9	5.4	17.4	3.1
42%		56.3%		52.2%

[a] Results of National Cancer Center Hospital[6]
[b] Results of Cancer Institute Hospital[7]

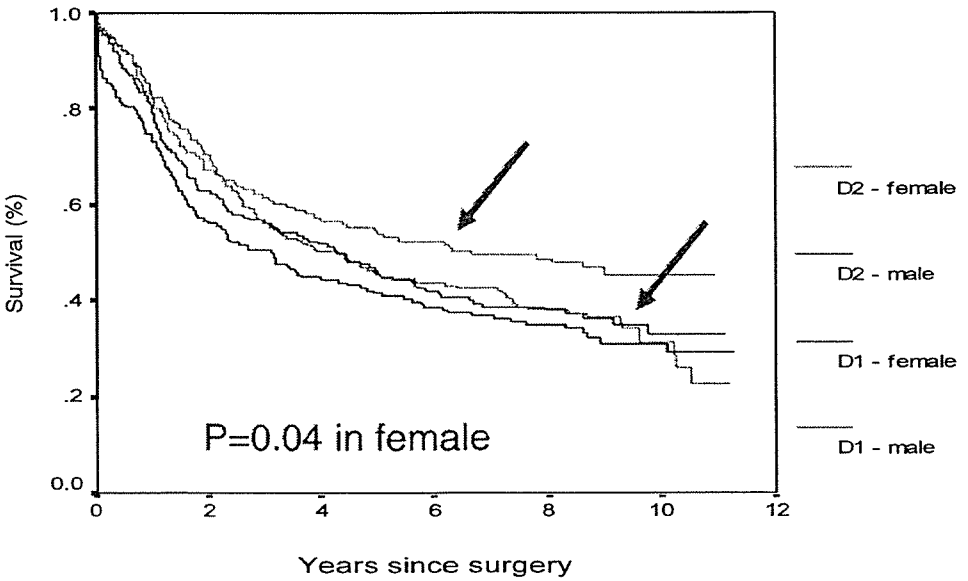

Fig. 1. D1 vs D2 for males and females. High postoperative mortality did not confound comparison in female patients

T2, 230 T3, and 13 T4 in the JCOG 9501. As to the treatment-related death rate (TRD), 1.1% was reported in IT-0116, and 0.8% in JCOG 9501. However, if the total population that could be candidates in this trial is considered, the TRD should be higher in IT-0116, because some postoperative deaths that occurred before enrolment in this trial were not counted. The survival results of IT-0116 are 50% at 3 years and 42% at 5 years, while the overall survival rate at 5 years is 71.4% in the JCOG 9501 study, although the observation time is not sufficient. As there is a non-inegligible difference of T-stage distribution between the two trials, this survival comparison is not fair. It is possible, however, to calculate the survival proportion by applying the survival rates of Japanese institutes by pT stage. The hypothetically estimated survival rates are then over 52%, which is about 10% better than the actual survival rate of the patients in the IT-0116 study (Table 5).

The results of the IT-0116 trial are interpreted as follows: (1) D0/1 surgery is proven to be inadequate treatment in terms of local control, (2) the results achieved are worse than the standard level of those treated by D2 surgery, (3) surgical under-treatment clearly undermined survival, (4) whether D0/1 + CRT can be as good as D2 alone should be tested by a RCT, (5) whether CRT after D2 can improve the results of this type of surgery alone is another question. At the same time, another question arose. Why was D2 not better than D1 in the western RCTs?

In fact, the Dutch and Medical Research Council (MRC) trials did not prove the effect of D2 dissection.[8,9] However, the quality of D2 dissection in these trials was questionable, with quite high postoperative mortality with extremely small hospital volume. The TRD rate of D2 was as high as 10% and the quality of postoperative care to avoid operative deaths was very poor, due to the small hospital volume. Not only in these trials but also in several other RCTs in surgery, a high TRD rate offsets the long-term effect of treatment. In the two trials on squamous cell carcinoma of the esophagus reported at the 39th annual meeting of the American Society of Clinical Oncology (ASCO), i.e., the German[10] and French[11] trials, a benefit of surgery after CRT was not seen in long-term survival, with a remarkable difference of the TRD rates between CRT alone versus CRT plus surgery. Based on the experience in these RCTs, we may say that proper D2 dissection is technically demanding surgery, requiring experience and specific postoperative care, and it should be carried out at specialist centers in the west.

In the Dutch trial, D2 started with a handicap of about 6%, within 3 months, but caught up with the curve of D1,

Table 6. Morbidity and mortality after D2 dissection for gastric cancer

Trial	Type	Number of patients	Number of D2 dissections per hospital/year	Mortality	Morbidity	Reference
Hong Kong[12]	RCT	30	7.5	3%	57%	Ann Surg
MRC[7]	RCT	200	1.5	13%	46%	Lancet
Dutch[6]	RCT	331	1.0	10%	43%	Lancet
Italian[13]	Phase II	191	8.0	3%	21%	JCO
Sue-Ling[14]	Retrospective	142	14.2	5%	17%	BMJ
Pacelli[15]	Retrospective	157	15.7	4%	22%	Br J Surg

Table 7. Mortality after major postoperative complications

Complications	Dutch trial (n = 711)		NCCH (1980s) (n = 1197)		P Value
Leakage	19/46	41.3%	12/84	14.3%	0.0005
Distal	9/22	40.1%	2/23	8.7%	0.012
Total	10/24	41.7%	10/60	16.7%	0.0047
Abscess/pancreatic fistula	19/91	20.9%	2/75	2.7%	0.0004

Experience is needed to manage major adverse effects to avoid treatment-related deaths TRD, which occur slightly more often in surgery than in chemotherapy. Hospital volume is a concern

although the difference never reached statistical significance. The hospital mortality for D2 and D1 showed a large difference, at nearly 10% for D2, and 4% for D1. But this difference was seen only in male patients, in whom hospital mortality was 4.2% for D1 versus 14% for D2. There was no difference in mortality between D1 and D2 in female patients. Accordingly, the hazard ratio between D1 and D2 by time for each sex is completely different. In female patients, the hazard ratio is almost constant. The survival curves by procedure by sex are shown in Fig. 1. As we would expect, the survival curves of the female patients do not cross, as typical model curves of survival showing a constant hazard, and the P value is 0.04. We can confirm that high immediate mortality easily offsets the long-term effect of any cancer treatment.

Table 6 shows the relation between the hospital volume and the TRD rates in many trials or consecutive series of D2 dissection for gastric cancer. The Dutch and MRC trials show extremely low numbers of patients treated per year, per hospital, and show extremely high hospital mortality, compared with other reports.

Table 7 shows the mortality after major complications, comparing the results of the Dutch trial and those of the National Cancer Center Hospital (NCCH) in the 1980s.[1] Even in a high-volume hospital, major complications, such as anastomotic leakage or intraabdominal abscess, were not rare. However, in the Dutch trial, over 40% of patients died when they developed anastomotic leak, while only 14% of such patients died in the NCCH. As to mortality after abdominal abscess, a difference of nearly ten times was observed. Experience is needed to manage major adverse effects to avoid TRD, which occurs slightly more often in surgery than in chemotherapy or CRT. In this regard, hospital volume is a concern.

The Japanese perspective of the role of D2 dissection in multidisciplinary treatment for advanced gastric carcinoma can be summarized as follows. The superiority of D2 has not been proven by RCTs. But all RCTs so far have a crucial problem in regard to the quality of treatment given in the D2 arm. D2 is not a dangerous procedure if it is done by specialists in large-volume hospitals. D0/1 plus CRT is better than D0/1 alone, but it may be worse than D2 alone. The survival benefit of CRT after D2 is an open question. Establishing standard adjuvant chemotherapy after D2 is a more urgent clinical issue. There is no reason to abandon D2 gastrectomy for curable gastric cancer in Japan.

References

1. Sasako M (2003) Principles of surgical treatment for curable gastric cancer. J Clin Oncol 23s(December 1 supplement):274–275
2. Gunderson LL, Sosin H (1982) Adenocarcinoma of the stomach: Area of failure in a re-operation series (second or symptomatic look) clinicopathologic correlation and implication for adjuvant therapy. Int J Radiat Oncol Biol Phys 8:1–11
3. Siewert JR, Boettcher K, Roder JD, et al. (1993) Prognostic relevance of systematic lymph node dissection in gastric carcinoma. Br J Surg 80:1015–1018
4. Macdonald JS, Smalley SR, Benedetti J, et al. (2001) Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal jucntion. N Engl J Med 345:725–730
5. Sano T, Sasako M, Yamamoto S, et al. (2004) 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 22:2767–2773
6. Sasako M, Sano T, Katai H, et al. (1997) Radical surgery in gastric cancer. In: Sugimura T, Sasako M (eds) Gastric Cancer. Oxford University Press, pp 223–248
7. Nakajima T, Yamaguchi T (1999) Appendix: Tubular analysis of Cancer Institute Hospital Data Base. In: Multimodality therapy for gastric cancer, pp 256
8. Bonenkamp JJ, Hermans J, Sasako M, et al. (1999) Extended lymph-node dissection for gastric cancer. N Engl J Med 340:908–914

9. Cuschieri A, Weeden S, Fielding J, et al. (1999) Patient survival after D1 and D2 resection for gastric cancer: long-term results of the MRC randomized surgical trial. Br J Cancer 79:1522–1530
10. Stahl M, Wilke M, Walz MK, et al. (2003) Randomized phase III trial in locally advanced squamous cell carcinoma (SCC) of the esophagus: chemoradiation with and without surgery. J Clin Oncol 22 (Proceedings of ASCO meeting 2003): 250
11. Bonnetain F, Bedenne L, Michel P, et al. (2003) Definitive results of a comparative longitudinal qualiy of life study using the Spitzer index in the randomized multicentric phase III trial FFCD 9102 (surgery vs radiochemotherapy in patients with locally advanced esophageal cancer). J Clin Oncol 22 (Proceedings of ASCO meeting 2003): 250
12. Robertson CS, Chung SCS, Woods SDS, et al. (1994) A prospective randomized trial comparing R1 subtotal gastrectmy with R3 total gastrectomy for antral cancer. Ann Surg 220:175–182
13. Degiuli M, Sasako M, Ponti A, et al. (1998) Morbidity and mortality after D2 gastrectomy for gastric cancer: results of the Italian Gastric Cancer Study Group prospective multicenter surgical study. J Clin Oncol 16:1490–1493
14. Sue-Ling H, Johnston D, Martin IG, et al. (1993) Gastric cancer: a curable disease in Britain. BMJ 307:591–596
15. Pacelli F, Doglietto GB, Bellantone R, et al. (1993) Extensive versus limited lymph node dissection for gastric cancer: a comparative study of 320 patients. Br J Surg 80:1153–1156

Int J Clin Oncol (2005) 10:165–170
DOI 10.1007/s10147-005-0486-9

FROM THE ASCO-JSCO JOINT SYMPOSIUM

Mitsuru Sasako

Clinical trials of surgical treatment of malignant diseases

Received: March 14, 2005

Abstract The Dutch Gastric Cancer Study Group Trial was the first clinical phase III trial to be carried out in the field of cancer surgery. In spite of the excellent quality of the trial, it was heavily criticized for the poor quality of the treatment itself. Actually, the hospital mortality after the new surgical treatment (D2 lymph node dissection for gastric cancer) was unacceptably high. In surgical trials, special attention should be paid to quality issues specific to surgery. The first and the most important issue is the quality of treatment given. Reproducibility, homogeneity, and verifiability are the greatest problems in surgical trials. There are also some patient factors. If the patient is old, or fragile, or obese, the results of the surgical treatment can easily be affected by these factors. The surgeon can also be a prognostic factor, especially in complicated procedures or those requiring experience and training. Experience, including postoperative care, and dexterity affect the results. If surgeons do not know how to manage complications, mortality becomes very high. Because blinding is impossible in surgical trials, the treatment may easily be affected by personal preference or prejudice. To minimize the influence of these hampering factors, the procedures should be defined in as detailed a way as possible. If pretrial training or a feasibility study (phase II) is needed, it should be carried out properly for the patients' sake. An excellent design and excellent statistical analysis cannot lead to meaningful results if the quality of treatment is poor. Nonsense in, nonsense out.

Key words Clinical trials of surgical treatment · Quality assurance of treatment · Gastric cancer · Lymph node dissection

M. Sasako (✉)
Gastric Surgery Division, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045 Japan
Tel. +81-3-3542-2511; Fax +81-3-3543-9321
e-mail: msasako@gan2.ncc.go.jp

The ASCO-JSCO Joint Symposium was held in Kyoto, Japan, on October 29, 2004.

Quality control in the Dutch Gastric Cancer trial

The Dutch Gastric Cancer Study Group Trial was the first well-designed, large-sized, randomized clinical trial (RCT) comparing the surgical procedures in cancer treatment (Fig. 1). In this trial, randomization was carried out before surgery, because the quality controller of the surgery, who usually came from outside the hospital, should be in the operation theater at every D2 dissection. So the group randomized patients before operation, based on the clinical staging, but they expected that some of these patients, about 30% of them, might have peritoneal seeding, and the operation would turn out to be non-curative in such patients. The estimated survival rates of the D1 and D2 surgery arms were 20% and 32%, respectively, but with these non-curative cases, the rates were 14% and 21% for D1 and D2, respectively in all randomised patients. The projected sample size was 531 in each arm.[1]

Not following the principles of phase III clinical trials, even the first patient in this RCT was randomized. When this trial started, only one Dutch surgeon knew what a D2 dissection was and had some experience of carrying out D2 gastrectomy. Although none of the other surgeons involved had ever had experience of D2 gastrectomy, they did not plan any feasibility study before starting a phase III study. Instead, they invited the author (M.S.) to carry out D2 dissections and to teach them how to do it. Therefore, they could randomize the first patient in whom he carried out a D2 dissection for the Dutch surgeons. Inviting a surgeon who knows well the new treatment seemed to be a good option and was much better than letting surgeons do a new treatment after just looking at a videotape of the procedure. However, the tutor could not stay there to participate in all D2 surgery during the entire period of the trial. Therefore, in just 4 months he had to teach them how to carry out the procedure. Surgery of this type is not easy to learn without doing it oneself. It was obvious that he could not teach all the participating surgeons of about 80 hospitals. This length of time was not sufficient to teach even the 12 quality controllers of the D2 surgery.[2] A feasibility study or intensive

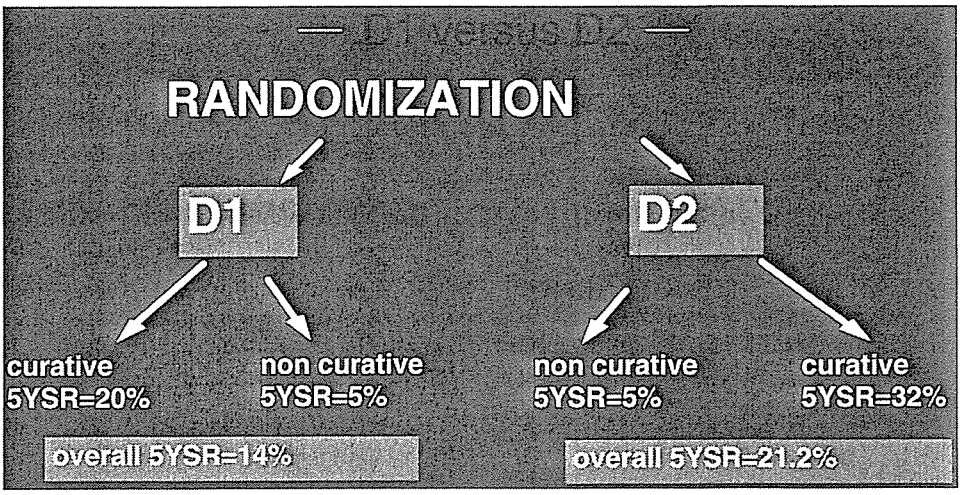

Fig. 1. Dutch trial on lymphadenectomy for gastric cancer.[1] Alpha = 0.05, power = 0.90, 531 patients in each arm requested; *5YSR*, 5-year survival rate

Table 1. Morbidity and mortality after D2 dissection for gastric cancer

Trial	Type	Number of patients	Number of patients per hospital/year	Mortality	Morbidity
Hong Kong[4]	RCT	30	7.5	3%	57%
MRC[5]	RCT	200	1.5	13%	46%
Dutch[1]	RCT	331	1.0	10%	43%
Italian[6]	P-II	191	8.0	3%	21%
Sue-Ling et al.[7]	Retro	142	14.2	5%	17%
Pacelli et al.[8]	Retro	157	15.7	4%	22%

pretrial training should have been carried out. From the scientific and ethical points of view, this kind of setting for a phase III trial of a new surgical technique is not allowed anymore.

The author's major task in this surgical trial was to teach the surgeons how to do a D2 gastrectomy. He himself did 27 operations and instructed the Dutch surgeons as the first assistant in operations for six patients. He also gave many lectures, using videotapes of this operation; the organizers distributed a videotape of the D2 operation on a Dutch patient, which was filmed during this period of the trial, and also distributed a booklet with detailed color photographs showing the anatomy and the technique. This is all that we did for teaching. However, this was not good enough for many of the quality controllers to master the technique sufficiently. Actually, in spite of all the efforts, the morbidity and mortality of this trial was shockingly high for the organizers. Postoperative hospital deaths reached nearly 10% in the D2 arm, much higher than in the D1 arm. This was something unexpected by them before they started this trial. Retrospectively, they should have stopped this trial much earlier and gone back to the feasibility study for the sake of the patients.

Causes of mortality and hospital volume

Theoretically, factors which may influence the morbidity and mortality after this type of surgery are patient factors, tumor factors, operative procedures, and hospital and surgeon factors. Obviously, older patients and obese patients may have more morbidities. But, unexpectedly, sex actually influenced the mortality in this trial very much. And, of course, so did tumor location and histology, the procedures, lymph node dissection, the type of gastrectomy (total or distal), and combined organ resection. Postoperative hospital mortality after D2 in women was as low as that for D1 dissection, but that in male patients reached 14%, or three times higher than that for D1.[3]

Table 1 shows the postoperative hospital mortalities after D2 dissection in various reports.[1,4–8] In the Dutch trial and the MRC (Medical Research Council) trial (British trial), each hospital had very small numbers of cases annually (hospital volume). These two trials had smaller hospital volumes and much higher hospital mortality than in other reports. With such a limited case load, learning how to manage these complications was almost impossible. Actually, the mortality after major surgical complications in the Dutch trial was significantly higher than that experienced at the National Cancer Center Hospital Tokyo (NCCH). The mortality after anastomotic leak and after intraabdominal abscess or pancreatic juice leakage was 41% and 20%, respectively, in the Dutch trial. But, in the same period, the 1980s, the corresponding figures at the NCCH showed much lower 14% after anastomotic leak, and only 3% after intraabdominal abscess.[3] This suggests that experience is needed to manage these major adverse effects to avoid treatment-related deaths. Even in patients with medical treatment, we should know how to manage febrile neu-