群で22例（15.6%）であり、縫合不全が10例、吻合部狭窄が4例、膵液漏が3例、また、腸閉塞、胆嚢炎、脳梗塞、創し開、逆流性食道炎がそれぞれ1例ずつであった。バイパス群の合併症は3例（14.3%）で、胆嚢炎、吻合部狭窄、心筋梗塞のそれぞれ1例ずつであった。手術関連死亡は、切除群で2例（1.4%）、バイパス群で1例（4.8%）であった。

3.手術後の食事摂取と在宅生活状況

手術後に食事摂取可能となった症例は、切除群で135例（95.7%）、バイパス群で19例（90.5%）であった。食事摂取不良であり退院時に中心静脈栄養管理となった症例は切除群で4例（2.8%）であった。バイパス群には中心静脈栄養管理となった症例はなかった。在宅期間中央値は切除群で223日（0-1620日）、バイパス群で108日（0-610日）であった。また在宅率中央値は、切除群で85.0%（0-99.0%）、バイパス群で66.0%（0-97.0%）であった。

4.生存期間と切除群における予後因子

切除群、バイパス群の50%生存期間は、それぞれ11.0ヶ月、5.9か月であった（p=0.02）。また、切除群における予後因子のlog-rank検定による単変量解析では、男性（p=0.02）、肝転移陽性（p=0.00）、遠隔転移陽性（p=0.02）、切除断端陽性（p=0.00）が有意な予後因子であり、年齢、出血、狭窄症状の有無、腹膜播種の有無、洗浄細胞診による有意差は認めなかった。

胃癌診療ガイドラインは根治手術が望めない症例に対する非治癒手術を減量手術と姑息手術に分類している。減量手術は、胃切除により腫瘍量を減らし、症状の出現や死亡までの時間を延長するのが目的である。また、非治癒切除症例でも出血や狭窄、低栄養などの切迫した症状を改善するための積極的な緩和手術が姑息的手術である。

たとえ緩和手術とはいえ根治手術と同様に安全に手術は施行されなければ意味がない。これまでに減量手術を含めた非治癒手術のmorbidityは12〜44%、mortalityは3〜14%と報告されている。一方でD2 vs D3 phaseⅢ試験（JCOG9501）におけるD2群のmorbidityは20.9%、mortalityは0.8%であったことを考慮すると、非治癒手術の危険性は高いと考えられる。

今回のわれわれの検討では、morbidityは15.4%、mortalityは1.9%であり比較的安全に手術が施行されていたと考えられる。姑息手術といえども、cancer boardで適応の検討を慎重に行い、安全に手術操作を行うことを心がけた結果と考えられる。

姑息手術は生存期間の延長が目標ではなく、症状改善が目的である。しかし、症状改善の一定の評価基準は定まっておらず、さらに高度進行胃癌の姑息手術後は生存期間が短いため、十分なquality of lifeの改善が認められないと感じられることもある。今回我々は、quality of lifeの改善の評価を手術後の食事摂取

状況と退院後の在宅状況を評価することとした。まず、食事摂取は両群で90%以上可能となり、また自宅での中心静脈栄養を必要とした患者は、胃切除群での4人（2.8%）のみであり、良好な摂食状況であった。在宅状況としては、在宅期間と在宅率を算出した。胃切除群、バイパス群における在宅期間中央値はそれぞれ223日、108日、また在宅率中央値は85.0%、66.0%であった。胃切除群では特に長期間在宅が可能であり高いquality of lifeが保てたと考えられた。Ouchiらは、術後在宅期間をhospital-free-survival （HFS）として3カ月以上在宅可能であった症例を手術別に比較検討しており、胃切除術群では82.8%、バイパス群では33.3%、非手術群間では56.2%であったと報告している。このことからOuchiらの非手術群と比較すると胃切除群は、在宅期間が延長すると思われた。またバイパス群では、今回我々が検討したバイパス群の在宅期間中央値が108日であることを考えると、Ouchiらのバイパス群の成績とほぼ同等と推察された。
以前より非根治症例においてバイパス群や非切除群と比較すると胃切除群は予後が延長すると報告されているものの、やはり多数の肝転移症例や広範囲の腹膜播種症例は予後不良である。我々の検討では、単変量解析にて肝転移、遠隔転移症例と切除断端陽性症例が予後不良であったが、これらの因子のある高度進行胃癌においても切迫した症状改善のために、何らかの処置を施行せねばならない状況がある。姑息的手術の術式の選択にははっきりとした基準はないが、もし可能であるのならば積極的な姑息的胃切除を行い、またバイパス術においても手術の浸襲を抑えるために腹腔鏡下バイパス術の検討や、狭窄症例においては、絶食期間、在院期間、コスト面などで有用であるという報告のある内視鏡下のステント挿入術の検討もすべきである。さらにはBest supportive careの方針とすべき症例かどうかも判断せねばならないと考えられる。

近年、新規抗癌剤の出現により、進行胃癌に対する奏効率も44.0〜76.0%と従来の治療法に比べても非常に良好な結果が報告されている。特にS-1はkey drugであり、姑息的手術後にS-1の経口摂取が可能となることで、種々の薬剤との併用療法もレジメンの選択肢となりうる。したがって、姑息的手術はこれまでの症状の緩和という目的だけでなく、少しでも予後の改善が認められるようその後の化学療法を見据えた外科的手段としての位置づけがなされるようになってきている。

以上、高度進行胃癌に対する姑息的手術について検討した。姑息的手術はquality of life改善のために有用であると考えられたため、全身状態が許せば積極的に施行すべきであり、その結果全身状態が改善すれば、新規抗癌剤を中心とした化学療法につなげていくことで予後の改善を目指すことができると考えられた。

D．倫理面への配慮

倫理面への配慮については、

資料提供者の個人情報の匿名化：本研究における個人情報の匿名化は当施設で行い、かつ個人識別情報は当施設に置いて厳重に管理している。また JCOG 臨床試験については当院の倫理委員会での審査を受け臨床研究が承認され、登録が可能となっている。

E．研究成果の刊行発表（本研究に関連する論文のみ。JCOG 研究および関連する研究発表など）

外国語論文

Gastrojejunostomy followed by induction chemotherapy for incurable gastric cancer with outlet obstruction

Yasuhiro Okumura, Manabu Ohashi, Souya Nunobe, Tomohiro Iwanaga, Tatsuo Kanda, Yoshiaki Iwasaki: *World J Gastroenterol* 2010 September 14; 16(34): 4367-4370

厚生労働科学研究補助金がん臨床研究事業（H20- がん臨床-一般-011）
分担研究報告書

終末期患者の在宅管理に関する研究

研究分担者　高金明典　函館五稜郭病院診療部長

研究要旨　治癒切除不能進行再発胃癌患者に対して、病診連携による在宅医療管理を行い、終末期医療における在宅の有用性ならびに問題点を明らかにし、終末期患者ならびに家族の安心と満足度の改善を図った 。

A.　研究目的

治癒切除不能進行胃癌患者の終末期は入院または在宅にて緩和医療を行うことになるが、特に在宅管理における問題を明らかにするためにretrospectiveに検討を行った。

B．研究方法

当院にて在宅管理を行った胃癌末期患者18例における治療経過や疼痛対策、栄養管理、在宅看取りに関する問題点を調べた。

C.　研究結果

終末期患者18例中12例(66.7%)は自宅で看取りができた。すべての症例でCVポートを埋め込みを行い、在宅中心静脈栄養管理がが行われた。治療開始後平均生存期間は391日と比較的長期にわたり生存可能であった。化学療法中止後は約3ヶ月間の生存であった。

D.　考察

終末期を少しでも長く在宅で過ごすためには栄養、疼痛、精神的ケアなどを病診連携で行わなければ難しい。我々は地域でがん連携を行っている4つの診療との終末期がん在宅管理を行うことができた。診療所、病院、訪問看護センター、緩和ケアチームによるカンファランスを開催し、終末期の管理を話し合うことにより、患者ならびに家族の安心を得られ在宅でも看取りを60%以上で可能となった。また、栄養管理や疼痛管理を在宅で行うことにより患者の　QOLの向上が可能であった。

E.　結論

治癒切除不能進行再発胃癌では化学療法中から栄養、疼痛管理を在宅で行うことで患者ならびに家族の安心と満足を得ることができる。

G．研究発表

1.　論文発表

1)高金明典.　病診連携による胃癌術後補助化学療法．病診連携の実際．外来癌化学療法．2(1)，48-52，2011

2) 胃切除後胆石症．別冊日本臨牀新領域別症候群シリーズ No. 15，肝・胆道系症候群（第２版）―その他の肝・胆道系疾患を含めて―，III 肝外胆道編 II胆嚢,結石．日本臨牀社．大阪，2011,393-394

3)高金明典．消化器がん診療地域連携クリティカルパスの実際．消化器外科NURSING，386-389，2009

4)高金明典,早川善郎,入野田 崇,その他.胃癌術後補助化学療法地域連携パスの有用性に関する検討．日臨外会誌　70(7)，1919-1925，2009

2.　学会発表

高金明典，早川善郎,入野田崇,他.胃癌末期患者の病診連携による在宅ケアを用いた化学療法．第48回日本癌治療学会．2010.9.28．京都

平成22年度厚生労働科研補助金分担研究報告書（センチネル関連業績を除く）

漿膜浸潤陽性胃癌に対する腹腔内化学療法を含む多剤併用補助化学療法の有用性に関する研究

分担研究者：
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研究要旨
漿膜浸潤陽性胃癌の根治的切除後生存に腹腔内投与を含む補助化学療法が寄与するかを評価した（JCOG 13 施設による第Ⅲ相試験）．1993 年 1 月から 98 年 3 月まで 268 症例を補助化療群（Cx 群，135 例）と手術単独群（S 群，133 例）にランダム割付し，レジメンはシスプラチン腹腔内投与とシスプラチン・5-FU 静注，UFT 経口投与としたが，本研究で用いられた術後補助化学療法は漿膜浸潤陽性胃癌の術後治療成績を改善しなかった．

研究目的
漿膜浸潤陽性胃癌の根治的切除後生存に腹腔内投与を含む補助化学療法が寄与するかを評価する（JCOG 13 施設による第Ⅲ相試験）．

研究方法
1993 年 1 月 5 日に登録を開始し，1998 年 3 月 31 日の登録終了まで，268 症例を補助化療群（Cx 群，135 例）と手術単独群（S 群，133 例）にランダム割付を行った．全例とも D2 以上のリンパ節郭清を伴う胃切除が行われた．補助化療はシスプラチン（70 mg/m2）腹腔内投与とその後のシスプラチン（70 mg/m2，day 14）と 5-FU（700 mg/m2，day 14-16）静注，および UFT（267 mg/m2，術後 4 週から 1 年）経口投与のレジメンを用いた．エンドポイントはプライマリーが全生存期間，セカンダリーが無病生存期間と再発形式とした．

研究結果
治療関連死（S 群 1 例，Cx 群 3 例）は術後合併症によるものであった．腹腔内投与により腎不全などの合併症を生じ，20 例で静注化療が中止となった．両群間の術後合併症発生割合は差がなかったが，補助化療全体のコンプライアンスは 39%であった．補助化療による生存期間の上乗せはなかった（5 年生存割合：Cx 62.0% vs. S 60.9%; P=0.482，5 年無再発生存割合：Cx 57.5% vs. S 55.6%;

P=0.512)．両群とも腹膜播種が最多再発形式であった．

考察

本研究で用いられた術後補助化学療法は漿膜浸潤陽性胃癌の術後治療成績を改善しなかった．本研究で得た教訓であるコンプライアンスの維持は重要であり，レジメン選択ではこの点も十分に配慮する必要がある．

結論

本研究で用いられた術後補助化学療法は漿膜浸潤陽性胃癌の術後治療成績を改善しなかった．

研究発表

1）宮代　勲，古河　洋，笹子三津留，他．漿膜浸潤陽性胃癌に対する腹腔内化学療法を含む多剤併用補助化学療法の有用性に関する第III相多施設共同臨床試験（JCOG9206-2）．第110回日本外科学会．2010年4月，名古屋．

2）Miyashiro I, Furukawa H, Sasako M et al. Randomized clinical trial of adjuvant chemotherapy with intraperitoneal and intravenous cisplatin followed by oral fluorouracil (UFT) in serosa-positive gastric cancer versus curative resection alone: final results of the Japan Clinical Oncology Group trial JCOG9206-2. Gastric Cancer 2011, Feb 19. [Epub ahead of print]

知的財産権の出願・登録状況

報告書執筆時点における本件に関する知的所有権の取得はない．

厚生労働科学研究費補助金（がん臨床研究事業）
分担研究報告書

進行胃癌における治療前の生検組織検体および化学療法後の摘出標本を用いた組織マイクロアレイに関する研究

研究分担者　肥田　圭介　岩手医科大学外科学講座　講師

研究要旨　免疫組織化学染色（以下、IHC：Immunohistochemistry）は病理組織診断および蛋白発現解析を行う手段として幅広く行われている。その利点は蛋白発現の有無を調べるだけでなく、形態を確認しながら発現解析できることである。さらに組織マイクロアレイ（以下、TMA：Tissue microarray）を用いることで一定の条件で多数例を解析でき、試薬も節約できる。また、TMAの材料であるパラフィン包埋ブロックは長期間の保存が可能であるため、過去の材料を再度解析することや異なる蛋白を対象として研究することが可能である。

A．研究目的

近年、切除不能進行胃癌に対する化学療法（以下、化療）が奏功し切除可能となる症例が増えているが、どの薬剤の効果が期待できるかについて治療前に診断することは困難である。また、化療による画像診断を含めた臨床的効果と組織学的効果の間に矛盾した判定が少なからず存在する。本研究の目的はその適正評価を行うにあたり、化療後に切除可能となった症例において特異的に発現している、あるいは発現していない蛋白をTMAおよびIHCを用いて同定することである。これにより、治療効果のある薬剤を選択するためのスクリーニングが可能になると考えている。

B．研究方法

2000年12月から2008年12月までの間、NAC後に胃切除可能となった計54例を対象とした。化療前の生検検体および摘出標本を用いてTMAブロックを作製しp53、MIB-1、pancytokeratinの免疫染色を行った。

（倫理面への配慮）

本研究でヒト材料に対して行われるのは、腫瘍原発巣の免疫染色である。本研究は院内における倫理委員会で承認されている。検体採取にあたり、患者・家族への十分な説明を行い文書による同意を得ている。

C．研究結果

レジメンはS-1/CDDP併用療法が最も多く、54例中32例（59.3 %）であった。組織型の内訳はtub2：46.7%、por1：16.7%、por2：23.3%、muc：6.7%、

sig・scc：各3.3%であった。HE染色では核濃縮・細胞質の好酸化・線維化・空胞化など多様な組織像を呈していた。化療後の免疫染色では、特にMIB-1において高率に染色性の低下を認めたが、組織型の違いによる染色性については明らかな傾向を認めなかった。

D．考察

TMA は多数の検体を組織レベルで形態の情報を失うことなく蛋白発現の局在や程度を観察できる技術である。本研究のように一定の目的のために作成されるカスタムメイドのTMAに関する報告はそれほど多くはなく、近年確立されつつある術前化療施行症例を組織・蛋白レベルで検証する特徴的なアプローチであるといえる。そして現在、この手段は臨床診断には使用されていないが、TMA を用いることによって実際の腫瘍の種類や進行度を判断し、個々の腫瘍に最も効果的な治療法を予測し体系的に研究することが可能となると考えられる。

E．結論

TMAはより多くの検体を同時かつ同一条件で観察することが可能である。今回の検討結果では、何らかの化学療法の影響で蛋白合成が低下していると結論づけられるが、さらに他の抗体パネルを使い検討することを考えている。さらに臨床的背景因子と組織学的治療効果との関連性について検証することは重要と思われ、それらの効果判定の不一致について、さらに症例を蓄積して化学療法の生物学的意義および効果判定法について検討する必要がある。

F．健康危険情報

（分担研究報告書には記入せずに、総括研究報告書にまとめて記入）

G．研究発表

1．　論文発表

現在、執筆中である。

2．　学会発表

第48回　日本癌治療学会　2010年10月

第4回　日本ハンガリー外科学会　2010年11月

H．知的財産権の出願・登録状況

（予定を含む。）

1．特許取得

特記なし

2．実用新案登録

特記なし

3．その他

特記なし

研究成果の刊行に関する一覧表

辻仲利政

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World J Surg
DOI 10.1007/s00268-010-0914-5

World journal of Surgery

Influence of Bursectomy on Operative Morbidity and Mortality After Radical Gastrectomy for Gastric Cancer: Results of a Randomized Controlled Trial

Hiroshi Imamura · Yukinori Kurokawa · Junji Kawada · Toshimasa Tsujinaka · Shuji Takiguchi · Yoshiyuki Fujiwara · Masaki Mori · Yuichiro Doki

Abstract

Background Bursectomy, a procedure dissecting the peritoneal lining covering the pancreas and the anterior plane of the transverse mesocolon, has been commonly performed with radical gastrectomy for gastric cancer patients. Although possibly improving the prognosis of gastric cancers, adverse events related to bursectomy should be evaluated in prospective studies.

Methods This prospective randomized controlled trial was conducted by experienced surgeons in 11 Japanese institutions. Patients with T2 or T3 gastric adenocarcinoma were intraoperatively randomized to radical gastrectomy plus D2 lymphadenectomy either with or without bursectomy. Postoperative morbidity and mortality were compared between the two groups.

Results A total of 210 patients were assigned to the bursectomy group (104 patients) and the nonbursectomy group (106 patients) between July 2002 and January 2007. Background characteristics were well balanced. Intraoperative blood loss was greater in the bursectomy group than in the nonbursectomy group (median 475 vs. 350 ml, $p = 0.047$), whereas other surgical factors did not vary significantly. The overall morbidity rate was 14.3% (30 patients), the same for the two groups. Likewise, the incidence of major postoperative complications, including pancreatic fistula, anastomotic leakage, abdominal abscess, bowel obstruction, hemorrhage, and pneumonia, were not significantly different between the two groups. The medians of the amylase level of the drainage fluid on postoperative day 1 were similar for the two groups (median 282 vs. 314 IU/L, $p = 0.543$). The hospital mortality rate was 0.95%: one patient per group.

Conclusions Experienced surgeons could safely perform a D2 gastrectomy with an additional bursectomy without increased major surgical complications.

Introduction

More than half of the new cases of gastric cancer occur in eastern Asia [1]. The surgical intervention for gastric cancers has rapidly developed in Japan. An extended radical lymphadenectomy, which is almost identical to the present D2 dissection, along with bursectomy was established as the standard treatment for advanced gastric cancers during the early 1960s [2, 3]. Bursectomy is a traditional surgical procedure to dissect the peritoneal lining covering the pancreas and the anterior plane of the transverse mesocolon with an omentectomy [4, 5]. This procedure is recommended in the Japanese Gastric Cancer Treatment Guidelines as part of the radical surgery for gastric cancer to remove micrometastases disseminated into the bursa omentalis [6]. As gastric cancer in the posterior wall sometimes shows peritoneal dissemination only in the bursa omentalis, its resection may improve survival [7].

On the other hand, a bursectomy causes some surgical stress when performed in addition to a D2 lymph node

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Published online: 16 December 2010

dissection. Therefore, the possible increase in the incidence of postoperative complications, including pancreatic fistula formation, intestinal obstruction, and hemorrhage, may be concerning. As the safety of a D2 lymph node dissection is still controversial in Western countries [8, 9], we should also carefully evaluate the safety of bursectomy. To elucidate the safety and usefulness of the bursectomy, we conducted a multiinstitutional randomized controlled trial. We hereby present our operative morbidity and mortality data, the secondary endpoints of this trial. The final analysis of survival data is scheduled to take place in 2012.

Patients and methods

Patients

Patient eligibility criteria for this study were as follows: (1) histologically proven primary adenocarcinoma of the stomach; (2) a preoperative and intraoperative classification of T2N0, T3N0, T2N1, or T3N1 according to 13th edition of the Japanese Classification of Gastric Carcinoma [10]; (3) a lack of noncurative surgical factors except for positive lavage cytology; (4) no Borrmann type 4 (linitis plastica) cases; (5) no prior chemotherapy or radiation therapy; (6) ages 20 to 80 years with a performance status of 0 to 2 according to the Eastern Cooperative Oncology Group (ECOG) scale; (7) no history of gastrectomy or other malignancy during the last 5 years. All patients gave written informed consent before undergoing randomization.

When the surgeon confirmed the above eligibility criteria immediately after the initial laparotomy, patients were then intraoperatively randomized to the bursectomy group (a D2 gastrectomy with bursectomy) or the nonbursectomy group (without bursectomy). Randomizations were made by the minimization method according to sex, clinical T stage (cT2 vs. cT3), and gastrectomy (total vs. distal subtotal gastrectomy).

Surgery

In both the bursectomy and nonbursectomy groups, the surgeon performed a total or distal subtotal gastrectomy and D2 lymph node dissection as a standard treatment for advanced gastric cancers [10]. With total gastrectomy for T2 or deeper tumors in the proximal third of the stomach, the spleen was removed in principle for splenic hilar lymphadenectomy. Pancreatectomy was confined to those patients whose pancreas was involved by tumor.

An omentectomy was performed for both groups in this study. In the bursectomy group, the peritoneal lining of the bursa omentalis was removed en bloc as much as possible from the anterior plane of the transverse mesocolon and the pancreas. In the caudal area of the bursa omentalis, the anterior lesion was removed with the minor omentum at the edge of the left lobe of the liver. The posterior and right-sided lesions were removed with lymph node dissection along the common hepatic artery (no. 8a), the splenic artery (no. 11p/d), the left gastric artery (no. 7), and in the hepatoduodenal ligament (no. 12a). As complete removal of the left side of the bursa omentalis did not allow a distal subtotal gastrectomy, pancreatic serosa was removed up to the proximal half of the splenic artery (no. 11p). For the transverse colon mesentery, the peritoneum was removed up to the left gastroepiploic artery (no. 4sb). In the nonbursectomy group, the right anterior surface of the transverse colon mesentery was partially removed around the root of the right gastroepiploic artery (no. 6). Only a small amount of peritoneum could be removed for lymph node dissection. Thus, the bursa omentalis peritoneal lining was preserved as much as possible in the nonbursectomy group. The type of reconstruction and the indication of prophylactic cholecystectomy were not specified in the protocol.

Patients were enrolled from 11 hospitals belonging to the Osaka University Clinical Research Group for Gastroenterological Surgery. More than 50 gastrectomies were performed each year in these 11 hospitals. All operations were performed or supervised by senior surgeons who were members of the Japanese Gastric Cancer Association. During the planning of the study, all participating surgeons reached an agreement concerning the technical details of bursectomy.

Postoperative evaluation

Operative methods and pathology results were recorded according to the 13th edition of the Japanese Classification of Gastric Carcinoma [10]. The number of dissected lymph nodes was measured by pathology. Drainage fluid was collected via an operatively placed drain on postoperative day (POD) 1 for measuring the amylase level. The six Representative data for the six major morbidities—pancreatic fistula, anastomotic leakage, abdominal abscess, bowel obstruction, hemorrhage, pneumonia—were prospectively collected. A pancreatic fistula was defined by a drainage output on or after POD 5 with an amylase content more than three times the upper normal serum value. Pneumonia, anastomotic leakage, abdominal abscess, and bowel obstruction were diagnosed radiologically or clinically. Postoperative hemorrhage requiring a transfusion was recorded as morbidity. Any other complications requiring pharmacologic or surgical treatment were recorded on a free format. Operative morbidity until 3 months after surgery was also analyzed in this study. Operating time, blood loss, duration of hospital stay after surgery, and reoperation details were also recorded. Hospital mortality

was defined as postoperative death of any cause within 30 days or death during the same hospitalization.

Patients were followed every 3 months until 5 years after the operation. Adjuvant therapy was not permitted before a recurrence of cancer.

Statistical Analysis

The primary endpoint was overall survival (OS). Secondary endpoints were recurrence-free survival, operative morbidity, and POD 1 drainage amylase levels. We planned initially to recruit 200 patients, with an alpha error of 0.1 and statistical power of 80%. This allowed detection of a 10% margin of noninferiority for the nonbursectomy group under the estimation of a 60% 5-year OS in the bursectomy group. The projected accrual period and follow-up period were 3 years and 5 years, respectively. After registration of 204 patients, we amended the sample size and analysis to correct the estimation of the 5-year OS in the bursectomy group as 75% and to reduce alpha error. The amended sample size was 464, with an alpha error of 0.05 and statistical power of 80%, with an 8-year accrual period (total) and 5-year follow-up.

In January 2007, the positive result of a large-scale randomized controlled trial to evaluate adjuvant S-1 chemotherapy for stage II/III gastric cancer patients was reported [11, 12]. Since then, adjuvant S-1 chemotherapy has been a new standard treatment for stage II/III gastric cancer patients in Japan. However, because any adjuvant treatment including S-1 was not allowed after surgery in our study, we decided to close the accrual of our study in January 2007.

The operative morbidity and mortality rates were based on the proportion of the number of cases divided by all registered patients based on the intention-to-treat principle. The differences in proportion between the two groups were evaluated using Fisher's exact test or chi-squared test. The differences of continuous variables, including age, body mass index, tumor size, operating time, blood loss, and the number of dissected lymph nodes for the two groups were tested with a Mann-Whitney U-test. All p values were two-sided, and statistical analysis was done using SPSS Statistics software, version 17.0 (SPSS, Chicago, IL, USA).

Results

Patients and surgery

Between July 2002 and January 2007, a total of 210 patients were randomly divided into 104 in the bursectomy group and 106 in the nonbursectomy group (Fig. 1). One patient in the bursectomy group did not undergo bursectomy, and one in the nonbursectomy group underwent

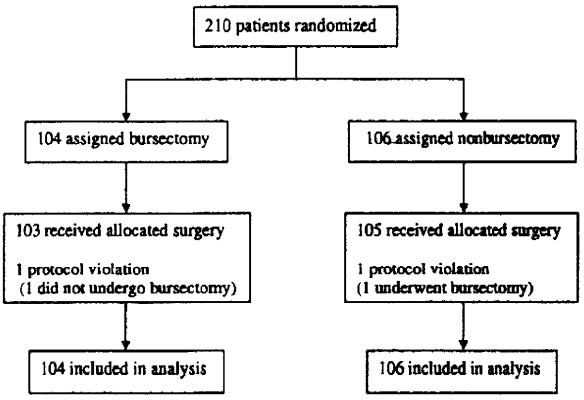

Fig. 1 CONSORT flowchart for patients

bursectomy. Most of the baseline characteristics were well balanced (Table 1). The bursectomy group had slightly older patients than the nonbursectomy group (median 65 vs. 63 years, $p = 0.099$). The number of patients with pathologically positive nodes was slightly higher in the bursectomy group than in the nonbursectomy group (52.9% vs. 43.4%, $p = 0.214$).

The operative details are shown in Table 2. A total gastrectomy was performed on 22 (21.2%) patients in the bursectomy group and on 27 (25.5%) patients in the nonbursectomy group. About one-half of patients in each of the two groups underwent a Roux-en-Y reconstruction procedure. A combined resection of other organs was performed for 103 patients in total. The resected organs were the gallbladder in 98 patients, spleen in 26 patients, part of the pancreas in 1 patient, the colon in 1 patient, the left adrenal gland in 1 patient, and the diaphragm in 1 patient. It was of note that although the difference was not statistically significant the number of patients with a combined resection was greater in the nonbursectomy group than in the bursectomy group (42.3 vs. 55.7%, $p = 0.055$). When we evaluated the operating time after dividing the patients into two subgroups, either with or without a combined resection of other organs, the bursectomy required a longer operating time (median 27 min in patients with a combined resection, 26 min in patients without a combined resection). The amount of blood loss significantly increased in the bursectomy group compared to the nonbursectomy group (median 475 vs. 350 ml, $p = 0.047$). There was no significant difference between the two groups regarding the number of dissected lymph nodes.

Operative morbidity and mortality

The overall operative morbidity rate was 14.3% (30 patients), which was the same in the two groups (Table 3). Prespecified complications, including pancreatic fistula, anastomotic leakage, abdominal abscess, bowel obstruction,

Table 1 Patient and tumor characteristics

Characteristic	Bursectomy ($n = 104$)	Nonbursectomy ($n = 106$)	p*
Age (years)			0.099
Median	65	63	
Range	31–79	34–78	
Sex			0.761
Male	73	77	
Female	31	29	
Body mass index			0.653
Median	22.3	22.5	
Range	15.7–28.9	15.6–29.4	
Tumor size (cm)			0.311
Median	4.3	4.5	
Range	0.9–11.0	1.5–12.0	
Histological type			0.784
Differentiated	47	50	
Undifferentiated[a]	57	56	
Clinical T stage[b]			0.572
cT2	61	67	
cT3	43	39	
Clinical N stage[b]			1.000
cN0	59	61	
cN1	45	45	
Pathologic T stage[b]			0.902
pT1	17	19	
pT2	62	64	
pT3-4	25	23	
Pathologic N stage[b]			0.119
pN0	49	60	
pN1	37	24	
pN2-3	18	22	
Residual tumor			1.000
R0	101	102	
R1	3	4	

* The p values were calculated by Fisher's exact test for sex, histological type, clinical T stage, clinical N stage, and residual tumor; by the chi-squared test for pathologic T stage and pathologic N stage; and by the Mann–Whitney U-test for age, body mass index, and tumor size

[a] Undifferentiated type included one endocrine cell carcinoma case in the nonbursectomy group

[b] T stage and N stage were according to the 13th edition of the Japanese Classification of Gastric Carcinoma

Table 2 Profile of surgical treatment

Treatment	Bursectomy ($n = 104$)	Nonbursectomy ($n = 106$)	p*
Gastrectomy			0.515
Total	22	27	
Distal subtotal	82	79	
Reconstruction method			0.705
Roux-en-Y	48	55	
Billroth I	54	49	
Other[a]	2	2	
Combined resection of other organs			0.055
Present	44	59	
Gallbladder	41	57	
Spleen	12	14	
Other[b]	1	2	
Absent	60	47	
Operating time (min)			0.368
Median	222	221	
Range	134–488	111–360	
Blood loss (ml)			0.047
Median	475	350	
Range	80–3970	55–2901	
No. of dissected lymph nodes			0.417
Median	38	37	
Range	11–98	7–97	

* p values were calculated by Fisher's exact test for gastrectomy and combined resection of other organs (present or absent); by chi-squared test for the reconstruction method; and by the Mann–Whitney U-test for operating time, blood loss, and the number of dissected lymph nodes

[a] Others included one Billroth II method and one intestinal interposition method in the bursectomy group and two Billroth II methods in the nonbursectomy group

[b] Others included one adrenal gland in the bursectomy group and one pancreas and one diaphragm in the nonbursectomy group

Table 3 Postoperative morbidity

Morbidity	Bursectomy ($n = 104$)	Nonbursectomy ($n = 106$)	p*
Any complication	15	15	1.000
Pancreatic fistula	3	7	0.332
Anastomotic leakage	4	3	0.720
Abdominal abscess	3	8	0.214
Bowel obstruction	2	1	0.620
Hemorrhage	1	0	0.495
Pneumonia	1	1	1.000

* The p values were calculated by Fisher's exact test

hemorrhage, and pneumonia, did not significantly differ between the two groups. Among the 10 patients with a pancreatic fistula, 6 underwent splenectomy, but no patients underwent pancreaticosplenectomy. Ten patients suffered from other complications, including two cases of chylous lymphorrhea, two of delayed gastric emptying without obstruction, and one case of afferent loop syndrome, acute cholecystitis, acute enteritis, arteriosclerosis obliterans of the leg, drug-induced hepatitis, and anastomotic stricture. The incidence of these miscellaneous complications tended

to be more frequent in the bursectomy group than in the nonbursectomy group (7.7 vs. 1.9%, $p = 0.057$). The median amylase levels in the drainage fluid on POD 1 were 282 IU/L in the bursectomy group and 314 IU/L in the nonbursectomy group ($p = 0.543$). Reoperation was required in four patients (1.9%): two for intestinal obstruction, one for afferent loop syndrome in the bursectomy group, and one for anastomotic leakage in the nonbursectomy group. The median hospital stay after surgery was 16 days in the bursectomy group and 15 days in the nonbursectomy group ($p = 0.744$).

There were two hospital deaths (0.95%). One patient in the bursectomy group and one patient in the nonbursectomy group died of sepsis after anastomotic leakage and pancreatic fistula formation, respectively. All other patients recovered from surgery and were discharged from the hospital.

Discussion

Two factors are necessary for bursectomy to be accepted as a standard treatment for advanced gastric cancers: safety and oncologic benefit. Only a randomized clinical trial can scientifically evaluate this proposition, and we are the first worldwide to conduct such a trial. This article is an early report of this trial with respect to operative safety. We found that overall morbidity and mortality were equivalent with and without bursectomy. Although the amount of surgical blood loss was significantly increased with bursectomy, overall we concluded that this procedure is safe and acceptable.

The safety of surgical treatments strongly depends on the surgeon's experience. Specific training is required to perform any surgical procedure, particularly when it is done for cancer treatment. There have been clinical trials studying the extent of lymph node dissection during gastric surgery. Two European randomized trials comparing D1 with D2 lymphadenectomy concluded that D2 was not acceptable as a standard treatment because D2 was associated with higher morbidity and mortality than D1 [8, 9]. On the other hand, two randomized trials comparing D1 with D2 and D2 with D3 lymphadenectomy in eastern Asia demonstrated that both D2 and D3 gastrectomy could be performed with low operative risk [13, 14]. This finding can be explained by the high volume of gastric cancer patients treated at that hospital and the high prevalence of gastric cancer in eastern Asia. In this study, all the patients were enrolled from an institution in which more than 50 gastrectomies were performed each year. In our trial the surgical procedures being performed by experienced surgeons accounted for the low mortality rates (0.95%) and low morbidity rates (14.3%).

Among various adverse events after surgery, we were concerned about the increased incidence of pancreatic fistulas after bursectomy because bursectomy requires resection of the capsule covering the pancreas [15]. However, we did not observe a significant increase in the incidence of pancreatic fistulas or inappropriate amylase levels in the postoperative drainage fluid, a surrogate marker of a pancreas fistula. This suggests that a pancreatic fistula is not caused by removal of a pancreatic capsule but may be caused by lymph node dissection adjacent to the pancreas parenchyma.

The next concern included the possibility of adhesion formation. Intestinal obstruction is the representative symptom of adhesion. In this study, two bursectomy patients and one nonbursectomy patient suffered from postoperative bowel obstruction, but there was no significant difference between the two groups. As 3 months' observation after surgery was not enough to evaluate the incidence of intestinal obstruction, a longer observation is necessary to draw a conclusion. Adhesion to the mesocolon and pancreas may cause specific local symptoms, such as delayed gastric emptying or afferent loop syndrome. It is of note that both delayed gastric emptying (two patients) and afferent loop syndrome (one patient) were observed only in the bursectomy group. Although this also did not reach statistical significance, careful observation is required in a larger cohort study.

In general, omentectomy and bursectomy are simultaneously performed for the same purpose, but their clinical pictures are somehow different. As the great omentum has numerous milky spots, which absorb ascites and actively incorporate cancer cells, peritoneal metastasis is frequently observed [16]. On the other hand, bursa omentalis, which is a semi-closed cavity, allows exfoliated cancer cells to remain. As for the surgical aspects, omentectomy is not difficult and does not increase the operating time or the blood loss. In contrast, the bursectomy technique is complicated and increases the operating time and bleeding. Considering the balance between the risk and benefit of each surgical procedure, we performed an omentectomy for all patients and randomly assigned each case to either with or without bursectomy. If we cannot find a benefit of bursectomy in this trial, we should elucidate the significance of omentectomy in the next step.

Conclusions

This study showed that experienced surgeons could safely perform a D2 gastrectomy with bursectomy. Although bursectomy resulted in more blood loss, the major operative complications and hospital deaths were not increased. Regarding the survival benefit of this procedure, we must

wait for the results of the final analysis when the data have matured sufficiently.

Acknowledgments We thank Professor Kunio Okajima for helpful advice and Dr. Tomoyuki Sugimoto for statistical analysis of this study.

Conflict of interest The authors declare no conflicts of interest.

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Experimental Chemotherapy

Chemotherapy

Chemotherapy 2010;56:436–443
DOI: 10.1159/000317762

Received: February 2, 2010
Accepted after revision: May 30, 2010
Published online: November 17, 2010

Effect of S-1 Adjuvant Chemotherapy on Survival following Recurrence and Efficacy of First-Line Treatment in Recurrent Gastric Cancer

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Key Words
Adjuvant chemotherapy · S-1 · Recurrent gastric cancer · Overall survival · Efficacy of chemotherapy

Abstract
Background: As S-1 monotherapy has recently become the standard adjuvant regimen for stage II-III gastric cancer patients after curative gastrectomy in Japan, the question whether adjuvant S-1 affects the subsequent clinical course of relapsed patients has attracted great concern. ***Patients and Methods:*** We retrospectively evaluated the effect of adjuvant S-1 on survival following recurrence and efficacy of first-line treatment in patients with recurrent gastric cancer after curative gastrectomy. A total of 89 patients were evaluated. Thirty patients received adjuvant S-1 (cohort A), 10 patients were given adjuvant chemotherapy with other oral 5-FU agents (cohort B) and 49 patients received no adjuvant chemotherapy (cohort C). ***Results:*** Median survival time following recurrence was 287 days in cohort A, 451 days in B and 547 days in C, with a significant difference between A and C ($p = 0.0034$). Response rates of the first-line chemotherapy after recurrence were 6.7, 30.0 and 42.9% in cohorts A, B and C, respectively, with a significant difference between A and C ($p = 0.0007$). On multivariate analysis, S-1 adjuvant chemotherapy was independently associated with poor prognosis after recurrence (hazard ratio 2.64). ***Conclusion:*** S-1 adjuvant chemotherapy significantly reduced survival and response to first-line chemotherapy following recurrence in patients with recurrent gastric cancer.

Introduction

Although several meta-analyses have suggested a survival benefit provided by adjuvant chemotherapy for gastric cancer [1–6], there have been only a few treatments with their efficacy established in large clinical trials. Postoperative radiotherapy with 5-FU plus leucovorin has become a standard adjuvant therapy in the US [7], while peri-operative triplet regimen with epirubicin, cisplatin and 5-FU is standard in the UK [8]. Recently in Japan, the ACTS-GC trial has verified the efficacy of S-1 adjuvant chemotherapy after curative gastrectomy for stage II-III disease [9]. However, around 30% of patients still develop recurrence afterwards despite adjuvant S-1. As the number of patients relapsing after S-1 adjuvant chemotherapy increases, it becomes of great concern whether adjuvant S-1 affects the subsequent clinical behavior of the recurrent disease.

This retrospective study was conducted to evaluate the effect of S-1 adjuvant chemotherapy, in comparison with other 5-FU agents or no adjuvant chemotherapy, on sur-

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vival following recurrence and efficacy of first-line chemotherapy given at the time of relapse in patients with recurrent gastric cancer after curative gastrectomy.

Patients and Methods

Patients

A total of 95 patients with recurrent gastric cancer after curative gastrectomy were found at our institution between April 1999 and October 2008. Among them, 89 patients enrolled in this retrospective study fulfilled the following criteria: (1) histologically proven recurrent gastric adenocarcinoma; (2) stage II, III or IV primary disease without any distant metastasis in accordance with the guidelines of the Japanese Gastric Cancer Association [10]; (3) either adjuvant chemotherapy with S-1 or other oral 5-FU agents (UFT or 5′-FUDR) lasting more than 4 weeks or no adjuvant treatment; (4) performance status of 2 or less on the Eastern Cooperative Oncology Group scale; (5) adequate bone marrow function (white blood cell count 4,000–12,000/mm^3, platelet count ≥100,000/mm^3 and hemoglobin ≥8.0 g/dl), hepatic function (total bilirubin ≤1.5 mg/dl, serum transaminases ≤100 μ/l) and renal function (serum creatinine ≤ the upper institutional limit); (6) no other severe medical conditions; (7) no other concurrent active malignancy.

Overall Survival, Efficacy of First-Line Chemotherapy and Statistics

Overall survival (OS) after recurrence was defined as the time from the date of recurrence to the date of death from any cause or the last follow-up. OS was calculated using the Kaplan-Meier method and compared with the log-rank test. Univariate and multivariate analyses were performed by the Cox proportional hazards model to identify variables independently associated with poor prognosis after recurrence.

During the first-line chemotherapy after recurrence, each patient with a measurable lesion was assessed for an objective response to treatment according to the Response Evaluation Criteria in Solid Tumors [11] with computed tomography scans performed every 2 to 3 months until disease progression. Disease control rate (DCR) represented the percentage of patients with complete response, partial response or stable disease (SD). Patients only with nonmeasurable lesions were evaluated as stable disease if neither complete disappearance (complete response) nor obvious progression of the recurrent disease were observed on computed tomography scans.

Differences in proportion were evaluated with the χ^2 test and the differential significance of age was estimated by the Kruskal-Wallis test. Statistical results were considered to be significant with a p value of less than 0.05.

Results

Patient Characteristics

Eighty-nine patients were categorized into the 3 cohorts shown in table 1. Thirty patients in cohort A, 18 males and 12 females with a median age of 62.5 years (range: 32–83), received S-1 adjuvant chemotherapy. S-1 was given orally using a standard dose and schedule (80 mg/m^2/day, for 28 consecutive days followed by a 14-day rest, repeated for 1 year) [9]. Nine patients completed the planned 1-year administration of adjuvant S-1, while 11 patients discontinued the treatment within the first 6 months and 10 patients in the second 6 months after the initiation of S-1 adjuvant chemotherapy. The reasons for treatment withdrawal were treatment toxicity in 1, and recurrent disease in 20 patients. The median duration of adjuvant S-1 administration was 211 days. In cohort B, 10 patients, 6 males and 4 females with a median age of 63.0 years (range: 35–78), were given adjuvant chemotherapy with oral 5-FU agents other than S-1. UFT (a combination of uracil and tegafur at a molar ratio of 4:1) was administered at a dose of 400 mg/body/day in 6 patients and 5′-DFUR (5′-deoxy-5-fluorouridine) at a dose of 800 mg/body/day in 4 patients. Two patients completed the planned 1-year administration of adjuvant UFT/5′-DFUR, while 3 patients discontinued the treatment within the first 6 months and 5 patients in the second 6 months after the initiation of adjuvant chemotherapy. The rea-

Table 1. Patient characteristics

	Cohort A S-1 adjuvant	Cohort B oral 5-FU	Cohort C no adjuvant	p value
Patients	30	10	49	
Gender				0.5254
Male	18	6	35	
Female	12	4	14	
Age, years				0.8537
Median	62.5	63	59	
Range	32–83	35–78	42–84	
Histology (Lauren's)				0.841
Intestinal	9	4	17	
Diffuse	21	6	32	
Stage				0.0053
II	2	4	11	
III	13	5	32	
IV	15	1	6	
Measurable lesions				0.6584
Present	19	6	26	
Absent	11	4	23	
Metastatic sites				0.2531
1	25	10	45	
≥2	5	0	4	
DFI				0.105
<1 year	19	5	19	
≥1 year	11	5	30	

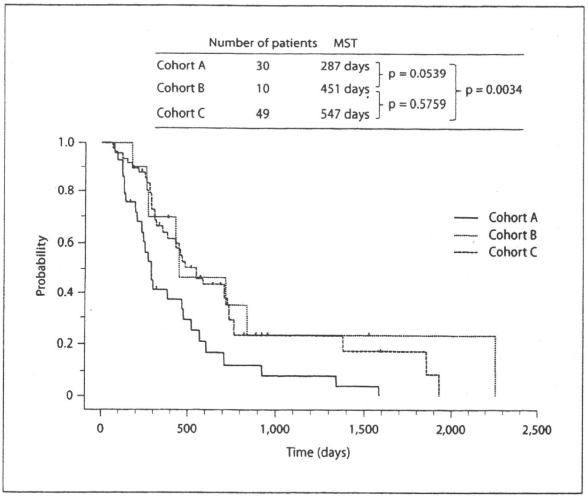

Fig. 1. OS after recurrence.

sons for treatment withdrawal were patient refusal in 1 and recurrent disease in 7 patients. The median duration of adjuvant 5-FU agent administration was 180 days. Forty-nine patients in cohort C, 35 males and 14 females with a median age of 59.0 years (range: 42–84), received no adjuvant chemotherapy. Histologically, around one third of patients had intestinal-type adenocarcinoma and two thirds had diffuse-type adenocarcinoma in each cohort. As for the initial stage of the primary tumor after curative gastrectomy, stage IV disease was significantly more frequent in cohort A than in the other cohorts ($p = 0.0053$). A measurable recurrent lesion was seen in 50–60% of each cohort and multiple metastatic sites were present in 10% of all patients. The disease-free interval (DFI), which was defined as the time from the date of surgery to the date of recurrence, was less than 1 year in approximately 40–60% of patients in either cohort.

Overall Survival

OS after recurrence was compared among the three cohorts. After a median follow-up time of 380 days from the date of recurrence (319 days in 71 dead patients and 560 days in 18 alive patents), the median survival time (MST) was 287 days in cohort A, 451 days in B and 547 days in C. OS was significantly shorter in cohort A than in cohort C ($p = 0.0034$), while there was no significant difference between cohorts B and A or C, as shown in figure 1. In cohort A, the duration of S-1 adjuvant chemotherapy was <6 months in 11 patients, 6 to <12 months in 10 and 12 months in 9. No significant difference in OS (MST, 246 vs. 287 vs. 464 days; $p = 0.4963$) was observed according to the duration of S-1 adjuvant chemotherapy, as shown in figure 2.

Efficacy of First-Line Chemotherapy

Regimens of the first-line chemotherapy delivered after recurrence are shown in table 2. Nine patients (30.0%) in cohort A received S-1-based therapy (S-1 monotherapy [12, 13] in 3, S-1 plus cisplatin [14] in 3, S-1 plus irinotecan [15] in 3, S-1 plus paclitaxel [16] in 0), although 9 patients were treated with paclitaxel monotherapy administered in a weekly fashion [17] and 12 patients with irinotecan-based therapy (irinotecan monotherapy [18] in 5, irinotecan plus cisplatin [19] in 7). In cohort B, 5 patients (50.0%) received S-1-based therapy, with 4 patients being treated with paclitaxel monotherapy and 1 patient with irinotecan plus cisplatin. In cohort C, 42 patients (85.7%) received S-1-based therapy, 4 patients were given paclitaxel monotherapy and 3 patients were given irinotecan plus cisplatin. It seemed inevitable for various regimens to

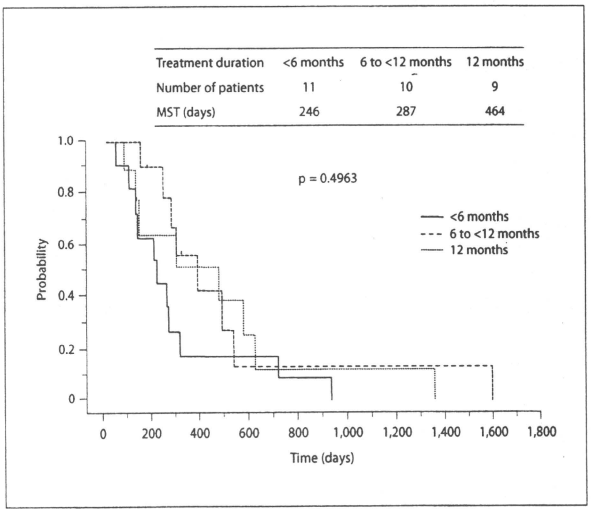

Fig. 2. OS according to the duration of S-1 adjuvant chemotherapy.

Table 2. Regimens of first-line chemotherapy after recurrence

	Cohort A (n = 30)	Cohort B (n = 10)	Cohort C (n = 49)
S-1-based therapy	9	5	42
S-1 monotherapy	3	3	26
S-1 + cisplatin	3	0	4
S-1 + irinotecan	3	1	7
S-1 + paclitaxel	0	1	5
Weekly paclitaxel	9	4	4
Irinotecan-based therapy	12	1	3
Irinotecan monotherapy	5	0	0
Irinotecan + cisplatin	7	1	3

have been given as the first-line treatment because it was obscure whether non-S-1-based therapy was more appropriate for patients relapsed after adjuvant S-1 or which should be chosen as a non-S-1 agent between paclitaxel and irinotecan for patients with recurrent gastric cancer. However, there was a tendency to prefer choosing S-1-based therapy as the first-line treatment after recurrence in cohort C, while non-5-FU regimens were more likely to be chosen in cohorts A and B. The best response to the first-line chemotherapy after recurrence was compared among these 3 cohorts, as shown in table 3. Response rates (RR) were 6.7% [95% confidence interval (CI) 0.8–22.1], 30.0% (95% CI 6.7–65.3), and 42.9% (95% CI 28.8–57.8) in cohorts A, B and C, respectively, with a significant difference between A and C ($p = 0.0007$). DCR were 50.0% (95% CI 31.3–68.7), 80.0% (95% CI 44.4–97.5) and 89.8% (95% CI 77.8–96.6) in cohorts A, B and C, respectively, with a significant difference between A and C ($p = 0.0001$).

Prognostic Factors for OS

The results of univariate and multivariate analyses of various factors, such as gender, age, histology, initial stage and presence of measurable lesion, number of metastatic sites, DFI and type of adjuvant chemotherapy for OS following recurrence are summarized in table 4. Among these, absence of a measurable lesion [hazard ratio 2.18 (95% CI 1.28–3.72)], presence of multiple metastatic sites [hazard ratio 2.89 (95% CI 1.28–6.52)] and S-1 adjuvant chemotherapy [hazard ratio 2.64 (95% CI 1.35–4.75)] were identified as significant independent factors for poor prognosis after recurrence.