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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１９年度　総括研究報告書

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研究要旨
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無作為化第Ⅲ相試験を2005年10月より開始した。2006年7月初めには16例を登録したが、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り、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た。そのため、本試験の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に変更し、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デザインにプロトコールを改訂して試験を再開した。2007年3月より登録が再開され、2008年2月末までに34例が登録された。登録予定は年間60例であり、予定登録数に追いつくべく施設を増やして行く予定である。

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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】多施設共同の第Ⅲ相ランダム化比較試験（優越性試験）：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、治癒切除可能な8cm以上の大型3型・4型胃がん症例。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】JCOGデータセンターで中央登録し、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＋術後 TS-1 による補助化学療法、試験治療は 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である。
【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】予定登録数はプロトコール改訂後期間で両群併せて300例とし、期待イベント数は276とする。すでに登録した16例と併せて全予定登録数は316である。
【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）
本研究は手術単独を対照群とした第Ⅲ相試験として開始したが、ACTS-GC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、プロトコールの改訂に取り組んだ。改訂プロトコールは2007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ている。

C．研究結果
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無作為化第Ⅲ相試験を2005年10月より開始した。2006年7月初めには16例を登録したが、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り、ステージⅡ以上の胃がんでは、TS-1の術後化学療法が標準治療となると考えられた。ACTS-GC試験の結果によるプロトコール改訂のため登録を一旦停止し、数ヶ月かけて改訂したプロトコールは2007年2月にJCOG効果・安全性評価委員会で承認された。施設によっては、改訂後に倫理審査委員会の再審査が必要で、当該各参加施設は施設内の倫理審査委員会にて改訂プロトコールを審査し、審査の終了した施設より逐次登録を開始した。月1-4例を登録し、1年間で34例を登録したが、予定の年間60例ペースにはかなり遅れているので、2008年3月1日に参加施設を2施設増加することがJCOG運営委員会で承認された。また、6月にもさらに2施設増加させる方向で検討中である。現時点までに明かなTRDは出ていない。

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。
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。また、2008年3月で2施設参加施設を増加する許可が下り、6月にもさらに2施設の増加を希望している。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。これらの対応により、年間60例の登録は可能と考えている。

E．結論
TS-1+CDDP療法による術前化学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っている。現在第Ⅲ相試験を施行中で、症例数を増やす努力をさらに継続していく。

F．健康危険情報

現在まで登録された症例では該当なし。

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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
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Sakuramoto, S., Sasako, M., et al.	Adjuvant Chemotherapy for Gastric Cancer with S-1, an Oral Fluoropyrimidine	The New England Journal of Medicine	357	1810-1820	2007
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Ⅲ．研究成果の刊行物・別刷

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Surgical Treatment of Advanced Gastric Cancer: Japanese Perspective

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Key Words
Esophagogastric junction · Gastric cancer, advanced · Surgical treatment

Abstract
The results of clinical trials regarding surgery of curable advanced gastric cancer and esophagogastric junction (EGJ) tumors are reviewed and summarized. Four clinical trials have evaluated D2 dissection for curable gastric cancer in the West. Two large trials in the UK and the Netherlands failed to prove the efficacy of D2 dissection. However, these trials had critical weak points. As they were carried out in a number of hospitals where there was no experience with this surgery, the quality of surgery and postoperative care were very poor making the hospital mortality unacceptably high. After these trials, an Italian group started a phase II study in 8 hospitals with a relatively high volume to confirm the safety of this procedure for Caucasians. They achieved 3% mortality, which was much smaller than that of even D1 in the former trials. These results first highlighted the importance of learning and hospital volume in D2 dissection. Survival results of the Dutch trial showed some difference between D1 and D2, but the difference was not statistically significant. This was attributed to the high hospital mortality and poor quality of surgery, especially low compliance of D2 and the high rate of extension of D1, making this comparison similar to that between D1.3 and D1.7. The results of the phase III study by the Italian group are awaited. Recently a Taiwanese trial proved the benefit of D2 dissection over D1 in a phase III trial. This was a single institutional trial with a sample size of 221 patients. The 5-year survival rate of D2 and D1 was 59.5 and 53.6%, respectively ($p = 0.04$). The Dutch trials for EGJ tumors showed a large difference in overall survival between the transthoracic and transhiatal approach for Siewert type 1 and 2 tumors, but this was not statistically significant, most likely due to the small sample size. In the subgroup analysis, they demonstrated that there was no survival difference in Siewert type 2 but a large difference in Siewert type 1. A Japanese study showed that there is no benefit to the thoraco-abdominal approach over the transhiatal approach for EGJ tumors whose invasion in the esophagus is 3 cm or less. These two trials clearly demonstrated that mediastinal dissection through a right thoracotomy is recommendable for Siewert type 1, while the transhiatal approach should be considered as standard for Siewert type 2.

Background

In the guidelines of the Japan Gastric Cancer Association, standard surgery for curable advanced gastric cancer is defined as a more than 2/3 gastrectomy with D2 dissection [1]. With the results of several important

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Table 1. Morbidity and mortality after D2 dissection and hospital volume

Trial	Type	n	Number of patients per hospital per year	Mortality %	Morbidity %	Reference
Hong Kong	RCT	30	7.5	3	57	Robertson et al. [7]
MRC	RCT	200	1.5	13	46	Cuschieri et al. [8]
Dutch	RCT	331	1.0	10	43	Bonenkamp et al. [2]
Taiwanese	RCT	211	18.5	0	17	Wu et al. [16]
IGCSG	Phase II	191	8.0	3	21	Degiuli et al. [4]
IGCSG	RCT	82	4.3	0	16	Degiuli et al. [6]
Italian study	Retro	451	21.5	2	17	Roviello et al. [9]

RCT = Randomized controlled trial; MRC = Medical Research Council; IGCSG = Italian Gastric Cancer Study Group.

clinical trials, not only in surgery but also multidisciplinary treatment, this policy of the Japanese guidelines might be challenged. In this article, the Japanese perspective of curative surgery for advanced gastric cancer is explained.

Results of European Trials

There have been four European clinical trials on D2 dissection for curable gastric cancer [2–5]. Three of them were phase III trials and the remainder was the only phase II trial in the world. The phase III trials were carried out by the Medical Research Council (MRC) [3], the Dutch Gastric Cancer Group (DGCG) [2] and the Italian Gastric Cancer Study Group (IGCSG) [5]. The first two trials have already shown negative results, while the long-term results of the last one are awaited. After the first two large phase III trials showed quite high hospital mortality after D2 dissection on Caucasians, the IGCSG started with a phase II study to confirm the safety of the D2 dissection in their population [4].

Morbidity and Mortality of D2 Dissection in These Trials

The Dutch and the MRC studies showed extremely high hospital mortality after D2 dissection, 10 and 13%, respectively. Such a high mortality is no longer accepted for any cancer surgery today. These results were heavily criticized and attributed to a very low hospital volume [6]. Table 1 shows the clear negative correlation between hospital volume and hospital mortality after D2 dissection in the literature. This high mortality was also attributed to splenectomy and pancreatectomy. Especially in the MRC trial, many surgeons thought that D2 distal gastrectomy included splenectomy, and splenectomy was carried out in many distal gastrectomy cases [10]. This was based on the misunderstanding of the definition of D2 gastrectomy by the Japanese Research Society for Gastric Cancer [11]. In Japan, splenectomy was included in D2 dissection only when a total gastrectomy was carried out. Together with thorough lymph node dissection of the lesser curvature, splenectomy causes serious ischemia of the remnant stomach, necrosis of the remnant stomach or anastomotic leakage. This was also the case in the DGCG trial [12]. In the multivariate analysis of hospital mortality, splenectomy was one of the factors most responsible for mortality. The lack of experience in treating major surgical complications after D2 dissection, namely, anastomotic leakage, pancreatic fistula (juice leak) or intra-abdominal abscess, led to a much higher mortality than a Japanese specialist center where a few hundred patients were treated yearly (table 2) [6]. With less than a few cases yearly, surgeons can never learn how to treat these major complications to avoid treatment-related death. This high mortality after D2 dissection in the Dutch trial might also be attributed to the greater fragility of the Dutch compared with the Japanese. However, the results of another Dutch trial comparing a transthoracic esophagogastrectomy via right thoracotomy with a transhiatal approach for esophagogastric junction (EGJ) tumors showed a much lower mortality in the both treatment arms, 4% for the former and 2% for the latter [13]. This trial was carried out exclusively in two major cancer hospitals which have a reasonably high hospital volume. This suggests that high mortality in the D1/D2 trial was not attributed to the fragility of the Dutch patients but to the very low hospital volume.

Table 2. Mortality after postoperative major surgical complications

Complication	Dutch trial (n = 711)			NCCH trial (1982–1987; n = 1,197)			p
	deceased patients	affected patients	%	deceased patients	affected patients	%	
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 or pancreatic fistula	19	91	20.9	2	75	2.7	0.0004

NCCH = National Cancer Center Hospital.

After these two trials with dismal short-term results, the IGCSG started a phase II trial to confirm the safety. Actually a 3% mortality was found in 8 hospitals with a total of 191 patients [4]. They avoided the routine use of distal pancreatectomy in cases of total gastrectomy; instead they adopted pancreas-preserving total gastrectomy, the so-called Maruyama technique [5]. Thus they avoided splenectomy in distal gastrectomy and distal pancreatectomy in total gastrectomy. The morbidity and mortality shown by the phase II study was confirmed by the results of the interim analysis of the IGCSG phase III trial. Hospital mortality was 1.3% after D1 but 0% after D2 gastrectomy in this study [6].

Survival Results after D2 Dissection

In the MRC trial, the survival curve of D2 was never better than that of D1 until the end of the trial. In the Dutch trial, the survival curve of D2 caught up with that of D1 after 4 years and remained superior, but the difference between D1 and D2 survival never reached statistical significance. Practically, in the MRC trial, there was no quality control of surgery and the quality seemed poor due to the mortality. In the Dutch trial, there were several efforts to control the quality of performance including direct tuition of the D2 dissection in the operation theater and quality evaluation by the number of dissected nodes. According to their results, there were many cases in the D1 group where more extended dissection than D1 was actually carried out and many patients in the D2 group underwent less than D2 dissection [14]. Eventually they compared D1.3 versus D1.7, for example, minimizing the difference between the arms. Low-quality surgery together with a much higher mortality immediately after surgery could explain why D2 dissection was not found to be beneficial. In fact, the Italian group showed much better survival results in their phase II trial than those of the Dutch trial [15]. The 5-year survival rates for stages IA, IB, II, IIIA and IIIB were 93, 88, 60, 40 and 20%, respectively, while those in the Dutch trial were 81, 61, 42, 28 and 13%, respectively. Survival results of the phase III study by the IGCSG are awaited.

Results of Taiwanese Trial

Recently a Taiwanese hospital published the results of a phase III study comparing D1 versus D2/3 surgery for curable gastric cancer in a single institution [16]. Their D3 includes lymph node stations in the hepatoduodenal ligament, on the superior mesenteric vein, behind the common hepatic artery and on the posterior pancreatic surface in addition to D2 dissection, according to the 1st English Edition of the Japanese Classification of Gastric Carcinoma [17]. They showed statistically significant improvement in survival by D2/3 surgery over D1. The 5-year overall survival of D2/3 and D1 was 59.5 and 53.6%, respectively ($p = 0.04$; fig. 1). This study included only three surgeons at a single institution, therefore the quality of surgery in this study seemed to be more identical than in multicenter trials. This is the first randomized controlled study which showed significantly better overall survival of D2/3 surgery than D1 in the world. There are several remarkable differences between this study and the Dutch study. Due to the much higher hospital volume and good quality control at a single institution, the hospital mortality after D2/3 was 0% in this study, while it was as high as 10% in the Dutch trial. More patients in the Taiwanese study had antral tumors and underwent distal subtotal gastrectomy than the Dutch trial. The proportion of those who underwent distal subtotal gastrectomy in this study and the Dutch study was 76 and 66%, respectively. Due to the rather small sample size and

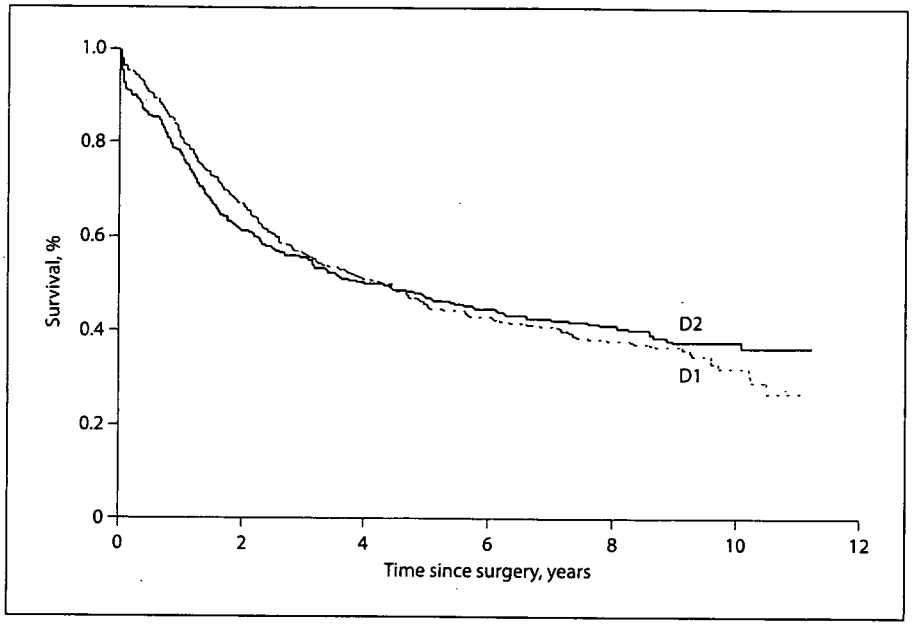

Fig. 1. Overall survival curves of the entire patient population by treatment groups in the Dutch trial.

modest survival benefit, this study cannot be considered as solid evidence for the superiority of D2 over D1 dissection.

Results of Adjuvant Chemoradiotherapy

A phase III study comparing surgery alone with postoperative adjuvant chemoradiotherapy (CRT), the INT0116/SWOG9008, showed a large survival benefit of CRT for curable gastric cancer; the median survival time of surgery alone was 27 months, compared with 36 months for CRT [18]. The hazard ratio for death was 1.35 (95% CI 1.09–1.66; p = 0.005). In this trial, the tested arm included curative surgery and radiation therapy of 45 Gy with combination chemotherapy using fluorouracil and leucovorin (5 courses of 5-day continuous infusion, including 2 courses of concomitant administration). However, detailed analysis of the type of surgery revealed that 54 and 36% of the patients underwent D0 and D1 surgery, respectively, while only 10% underwent D2 dissection. Although there was no statistically significant interaction between the subgroups divided by the degree of lymph node dissection and the effect of treatment, a benefit from treatment was observed only in the D0 or D1 group in the subset analysis [19]. In the retrospective detailed analysis, the researchers of this study found that surgical undertreatment clearly undermined the survival of patients [20]. Thus this study for the first time proved the efficacy of local control by radiation for gastric cancer and proved that limited surgery alone cannot be sufficient treatment for this cancer.

The patient population enrolled in the test arm of this study was by chance quite similar to the population enrolled in a Japanese clinical trial comparing surgery alone with surgery followed by adjuvant CTX (JCOG9206-2) [21]. Table 3 shows the tumor and patient characteristics of the 2 groups. Most of the prognostic factors, i.e., histological type, tumor location, age, tumor size, and, most important, tumor depth, were reasonably comparable between the groups. Although these 2 groups were the patients of two different trials with two different treatment methods, they are identical and therefore the treatment results are more or less comparable. The 5-year overall survival was 42 and 61% in the INT0116 and JCOG9206-2, respectively. This suggests strongly that D2 surgery alone might produce better survival than limited surgery followed by CRT and that the effect of adjuvant CTX might not be expected after D2 as suggested by the subgroup analysis.

Surgical Treatment for Esophagogastric Junction Tumors

Hulscher et al. [13] reported the results of a phase III trial for Siewert type 1 and 2 tumors, comparing two surgical approaches, a transthoracic esophagogastrectomy

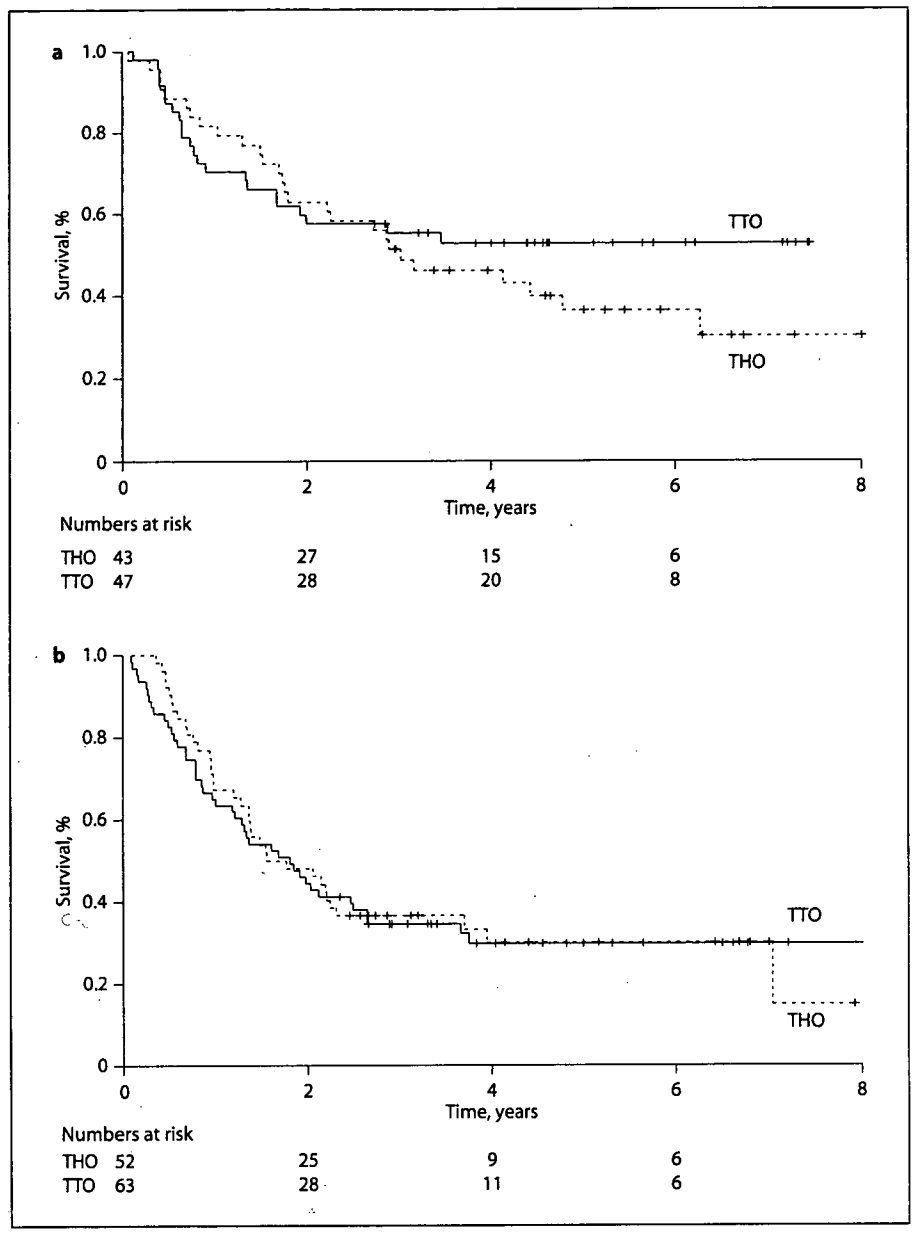

Fig. 2. Overall survival curves in patients with Siewert type 1 (**a**) and Siewert type 2 (**b**) tumors, by treatment groups. THO = Transthoracic esophagectomy; TTO = transhiatal esophagectomy.

via right thoracotomy with transhiatal one. The overall survival in the entire study population did not show statistically significant differences between the 2 groups. However, the actual difference in the survival curves was impressive and the overall 5-year survival rate was 29% for the transhiatal approach and 39% for the transthoracic one (p = 0.38; fig. 1). In the subgroup analysis according to the Siewert classification, the difference in overall 5-year survival was as large as 17% (95% CI –3 to 37%) for Siewert type 1 (n = 90), while it was only 1% for Siewert type 2 (n = 115; fig. 2) [22]. Due to the small sample size, this study was not able to show any statistically significant difference, but the results strongly suggest that thorough mediastinal dissection via right thoracotomy is needed for Siewert type 1 but not for type 2. With higher morbidity after transthoracic dissection, the transhiatal approach might be better treatment for Siewert type 2.

Sasako et al. [23] reported the results of a phase III trial for Siewert type 2 and 3 tumors, comparing a left thoraco-abdominal approach versus a transhiatal one. All these tumors were diagnosed to have esophageal in-

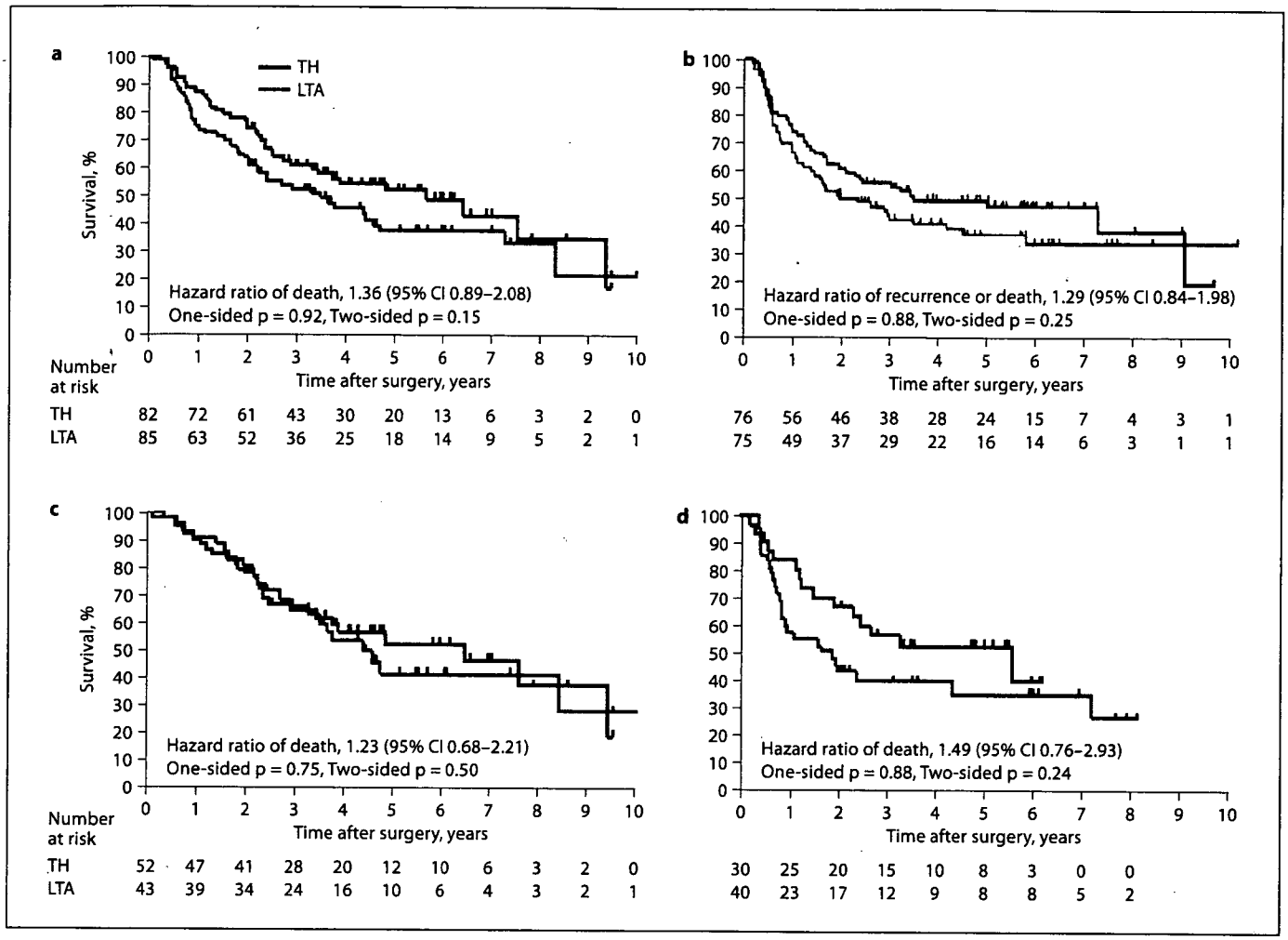

Fig. 3. Overall survival (**a**) and disease-free survival (**b**) of the entire patient population and overall survival in patients with Siewert type 2 (**c**) and type 3 (**d**) tumors by treatment groups. TH = Transhiatal; LTA = left thoraco-abdominal. Reprinted with permission from *The Lancet Oncology* [23].

Table 3. Comparison between the INT0116 study and JCOG9206-2 study

	INT0116/SWOG9008	JCOG9206-2
Surgery (D0/1/2), %	54/36/10	4/67/33
Adjuvant	Rad (45 Gy)+CX (5FU+LV)	CDDP+5FU+UFT (50%), none (50%)
Number of patients	281 (tested arm)	268 (control = 133, tested = 135)
Tumor location	A (53%), Corp (24%), cardia (21%), multifocal (2%)	L (31%), M (32%), U (28%), wide (9%)
pT (T1/T2/T3/T4)	14/74/175/18	5/87/165/11
Proportion of T3/4, %	69	66
Node positive, %	85	72
TRD	3 (1.1%)	4 (1.5%)
Overall survival (5 years), %	42	control 61, tested 62

Rad = Radiation; CX = chemotherapy; LV = leucovorin; 5FU = 5-fluorouracil; CDDP = cis-diamminedichloroplatinum; UFT = uracil-ftegafur; A = antrum; Corp = gastric body; L = distal one third; M = middle one third; U = upper one third; wide = wide spread; TRD = treatment-related death.

vasion of 3 cm or less. They clearly demonstrated that there was no survival benefit from the left thoraco-abdominal approach which was accompanied by a much higher morbidity and more remarkable deterioration of pulmonary function than the transhiatal approach. The subgroup analysis showed no survival benefit for both Siewert type 2 and 3. Especially for Siewert type 3, the transhiatal approach showed much better survival than the left thoracotomy approach (fig. 3).

From these two trials, the transhiatal approach is regarded as the standard treatment for Siewert type 2 and 3 tumors, while the transthoracic approach via right thoracotomy is recommended for Siewert type 1 tumors.

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ORIGINAL ARTICLE

Adjuvant Chemotherapy for Gastric Cancer with S-1, an Oral Fluoropyrimidine

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ABSTRACT

BACKGROUND

Advanced gastric cancer can respond to S-1, an oral fluoropyrimidine. We tested S-1 as adjuvant chemotherapy in patients with curatively resected gastric cancer.

METHODS

Patients in Japan with stage II or III gastric cancer who underwent gastrectomy with extended (D2) lymph-node dissection were randomly assigned to undergo surgery followed by adjuvant therapy with S-1 or to undergo surgery only. In the S-1 group, administration of S-1 was started within 6 weeks after surgery and continued for 1 year. The treatment regimen consisted of 6-week cycles in which, in principle, 80 mg of oral S-1 per square meter of body-surface area per day was given for 4 weeks and no chemotherapy was given for the following 2 weeks. The primary end point was overall survival.

RESULTS

We randomly assigned 529 patients to the S-1 group and 530 patients to the surgery-only group between October 2001 and December 2004. The trial was stopped on the recommendation of the independent data and safety monitoring committee, because the first interim analysis, performed 1 year after enrollment was completed, showed that the S-1 group had a higher rate of overall survival than the surgery-only group (P=0.002). Analysis of follow-up data showed that the 3-year overall survival rate was 80.1% in the S-1 group and 70.1% in the surgery-only group. The hazard ratio for death in the S-1 group, as compared with the surgery-only group, was 0.68 (95% confidence interval, 0.52 to 0.87; P=0.003). Adverse events of grade 3 or grade 4 (defined according to the Common Toxicity Criteria of the National Cancer Institute) that were relatively common in the S-1 group were anorexia (6.0%), nausea (3.7%), and diarrhea (3.1%).

CONCLUSIONS

S-1 is an effective adjuvant treatment for East Asian patients who have undergone a D2 dissection for locally advanced gastric cancer. (ClinicalTrials.gov number, NCT00152217.)

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META-ANALYSES HAVE SHOWN THAT adjuvant chemotherapy is effective in treating gastric cancer.[1-6] However, the effectiveness of specific regimens has not been verified in large clinical trials. In 2001, the Intergroup-0116 (INT-0116) study investigators reported that postoperative chemoradiotherapy was effective in treating adenocarcinoma of the stomach or gastroesophageal junction.[7] Subsequently, the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial[8] showed the efficacy of perioperative chemotherapy. Both studies assessed the benefits of adjuvant therapy after only limited surgery, but the type of surgical procedure for gastric cancer can influence the results of postoperative chemotherapy.[9,10] In Japan, gastrectomy with extended (D2) lymph-node dissection alone is considered standard treatment.[11]

S-1 (TS-1, Taiho Pharmaceutical) is an orally active combination of tegafur (a prodrug that is converted by cells to fluorouracil), gimeracil (an inhibitor of dihydropyrimidine dehydrogenase, which degrades fluorouracil), and oteracil (which inhibits the phosphorylation of fluorouracil in the gastrointestinal tract, thereby reducing the gastrointestinal toxic effects of fluorouracil) in a molar ratio of 1:0.4:1.[12,13] The rate of response to treatment with S-1 alone exceeded 40% in two late phase 2 trials involving patients with advanced or recurrent gastric cancer.[14,15] The pharmacokinetics of the fluorouracil that is derived from S-1 is not influenced by gastrectomy,[16] and for this reason, S-1 is suitable for the postoperative adjuvant setting. In a pilot study,[17] we examined the feasibility of using S-1 postoperatively in patients with gastric cancer. We report the results of a large-scale trial — the Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer (ACTS-GC) — involving patients with stage II or III gastric cancer who underwent D2 surgery.

METHODS

The trial was conducted in accordance with the World Medical Association Declaration of Helsinki and Japanese Good Clinical Practice guidelines. The protocol was approved by the institutional review board of each participating hospital. Written informed consent was obtained from all patients.

All members of the steering committee and the sponsor jointly designed the trial and collected the data, which were held by the independent ACTS-GC Data Center. The data were analyzed by the independent data and safety monitoring committee. All academic members of the steering committee vouch for the validity and completeness of the data and the analysis. All of the authors reviewed and approved the final version of the manuscript before submission.

ELIGIBILITY CRITERIA

The criteria for eligibility were histologically proven gastric cancer of stage II (excluding T1 cases), IIIA, or IIIB; D2 or more extensive lymph-node dissection with R0 surgery (with the result of no residual tumor[18]); no hepatic, peritoneal, or distant metastasis; no tumor cells in peritoneal fluid on cytologic analysis; an age of 20 to 80 years; no previous treatment for cancer except for the initial gastric resection for the primary lesion; and adequate organ function (a leukocyte count of at least 4000 per cubic millimeter or the lower limit of the normal range; a platelet count of at least 100,000 per cubic millimeter; a total bilirubin level of no more than 1.5 mg per deciliter [25.7 μmol per liter], aspartate aminotransferase and alanine aminotransferase levels no more than 2.5 times the upper limit of the normal range; and a serum creatinine level no greater than the upper limit of the normal range). Stage classification and the evaluation of resected specimens were performed in accordance with the guidelines of the Japanese Gastric Cancer Association.[18]

STUDY DESIGN AND TREATMENT

The primary end point was overall survival; secondary end points were relapse-free survival and the degree of safety of S-1. Patients were enrolled, within 6 weeks after surgery, over the telephone or by fax by staff at the ACTS-GC data center. Patients were randomly assigned to either the S-1 group or the surgery-only group, with the assignments made at the ACTS-GC data center by means of the minimization method and according to the cancer stage (II, IIIA, or IIIB). Zelen's adjustment[19] was applied to balance the numbers of patients between each group at each participating hospital.

Patients assigned to the S-1 group received two oral doses of 40 mg of S-1 per square meter of body-surface area per day, for 4 weeks, followed by 2 weeks of no chemotherapy. Specifically, during the treatment weeks, patients with a body-surface