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「消化器外科手術における合成吸収糸使用の手術部位感染抑制効果に関する多施設共同並行群間無作為化比較試験」

平成21年度　総括研究報告書

研究代表者　前原　喜彦

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厚生労働省科学研究費補助金（医療技術実用化総合研究事業）
総括研究報告書

消化器外科手術における合成吸収糸使用の手術部位感染抑制効果に関する多施設共同並行群間無作為化比較試験

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研究要旨　　皮下・腹壁縫合糸については、欧米において絹糸と合成吸収糸の無作為化臨床試験とメタアナリシスで、合成吸収糸の有効性が確立しているが、腹腔内で合成吸収糸を使用することで手術部位感染(Surgical Site Infection：SSI)が減少するというエビデンスは確立していない。本臨床試験の目的は、以下の点である。推奨されている周術期の患者管理を行い、消化器手術の腹腔内での絹糸使用群と合成吸収糸使用群のSSI発生率を比較し、合成吸収糸使用の有効性を検討する。これまでに、上部消化管、下部消化管、肝、膵の臓器別に吸収糸群、非吸収糸群の目標症例数を設定し、2年間の症例登録期間を経てSSI発生率を比較する。effect size（2 群間の治療効果の差）を推定し、将来の大規模臨床第Ⅲ相試験を実施するためにランダム化臨床第Ⅱ相試験を行う。主要評価項目を手術部位感染(SSI)の総発生率とし、副次評価項目は部位別(表層、深部、臓器体腔)感染発生率、SSI発生後治癒確認までの日数、術後在院日数とする。胃切除術270例、大腸切除術270例、肝切除術320例、膵頭十二指腸切除術290例　合計1150例を設定し、2年間の症例登録期間を経てSSI発生率を比較する無作為化臨床第Ⅱ相試験を行う。試験プロトコールの作成の中で、症例の選択基準、除外基準、SSI防止に関する予防策の統一など、試験結果の精度に関する議論を十分に重ねてきた。生物統計家により登録症例数設計を行い、胃切除術270例、大腸切除術270例、肝切除術320例、膵頭十二指腸切除術290例　合計1150例を計画した。インターネットを利用した登録システムであるEDCシステムを準備し、平成21年2月16日より症例登録を開始した。平成22年3月10日現在、胃：271例、大腸228例、肝臓：337例、膵臓：247例、合計1083例が登録され、胃、肝臓は症例登録を終了し、試験観察化期間も全症例終了している。現在、この２臓器に関して、症例報告データを集計し、データマネジメント作業の上、データ固定を目指している。大腸、膵臓に関しても、平成22年5月には、登録終了予定である。臨床試験の性格上、結果は症例登録終了、結果解析後である。臓器別で進捗に差が出ているが、研究予定期間の３年以内には最終解析結果を出せる進捗状況である。

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A. 研究目的

欧米先進諸国では、消化器手術において手術用絹糸は使用されなくなっている。これは、合成吸収糸が発売された当初、多くの動物実験と臨床試験において絹糸と合成吸収糸の比較試験が行われ、皮下、腹壁縫合における合成吸収糸の有効性が証明された結果である。米国CDC(Center for disease control and prevention)の手術部位感染(SSI)防止ガイドライン中に多くの参照文献として掲載されており、ガイドラインの本文には、絹糸の存在下では感染の危険性が増加すると記載されている。手術創に絹糸が存在すると、細菌が付着しやすく感染を助長する(Elek et al.,Br J Exp Pathol 1957)。一方わが国では、依然として手術用絹糸が広く使用されている。皮下・腹壁縫合については、欧米において絹糸と合成吸収糸の無作為化臨床試験とメタアナリシスで、合成吸収糸の有効性が確立している(Weilland et al,Am J Surg 1998;Riet,et al,Br J Surg 2001)が、腹腔内で合成吸収糸を使用することで手術部位感染(SSI)が減少するというエビデンスは確立していない。本臨床試験の目的は、以下の２点である。

1) CDCにより推奨されている周術期の患者管理を行い、消化器手術の腹腔内での絹糸使用群と全合成吸収糸使用群のSSI発生率を比較し、合成吸収糸使用の有効性を検討する。

2) 腹腔内感染発症例において、絹糸使用群と合成吸収糸使用群の治癒期間について比較検討する。

これまでに、九州大学第二外科にて腹腔内での結紮・縫合糸に関する調査を盛り込むSSIサーベイランス(総数903例)がプロスペクティブに施行され、特に大腸手術(386例)において吸収糸群のSSIが絹糸群に比べて有意に低率であったと報告し(吸収糸群13.9%、絹糸群22.4% P=0.03)、吸収糸の有用性を示唆している(Watanabe et al,Surgery Today, 2008)。しかしながら、腹腔内の絹糸使用と合成吸収糸使用における手術部位感染についての臨床比較試験は行われておらず、本臨床試験でエビデンスの創出を図る。絹糸がSSI発生の点で劣っていることを示唆する報告は散見されるが、腹腔内での吸収糸・非吸収糸の使用とSSIに関するmega-RCTは存在せず、どの種類の消化器手術で吸収糸使用がどれくらい有用なのか、本臨床試験で明らかにする意義は大きい。

外科術後感染症で最も多い感染症が手術部位感染(SSI)であり、その発生は患者満足度を低下させるだけでなく入院期間の延長を伴い、医療経済上も大きなマイナスインパクトを与える。本研究は開腹消化器手術における吸収糸の使用が手術部位の感染症発症を抑えるという効果の臨床的エビデンス創出に関する研究である。本研究で手術部位感染症が予防できれば術後の合併症を減らすことが可能となり、消化器手術を受ける国民の医療が安全に行え、在院日数が短縮し、通常の包括医療で済む患者の割合が増す。本臨床試験の結果は、科学的な根拠に基づいた質の高い医療の国民への提供と医療経済の効率化に貢献できると考える。

B. 研究方法

上部消化管、下部消化管、肝、膵の臓器別に吸収糸群、非吸収糸群について目標症例数を設定し、２年間の症例登録期間を経てSSI発生率を比較する。effect size(2群間の治療効果の差)を推定し、将来の大規模臨床第Ⅲ相試験を実施するために臨床第Ⅱ相試験を行う。

「消化管外科手術における合成吸収糸使用の手術部位感染抑制効果に関する多施設共同並行群間無作為化比較試験」

「肝切除および膵頭十二指腸切除における合成吸収糸使用の手術部位感染抑制効果に関する多施設共同並行群間無作為化比較試験」

上記二つの臨床第Ⅱ相試験を行う。

(1) 研究計画および方法

1) 多施設共同並行群間無作為化比較試験

2) 試験材料：滅菌済み手術用絹糸、合成吸収性縫合糸(Polyglactin910,Polydioxanone)

3) 対象疾患：本研究の対象疾患は、以下の通りとする。

胃部分切除術：胃全摘術

合成吸収糸群135例、絹糸群135例

結腸・直腸切除術：

合成吸収糸群135例、絹糸群135例

肝切除手術：

合成吸収糸群160例、絹糸群160例

膵頭十二指腸切除手術：

合成吸収糸群145例、絹糸群145例

割り付け因子

消化管：施設、術式、腹腔鏡補助

肝膵：施設、　　(肝) 肝硬変の有無

　　(膵) 糖尿病の有無

4) 周術期管理法を下記の項目について規定する。

術前の患者準備、抗菌薬の予防投与を統一する。

手術手技：筋膜には合成吸収糸を使用し、閉鎖式(吸引)ドレーンを用いる。

術後の管理法：手術部位感染が疑われた場合には必ず細菌培養検査を提出する。

5) 評価項目

主要評価項目：手術部位感染(SSI)の総発生率

副次評価項目：部位別(表層、深部、臓器体腔)

感染発生率、SSI発生後治癒確認までの期間術後在院日数

6) 手術部位感染(SSI)の評価基準：CDCによる手術部位感染の定義に準拠

①表層切開部創感染

②深部切開部創感染

③臓器体腔創感染

7) 登録の手順

施設登録及び症例登録は、データセンターにおける中央登録制とする。

8) 症例登録期間：平成21年2月16日～

追跡終了日：最終症例登録の1ヶ月後

全研究期間：2年1ヶ月

(2) 研究体制

研究代表者および研究分担者の施設で対象患者の登録をEDCシステムを用いて登録・データセンターに行う。無作為化割付された術式を行い、決められた術後管理を行い手術部位感染率を比較する。割り付け結果の施行確認を手術室で第三者施行。通常直接介助の看護師を想定する。SSIの判定は、割り付け結果を知らないSSI判定能力のある主治医・術者以外の医療者が行う。（他の外科医、ICTリンクナース、ICTメンバー）

(倫理面への配慮) 本試験に関与するすべての者は「世界医師会ヘルシンキ宣言」、および「臨床研究に関する倫理指針」に従う。

説明文書・同意書(様式)および同意撤回書は試験責任医師が作成する。また、作成した説明文書・同意書(様式)は試験開始前に所属する医療機関の倫理審査委員会に提出し、その承認を得る。試験に携わる関係者は被験者の個人情報保護に最大限の努力をはらう。

データセンターが医療機関へ照会する際の被験者の特定は、試験責任医師および試験分担医師が管理する被験者識別コードまたはデータセンターが発行した登録番号を用いて行う。原資料の直接閲覧を行ったモニタリング担当者、監査担当者、規制当局の担当者などは、そこで得られた情報を外部へ漏洩しない。

主任研究者等が試験で得られた情報を公表する際には、被験者が特定できないよう十分に配慮する。

C. 研究結果

＜プロトコル＞

平成20年度の当該研究課題「消化器外科手術における合成吸収糸使用の手術部位感染抑制効果に関する多施設共同並行群間無作為化比較試験」の採択に際して、当研究のプロトコルの細部に関して推敲を重ねてきた。平成20年9月9日に東京で

開催された班会議において、研究代表者、研究分担者により具体的なプロトコル内容について審議を行い、最終的には平成20年11月6日にプロトコルが完成した。各研究分担者へ発送し、現在、各研究分担者施設の倫理審査委員会の承認を得た。また審議の過程で、消化管領域の参加施設が１１施設、肝・胆・膵領域の参加施設が１７施設へと拡大し、より迅速な症例の集積が可能となった。

＜症例登録およびデータマネジメント＞

上記プロトコルの検討・確定とともに、臨床試験遂行にあたり症例登録・データマネジメントを外部機関に委託することを決定した。データマネジメント部分を研究担当者から切り離し、データの質および信頼性を確保する目的である（品質保証・管理）。イーピーエス株式会社と契約を進め、Ｗｅｂシステム（ＥＤＣシステム）による症例登録、データ収集管理構築を鋭意進めている。また、臨床試験のプロトコルは大学病院医療情報ネットワーク（UMIN）「臨床試験登録システム」に登録を行った。

上記進捗状況を踏まえて平成21年2月16日から症例登録、試験治療を開始した。平成22年3月10日現在、胃：271例、大腸228例、肝臓：337例、膵臓：247例、合計1083例が登録された。大腸が登録の進捗が遅いために、平成21年8月研究協力施設を募集し、17施設の参加を得て、順調に登録が進んだ。胃、肝臓は症例登録を終了し、試験観察期間も全症例で終了している。現在、この２臓器に関して、症例報告データを集計し、データマネジメント作業の上、データ固定を目指している。大腸、膵臓に関しても、平成22年5月には、登録終了予定である。

D. 考察

臨床試験の性格上、結果は症例登録終了、結果解析後である。

E. 結果

臓器別で進捗に差が出るが、研究予定期間の３年以内に最終解析結果を出せる進捗状況である。

F. 健康危険情報

特記すべきことなし。

G. 研究発表

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研究成果の刊行に関する一覧表

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著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
	該当なし						

雑誌

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ORIGINAL ARTICLE

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Systemic use of antibiotics does not prevent postoperative infection in elective colorectal surgery: a randomized controlled trial

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Abstract We assessed the clinical impact of the systemic use of antibiotics on postoperative infection in colorectal surgery. Perioperative administration prevents postoperative infection: a statement which is based on the results of five randomized controlled trials performed in the 1970s and 1980s. Our study design was a randomized controlled trial. We created two groups, one using the systemic antibiotic cefotiam (CTM), and the other using no antibiotic as the control. The primary end point was the overall postoperative infection rate. There were 100 patients assigned to this study. The patients were divided into two groups; the control group consisted of 51 cases and the CTM group had 49 cases. The backgrounds of the patients in the two groups were not significantly different. The overall postoperative infection rate was 28/51 (54.9%) in the control group and 25/49 (51.0%) in the CTM group. The surgical site infection (SSIs) (superficial, deep, and space/organ) were 23/51 (45.1%) in the control group and 20/49 (40.8%) in the CTM group. No significant difference was observed between the CTM group and the control group regarding postoperative infection after elective colorectal surgery.

Key words Colorectal surgery · Postoperative infection · Systemic use · Antibiotic · Randomized controlled trial · Prophylaxis

Introduction

An antimicrobial agent must be administered at the location of an infection. However, if prophylactic antibiotics are administered to the locus where no infection exists, will they prevent infection? In order to address this question, we must reconsider the administration of antibiotics that are used to prevent postoperative infection. The conclusion that "perioperative administration prevents postoperative infection" was based on the results of five randomized controlled trials performed in the 1970s and 1980s.[1–5] However, both the antimicrobial agents and postoperative care have changed greatly in the past 30 years. As a result, we decided to investigate whether the "perioperative administration of antibiotics can prevent postoperative infection" at the present day. Regarding the use of second-generation cephalosporin (cefotiam, CTM) as a prophylaxis of colorectal postoperative infection, we followed both the Japanese and the US guidelines.[6,7]

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Methods

The study design was a randomized controlled trial, which began in July 2002. Colorectal surgery was about to be performed for each patient, and informed consent had been obtained in writing from the patients preoperatively. We divided the patients into two groups, one of which received systemic antibiotics, while the other received no antibiotics and thus was used as a control. The study was carried out in two hospitals that were both affiliated to the Nihon University School of Medicine. The study was registered as a randomized controlled trial with university hospital medical information network (UMIN). The registration number was 000000870, and the study was entitled "The evaluation of a systemic antibiotic effect for colorectal surgery." The trial received the approval of the Ethics Committee. All the patients who had the operation had been diagnosed with colon cancer. This was a criterion for choice, and all other patients were excluded from the study. The subjects were any man or woman who had undergone either an open colectomy or a laparoscopic colectomy between the ages of 16 and 79 years.

The following groups were automatically excluded from the study.

1. Those who had had a total colectomy, a dirty or contaminated operation, an operation for a perforation, or an emergency operation.

2. Those who were 15 years old or younger, and those who were 80 years old or older.
3. Patients with serious complications (e.g., heart, lung, liver, kidney dysfunction, diabetes, a tendency to hemorrhage, etc.).
4. Patients with a preoperative infection.
5. Patients who had undergone long-term administration of adrenocortical hormones.

Duration and alterations of randomized controlled trials

1. We checked for signs of infection (fever, white blood cell count, and C-reactive protein), and if the patient had no infection we did not administer any antibiotics to either group after the 4th postoperative day.
2. If the patient had an infection, we administered the appropriate antibiotics to the patient at that time.

Sepsis followed the definition of systemic inflammatory response syndrome (SIRS), and SSI was assessed by the definition of the National Nosocomial Infections Surveillance (NNIS) system. We determined the presence of antibiotics by consulting the patient's family doctor.

We checked laboratory and chest X-ray results between the 3rd and 7th postoperative days, and examined a patient at any time it was deemed necessary.

The criteria of postoperative infection were as follows:

1. Fever: over 38.0°C;
2. White blood cell count: over 12000/μl or less than 4000/μl;
3. C-reactive protein: over 10 mg/dl.

We started antibiotics in cases of infection that satisfied two or more of the conditions mentioned above. The final judgment occurred between the 10th and 14th postoperative days or at discharge.

Administrative procedures

In the antibiotic group, CTM was administered with a drip infusion before the skin incision. In cases where a long operation was needed, CTM was added every 3 h. From the 1st to the 3rd postoperative day, 1 g CTM was administered every morning and evening. In the control group, no antibiotic was administered. All patients agreed to this study arrangement, and approval was received from the Ethics Committee.

Entry and stratification

The sample size was set at 100 cases because the postoperative infection rate is normally expected to be around 20% when prophylactic antibiotics are used. Preoperatively, the patients were grouped according to the type of surgery (i.e., the colon or the rectum), according to age (i.e., either 60 years or older, or below 60 years), and those with a preoperative total protein volume of 6.5 g/dl or less.

Surveillance system

The surveillance data recorded were age, sex, diagnosis, total preoperative protein, American Society of Anesthesiologists (ASA) classification, date of operation, operative procedure, colostomy/closure, operating time, hemorrhage, transfusion, type of postoperative infection, and date of outbreak.

Prophylaxis procedures before, during, and after the operation

The following procedures were carried out routinely for all patients.

Before the operation. A 500-ml saline enema 2 days before the operation, fasting and a laxative 1 day before the operation, and a glycerin enema on the day of the operation. Standard mechanical preparations were enforced for all patients

During the operation. Employment of a wound protector, absorbable string against muscle fascia, peritoneum sutures, and suction drainage. Change of surgical globe. The intra-abdominal cavity was washed at the end of the operation. Use of a double-stapling technique for auto-sutures, and povidone–iodine sterilization for the anal side of the anastomotic region in a low anterior resection.

After the operation. Employment of a hydrocolloid dressing and no wound sterilization. The nasogastric tube was pulled out on the 1st or 2nd postoperative day.

Statistical analysis

The clinical and surgical data were compared between the two groups using the *t*-test/Fisher's extra test. *P* values of < 0.05 were considered to be statistically significant. An analysis was carried out on an intention-to-treat basis using the statistical package for social science. The effect of prophylactic antibiotics on primary outcomes was tested using a two-tailed Pearson χ^2 test.

Results

One hundred patients were assigned to this study from July 2002 to January 2007. Seven patients could not be included, but were analyzed by the rules of intention to treat, and the patients were divided into two groups. The control group consisted of 51 cases and the CTM group had 49 cases (Fig. 1). Of these cases, 56 were men and 44 were women. There were no differences in age, preoperative total protein, or number of preoperative oral anticancer agents between the two groups (Table 1). The operative procedures were partial colectomy in 26 cases, low anterior resection in 14 cases, and abdominoperineal resection in 5 cases in the control

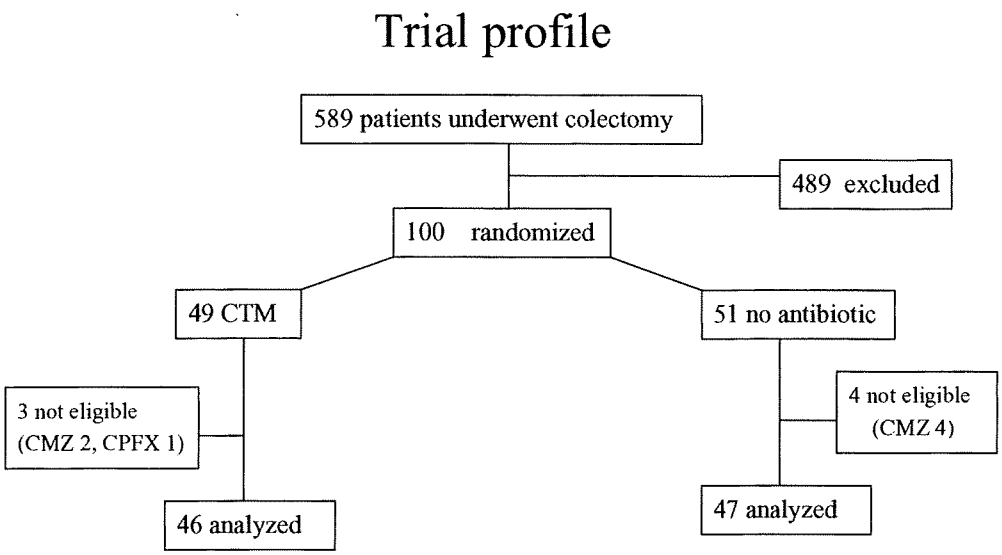

Fig. 1. Analysis was carried out on intention to treat. There were no cases of death during hospitalization

Analysis was carried out on intention to treat. There were no cases of death during hospitalization

Table 1. Baseline characteristics

	CTM (49)	Control (51)
male/female	32/17	24/27
age	63 (37–79)	64 (41–79)
colon/rectum	28/21	31/20
total protein (g/dl)	6.7 (5.6–7.7)	6.8 (5.8–8.0)
preop, oral anti cancer agent (UFT or UFT/UZEL) case	12	12
ASA score	1.8 (1–3)	2.1 (1–3)
post surgical hospital stay	24 (10–68)	21 (9–66)

Table 2. Operative procedure

	CTM (49)	Control (51)	P value
Type of Surgery			
partial resection	21 (7)	26 (13)	N.S
low ante, resection	15 (10)	14 (7)	N.S
hemicolectomy	5 (0)	6 (3)	N.S
abdominoperineal	8 (8)	5 (5)	N.S
* laparoscopic resection	3 (2)	4 (1)	N.S
Combined resection/procedure			
colostomy/closure	4 (2)	3 (2)	N.S
liver	1	(1)	N.S
stomach	2	0	N.T
urinal bladder	0	1	N.T
adrenalectomy	0	1	N.T
myoma enucleation	0	1	N.T

Parenthetic number is the postoperative infection number regarding type of surgery and combined resection/procedure
The parentheses under the type of surgery show the postoperative infection case numbers

group, and partial colectomy in 21 cases, low anterior resection in 15 cases, and abdominoperineal resection in 8 cases in the CTM group (Table 2). There were the same number of right and left hemicolectomies in both groups. The organs of combined resection and colostomy/closure are shown in Tables 1 and 2. There was no difference in the duration of postsurgery hospital stay between the two groups. The type of surgery, age, and preoperative total protein were stratified preoperatively, and there were no significant differences in postoperative infection between the two groups.

The overall postoperative infection rate was 28/51 (54.9%) in the control group and 25/49 (51.0%) in the CTM group, and SSIs (superficial, deep, and space/organ) were 23/51 (45.1%) in the control group and 20/49 (40.8%) in the CTM group. There were 15 cases of superficial SSI in the control group, but the bacteria were not detected in one case. In the CTM group, there were only three superficial SSIs. There were significantly more instances of superficial SSIs in the control group than in the CTM group. All the abdominal abscesses (space/organ SSI) were caused by leakage in the anastomosis region in both groups. Remote infection (RI) occurred in nine cases in both groups. In the control group, there were three respiratory tract infection (RTI), urinary tract infection (UTI), and sepsis cases, but in the CTM group there were six RTI cases. There were five anastomotic leakage cases in the control group and seven in the CTM group. Except for abdominal abscesses and RI infections, there were no significant differences, even from the total SSI, between the two groups (Table 3).

The presence of numerous anaerobes was detected at the focus of SSIs. Out of 66 strains in the control group, 27 were anaerobes, and of 70 strains in the CTM group, 30 were anaerobes. Anaerobes accounted for more than 40% of all detected strains in both groups. Aerobic gram negative rods (GNR) and gram positive cocci (GPC), and various anaerobes and fungi were detected from other specimens (Table 4).

Discussion

Since the discovery of penicillin by Fleming, antibiotics have been used for the treatment of various infections. An

Table 3. Postoperative Infection

Overall	CTM (49) 25/49 (51.2%)	Control (51) 28/51 (54.9%)	P = 0.8293* SSI+RI
SSI	20 (40.8%)	23 (45.1%)	
Superficial	3	14	
Deep	10	4	
space/organ	7	5	
*anast, leakage	7	5	
RI			
RTI(event)	6	3	(respiratory tract infection)
UTI	1	3	(urinary tract infection)
Sepsis	1	3	
Colitis	1	2	
BTI	0	1	(biliary tract infection)
CV cathe,inf,	1	1	(central venous catheter infection)

*(including duplicate cases)
There was no significant in SSI and RI infection rate between the CTM group and the control group, but it is supposed that RI rate of the control group is greater than the CTM group

Table 4. Detected organisms

	CTM (49)	Control (51)
Pus		
anaerobe	30	27
aerobe	40	39
Sputum		
GNR	7	3
GPC	2	1
C.albicans	1	2
Blood		
S.marcescens	1	1
S.aureu	0	1
anae.GPR	0	1
Urine		
E.faecalis	0	2
Entero.spp	1	0
S.maltophilia	1	0

Detected rate of anaerobes of both groups accounted for over 40% of SSI. Methicillin resistant *Staphylococcus aureus (MRSA)* was only one strain of all of the SSIs

antibiotic inhibits bacteria in the locus where the infection is present, but acquired resistance against antibiotics and microbial alternation can also occur after the administration of antibiotics.[8] Can antibiotics be used as prophylaxis to prevent infection? To address this question, a randomized controlled trial was performed in the 1970s and 1980s between a systemic-use group and a control group after an operation, and the results showed that the postoperative infection rate in the antibiotic group was lower than that in the control group.[1–5] We accepted this result, and antibiotics were also used preoperatively in preparation for bowel operations. The effectiveness of such treatment has been reported.[9–14] However, postoperative infection did occur even when we administered prophylactic antibiotics, and the organisms detected from SSIs showed resistance to the antibiotics.[15] In their 1999 guidelines,[6] the Center for Disease Control and Prevention (CDC) states that "antimicrobial prophylaxis does not pertain to prevention of SSI caused by postoperative contamination." Will the infection rate reported in some documents thus confirm the effectiveness of antibiotics as a preventive treatment? To elucidate this point, it was necessary to set up a control group in which no antibiotics were used, and then compare the postoperative infection results for the group receiving antibiotics with those of the one that did not receive them. Nichols[16] insisted that antibiotic administration needed to be continued for 72 h in order to restore a wound. We agree with this approach, and therefore we administered an antibiotic for 3 days after each operation. We do not currently perform the chemical preparation because postoperative methicillin-resistant *Staphylococcus aureus* (MRSA) colitis occurred frequently in the first half of the 1990s and the latter half of the 1980s. The CDC recommended a preoperative oral antibiotic, and emphasized the effect of prophylaxis. However, this is controversial because Wren et al.[17] reported that oral nonabsorbable antibiotics resulted in a higher rate of *Clostridium difficile* infection, and Espin-Basany et al.[13] recommended that oral antibiotics should not be used prior to colorectal surgery. In this randomized controlled trial, no significant difference was found for the postoperative infection rate between the 51 people in the control group and the 49 people in the CTM group. It seems that these results can be interpreted as indicating that it was not effective to use CTM systemically for the prevention of postoperative infection in patients undergoing colorectal resection. We set up very precise criteria for postoperative infection, and checked all wounds meticulously. Accordingly, the postoperative infection rate was high. There was no difference between groups in total SSIs, but the infection rate was lower in the CTM group for superficial SSIs. From this result, we believe that the administration of an antimicrobial agent should be considered very carefully.

Anastomotic leakage was present in 7 cases in the CTM group, but the inner 6 were rectal cases. In all these 6 cases, anastomosis was carried out by the double-stapling technique (DST), but it seemed that those surgeons had not become accustomed to the anastomotic apparatus. However, 4 out of 5 cases in the control group were colon cases, and because they were difficult they were assumed to be more suitable for Albert–Lemberrt hand sutures.

Laparoscopic surgery causes low levels of stress, and is said to result in few cases of postoperative infection. Four patients in the control group and 3 patients in the CTM group underwent laparoscopic surgery. Postoperative infection was present in one out of 4 cases in the control group, and in 2 out of 3 cases in the CTM group, but these numbers are very small, and any comparison of postoperative infection rates between conventional and laparoscopic surgery is very difficult. In the future, it will be necessary to check the postoperative infection rates for laparoscopic surgery only. We compared the results of this study with those of previous RCT studies.

We could only find one previous study which was similar to ours and which investigated postoperative infection after the administration of a single antibiotic,[1] but in that study they evaluated only 32 colorectal cases. According to the findings of four other studies in the literature, in general 2 or 3 antibiotics or chemical preparations tend to be used systematically before surgery. As a result, it is difficult to compare the findings of our study with those of previous studies since most other studies used multiple antibiotics. Therefore, we believe that our findings are unique. Regarding the excluded cases, there were three examples in the CTM group and four examples in the control group. Most of the reasons for an exclusion were a misunderstanding. However, in one case in the CTM group, severe nausea developed during administration on the 1st postoperative day, so the patient was excluded and given another drug (with a grade 2 side effect). Apart from such complications, no grave incidents (such as a death) occurred during this study period. Regarding the length of the postsurgical hospital stay, there was no significant difference between the control group and the CTM group. We compared postsurgical hospital stays between the group of postoperative infection-positive cases and the group with no infection in these 100 cases, but no difference was found. It is therefore presumed that postoperative infection was minimal. It is very difficult to make general comparisons between Japan and the USA regarding postoperative hospitalization owing to the fact that all Japanese people have universal health insurance. In addition, the hospital stay for most patients tends to be longer in Japan since such costs are covered by the health insurance system. A large number of postoperative wound infections were observed after abdominoperineal resections. We separated the rectum and sigmoid colon at the inferior border of the sacral bone with an air-contrast enema, but according to the report of the COLO group of National Nosocomial Infections Surveillance (NNIS), no clear border has yet been established between colon and rectal operations. As a result, we should be careful to distinguish between the colon and the rectum when reporting on colorectal surgery.[18]

Conclusion

Based on the above findings, no significant difference was observed between the CTM group and the control group regarding postoperative infection after colorectal surgery.

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ORIGINAL ARTICLE

Is an estimation of physiologic ability and surgical stress able to predict operative morbidity after pancreaticoduodenectomy?

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Abstract
Background Mortality rates after pancreaticoduodenectomy (PD) are below 4% in high volume centers, although morbidity rates still remain high. Therefore, it is important to clarify a predictor associated with operative morbidity after PD. The estimation of physiologic ability and surgical stress (E-PASS) score has been developed for comparative audit in general surgical patients.
Objective To evaluate whether E-PASS scoring system could predict the occurrence of complications after PD.
Methods We performed retrospective analysis of 69 patients (42.0% pancreatic cancer, 31.9% bile duct cancer, and others) who underwent PD using the E-PASS as a predictor of morbidity. Correlations between the incidence rates of postoperative complications and the preoperative risk score (PRS), surgical stress score (SSS) and comprehensive risk score (CRS) of the E-PASS scoring system were evaluated.
Results Of the 69 patients 30 (43.5%) experienced a total of 54 postoperative complications. All E-PASS scores, especially PRS and CRS were significantly higher in the patients with postoperative complications than in the patients without complication. The complication rate gradually increased as the PRS, SSS and CRS score increased. Under receiver operating characteristic analysis, if a cut-off point of CRS was 0.75, sensitivity and specificity for the prediction of operative morbidity after PD was 80.0 and 79.5%, respectively. Neoadjuvant chemotherapy and intraoperative radiation therapy (IORT) did not influenced on operative morbidity after PD.
Conclusion E-PASS scoring system is useful to evaluate for morbidity after PD. Neoadjuvant chemotherapy and IORT could be adapted without significant extra risk for surgical complication.

Keywords E-PASS scoring system · Pancreaticoduodenectomy · Complications

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Introduction

Mortality of pancreaticoduodenectomy (PD) has decreased to below 4%, but the complication rate remains high, between 30% and 60%, despite the advances of surgical technique and perioperative care [1–10]. The majority of perioperative complications are not life threatening, although they amount to increased length of hospital stay and cost, re-admission for care, and delay in adjuvant therapy. Thus it is important to evaluate predictive and intra-operative risk factors associated with operative morbidity after PD.

Haga et al. [11] devised and validated the estimation of physiologic ability and surgical stress (E-PASS) scoring system for risk stratification of patients undergoing elective general gastrointestinal (GI) surgery. Furthermore, it has been externally validated in a different geographical setting from where it was originally developed and has been shown to be reproducible in accurately predicting outcome following elective GI surgery [12]. This system comprises a preoperative risk score (PRS), a surgical stress score (SSS), and a comprehensive risk score (CRS), which is calculated from the PRS and SSS. E-PASS was based on

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the premise that morbidity and mortality rates can be correlated with the patient's physiologic risk and the surgical stress applied.

The aims of this study were to evaluate not only whether E-PASS scoring system could be useful for predicting postoperative complications in patients undergoing PD but also the influences of neo-adjuvant chemotherapy and Intraoperative radiation therapy (IORT) using E-PASS scoring system.

Patients and methods

Patients and treatments

Between April 2005 and December 2007, consecutive 69 patients underwent PD at Kumamoto University for periampullary malignant and benign diseases. Written informed consents were taken from all the patients before the treatment.

PD was performed with various extents of lymph node dissection according to the primary lesions. D2 and middle paraaortic lymph node dissection was performed in patients with pancreatic cancer [13]. D2 dissection of lymph nodes was performed in patients of bile duct cancer and papilla of Vater cancer [14]. IORT was adopted in 15 patients with pancreatic cancer. Following dissection, a dose of 30 Gy with 12 Mev electron beam radiation was administered to the operative field, as described previously [15–17]. In 24 patients with possible portal/superior mesenteric vein invasion, combined resection of the vein and reconstruction was performed. We adopted neoadjuvant chemotherapy in 23 patients with pancreatic cancer. They were received intravenous systemic infusion of gemcitabine (at a dose of 800 mg/m^2 on days 1 and 8) and continuous regional arterial infusion of 5-fluorouracil (at a dose of 125 mg/m^2 on days 1–5 and 8–12) from celiac artery for the neoadjuvant chemotherapy. They underwent PD after a rest for one week.

E-PASS scoring system

The equations of the E-PASS scoring system are shown in Table 1. The PRS is calculated using factors such as age, presence or absence of severe heart disease, severe lung disease, and diabetes mellitus, American society of anesthesiologists (ASA) physiological status classification, and performance status index defined by the Japanese society for cancer therapy [18], which is the same as that defined by the Eastern Cooperative Oncology Group. The performance status index was defined as follows: grade 0, conditions without symptoms that restrict social activities; grade 1, conditions with mild symptoms that restrict muscular labor but do not restrict walking or mild exertion; grade 2, conditions that require some physical assistance for daily living; grade 3, conditions that require frequent physical assistance for daily living; grade 4, conditions that require constant physical assistance. Patients in grade 2 are not in bed for more than half of the day, those in grade 3 are in bed for more than half of the day, and those in grade 4 are in bed all day long. The expected in-hospital mortality rate was estimated as $Y = -0.465 \pm 1.192(\mathrm{CRS}) \pm 10.91(\mathrm{CRS})^2$, according to a previous study [19].

Postoperative complication

According to our previous report about E-PASS in patients with esophageal cancer, postoperative complications were assessed according to the National Cancer Institute

Table 1 Equations for estimation of physiologic ability and surgical stress (E-PASS) scoring system

Preoperative risk score (PRS)

$= -0.0686 + 0.00345X_1 + 0.323X_2 + 0.205X_3 + 0.153X_4 + 0.148X_5 + 0.0666X_6$

Where X_1 is age, X_2 is presence (1) or absence (0) of severe heart-disease[a], X_3 is presence (1) or absence (0) of severe pulmonary disease[b], X_4 is presence (1) or absence (0) of diabetes mellitus, X_5 is performance status index[c] (0–4), X_6 is American society of anesthesiologists physiological status classification.

Surgical stress score (SSS)

$= -0.342 + 0.0139X_1 + 0.0392X_2 + 0.353X_3$

Where X_1 is blood loss/body weight (ml/kg), X_2 is operation time (h), X_3 is extent of skin incision (0 = minor incision for laparoscopic or thoracoscopic surgery, 1 = laparotomy or thoracotomy alone, 2 = both laparotomy and thoracotomy).

Comprehensive risk score (CRS)

$= -0.328 + 0.936\ (\mathrm{PRS}) + 0.976(\mathrm{SSS})$

[a] Severe heart disease was defined as heart failure of New York Heart Association Class III or IV or severe arrhythmia requiring mechanical support

[b] Severe pulmonary disease was defined as a condition with a %VC <60% or a %FEV 1.0 < 50%

[c] Performance status index was based on the definition by Japanese society for cancer therapy

common terminology criteria for adverse events version 3.0 (NCI CTCAE v.3.0) including pancreatic fistula [20, 21]. In this study, adverse events of grade 2–5 within 30 days after surgery were expediently judged as postoperative complications. Adverse events of grade 1 were excluded, because no medical treatment was required. Overall complication rate was defined as the rate of patients with at least one complication. Operative and hospital mortality was also defined as death within 30 days after surgery, and during the hospitalization, respectively.

Statistical analysis

We used the chi-squared test, Fisher's exact test and Mann–Whitney's U test for statistical analysis as appropriate. Receiver operator characteristic (ROC) curves were plotted to assess the extent to which CRS, PRS and SSS could accurately predict morbidity, and the area under the receiver operator curve (AUC) was used as a measure of overall diagnostic accuracy. Statistical difference was considered to be significant at $P < 0.05$.

Results

Patients' characteristics

Study subjects included 34 female and 35 men. The median age of the patients was 66.4 years ranging from 51 to 81 years old. Fifty-eight patients (84.1%) had malignant disease, including pancreatic cancer in 29, bile duct cancer in 20, papilla of Vater cancer in five, malignant intraductal papillary mucinous neoplasm (IPMN) in three, and metastatic pancreatic tumor in one. The remaining 11 patients (15.9%) had benign diseases, including benign IPMN in six, islet cell tumor in four, and duodenal carcinoid in one.

Morbidity and mortality associated with pancreaticoduodenectomy

Of 69 patients 30 (43.5%) experienced a total of 54 postoperative complications. The complications are listed in Table 2. There were two patients with hospital death. The overall mortality rate was 2.9%. One patient, who underwent PD and IORT combined with resection of portal vein for pancreatic cancer, suffered from intra-abdominal hemorrhage from pseudo-aneurysm caused by pancreatic fistula. The other patient, who underwent PD for papilla of Vater cancer, suffered from fungemia, renal failure and disseminated intravascular coagulation. Pancreatic fistula was the most frequent complication (23.2%) in this study.

Table 2 Postoperative complications

Complications	*n*	Death
Pancreatic fistula	16	0
Wound infection	12	0
Delayed gastric emptying	5	0
Abdominal abscess	5	0
Intraabdominal bleeding	3	0
Enterocolitis	2	0
Delirium	2	0
Sepsis	2	2
Intestinal fistula	2	0
Ascites	2	0
Others	3	0
Total	54	2

Correlation between the E-PASS scores and postoperative complications

All E-PASS scores, especially PRS and CRS were significantly higher in the patients with postoperative complications than in the patients without complication (Fig. 1). The expected mortality rate estimated by E-PASS scoring system in the patients with postoperative complications was 8.0%. The CRS of the former patient with hospital death was 0.87, and that of the latter was 1.39.

The relation between the PRS, SSS and CRS and complication rate is shown in Fig. 2. The complication rate gradually increased as the PRS, SSS and CRS increased. There was no probability of complications, when the PRS lower than 0.25 and/or CRS lower than 0.5. On the other hand, the PRS and/or CRS greater than 1.0 revealed very high probability of postoperative complications (100.0% and 88.9%).

Receiver operating characteristic analysis of the E-PASS scores for morbidity

The E-PASS scores showed good predictive power for morbidity associated with PD, which was demonstrated by wide areas under the receiver operating characteristic (ROC) curve in Fig. 3. The AUC in PRS was 0.87 (95% confidence interval [CI] 80–0.96). The AUC in SSS was 0.71 (95% CI 58–83). The AUC in CRS was 0.88 (95% CI 80–96). The ROC curves show the strong relation between each of PRS, SSS, CRS, and morbidity. Figure 3 showed various cut-off points on each graph. For CRS, a cut-point of 0.75 would give a decision rule that has approximately sensitivity of 80.0% and specificity of 79.5% for the prediction of morbidity (Fig. 3c).

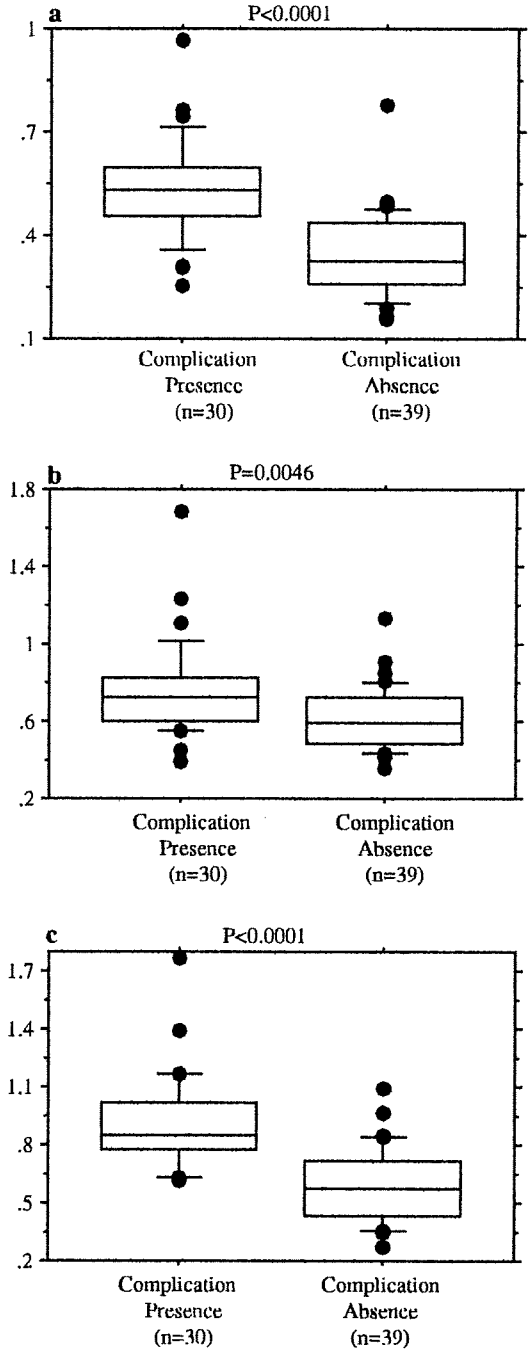

Fig. 1 Relationship between postoperative complications and E-PASS scores (**a** PRS, **b** SSS, and **c** CRS). *Boxes* show 95% confidence intervals

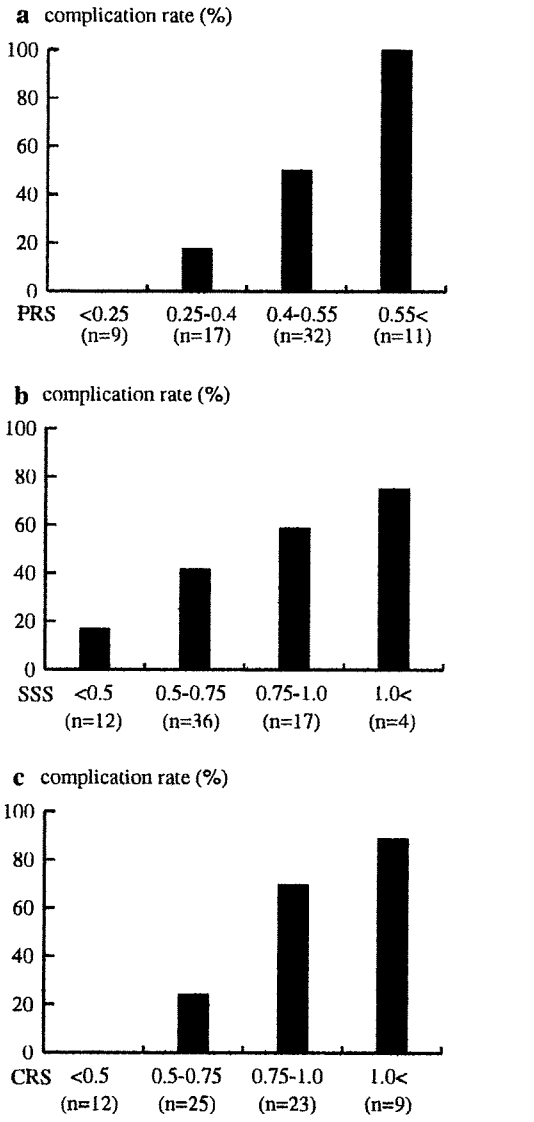

Fig. 2 Incidence of morbidity according to E-PASS scores (**a** PRS, **b** SSS, and **c** CRS)

Correlation between preoperative chemotherapy and postoperative complications

The relationship between preoperative chemotherapy and postoperative complications was shown in Table 3. There was no significant difference of incidence of postoperative complications between with and without preoperative chemotherapy. The relationship between preoperative chemotherapy and E-PASS scores was shown in Fig. 4. There was no significant difference in E-PASS scores between groups with and without preoperative chemotherapy.

Correlation between IORT and postoperative complications

The relationship between IORT and postoperative complications was shown in Table 3. There was no significant difference of incidence of postoperative complications between with and without IORT. The relationship between IORT and E-PASS scores was shown in Fig. 5. There was

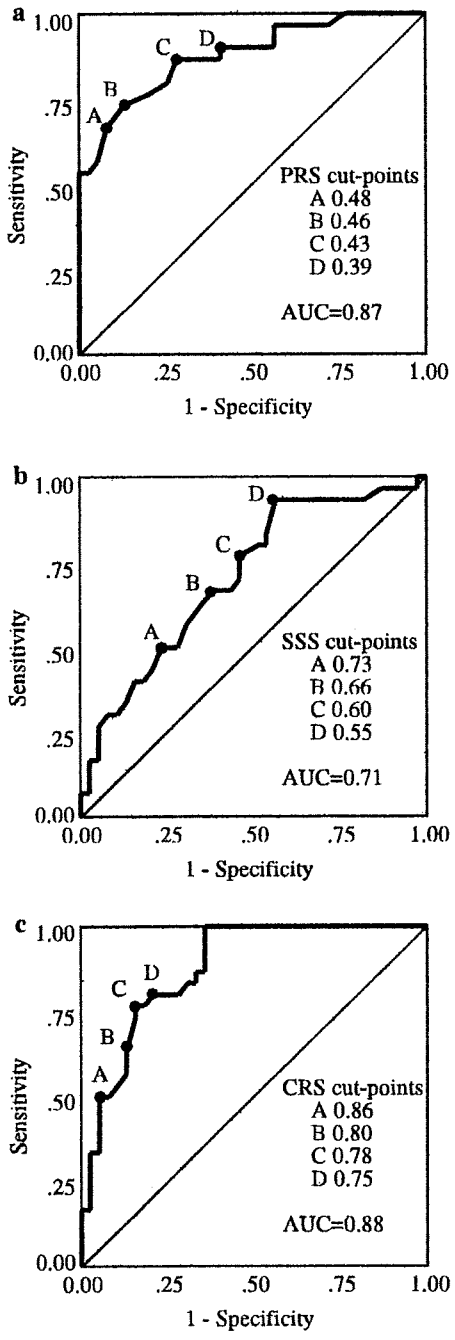

Fig. 3 ROC curves for morbidity, by the E-PASS scores (**a** PRS, **b** SSS, and **c** CRS)

no significant difference in E-PASS scores between groups with and without IORT.

Discussion

While pancreatic surgery is currently associated with low mortality rates, especially in high-volume centers, morbidity has been considered remains high. The morbidity rate of 43.5% after PD in this study is also comparable with the reported morbidity rates previously [1–10, 22, 23].

Table 3 Relationship between preoperative chemotherapy, IORT and postoperative complications

		Patients	Complications		*P* value
			Presence	Absence	
Preoperative chemotherapy	Presence	23	9	14	0.7467
	Absence	46	21	25	
IORT	Presence	15	5	10	0.5475
	Absence	54	25	29	

The E-PASS scoring system, which developed for the spectrum of general surgical audit, has been applied to the sub-specialties [12, 19, 21, 24, 25]. The system is easy to use, because required data could be retrieved from pre-anesthetic sheets and the operation notes. We applied the E-PASS scoring system to operative morbidity after PD in this study. Our results indicate that the strong correlation between PRS and incidence of postoperative complication. It could be useful for surgeons not only to predict operative morbidity after PD but also to inform patients about risk of complications in each patient before surgery. Although Tang et al. [24, 25] indicated good predictive power of E-PASS scores for both mortality and morbidity as demonstrated by high areas under the ROC curve in patients undergoing elective open AAA repair, ROC analysis of E-PASS scores in elective digestive surgery was not evaluated before. ROC analysis in this study indicated that CRS was more useful predictor of postoperative complication than PRS. Our results was comparable to the result indicated by Tang et al. [24, 25]. Surgeons could identify a high-risk group of morbidity just after surgery, because CRS could be quickly calculated immediately after PD. The mortality of 2.9% in the present study is comparable with the accepted mortality rate reported previously [1–7, 22, 23]. This was lower than the mortality of 8.0%, which was calculated by the E-PASS scoring system [19].

The leading complication in this study was pancreatic fistula. Previous studies have reported that a soft pancreatic texture is one of the most important predictors for postoperative pancreatic fistula [1, 5, 8, 10]. Pancreatic texture is not included in E-PASS scores. Pancreatic fistula may occur in patients with a soft pancreatic texture even if they have a low E-PASS score. We could not investigate a relationship between pancreatic texture and E-PASS scores, because our data about pancreatic texture of patients underwent PD was incomplete. Further study is necessary to investigate this problem.

We already reported that E-PASS scoring system was useful in predicting complications after elective

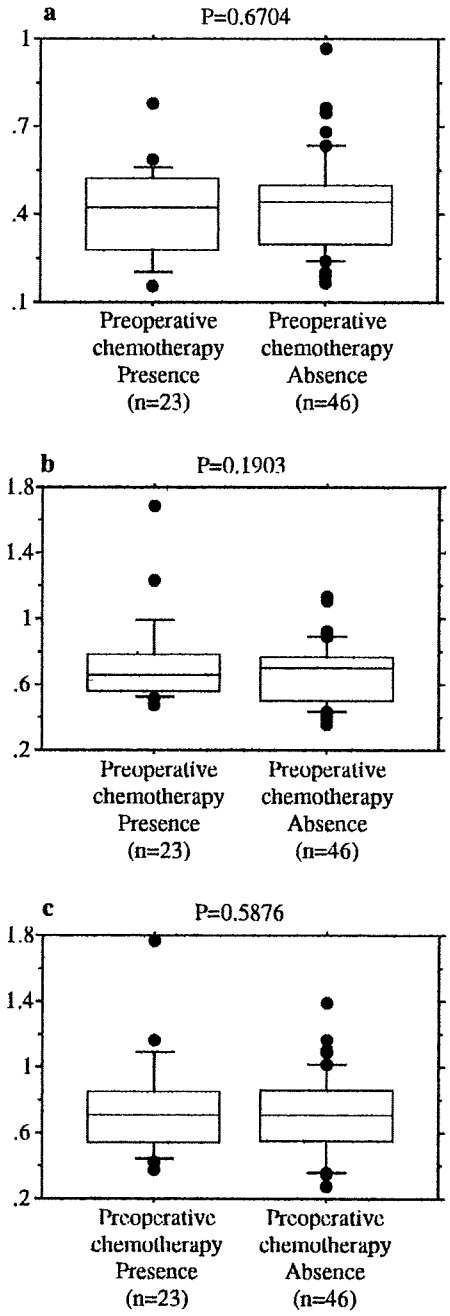

Fig. 4 Relationship between preoperative chemotherapy and E-PASS scores (**a** PRS, **b** SSS, and **c** CRS). Boxes show 95% confidence intervals

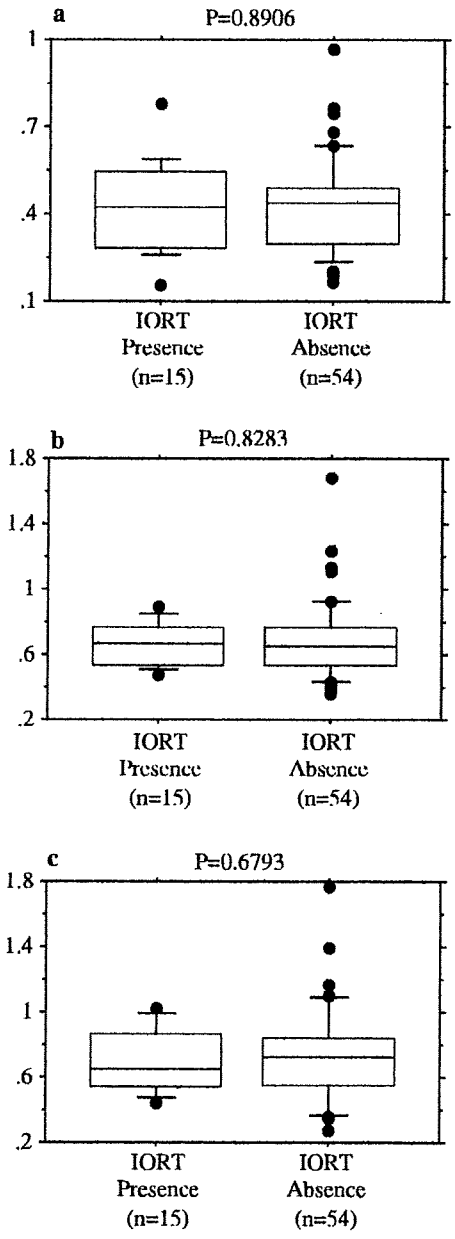

Fig. 5 Relationship between IORT and E-PASS scores (**a** PRS, **b** SSS, and **c** CRS). *Boxes* show 95% confidence intervals

esophagectomy for esophageal cancer [21]. In that study, the patients undergoing salvage esophagectomy with preoperative definitive chemoradiotherapy (CRT) had higher probability to have postoperative complications than those without preoperative CRT. Moreover, the SSS and CRS scores of patients with preoperative definitive CRT were significantly higher than those of patients without preoperative CRT. On the other hand, our present study indicated that there was no significant difference of morbidity rates and E-PASS scores between with and without preoperative chemotherapy and IORT. It indicated that preoperative chemotherapy and IORT could be adapted without significant extra risk for surgical complications.

In conclusion, E-PASS scoring system is a useful predictor associated with operative morbidity after elective PD. Neoadjuvant chemotherapy and IORT for periampullary carcinomas could be adapted without significant extra risk for surgical complication.

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A New Prediction Model of Postoperative Complications after Major Hepatectomy for Hepatocellular Carcinoma

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Key Words
Hepatocellular carcinoma · Hyaluronic acid · Remnant liver volume ratio · Postoperative complications

Abstract
Background/Aims: Serum hyaluronic acid (HA) concentrations reflect the degree of hepatic dysfunction and may have potential for predicting postoperative complications in a major hepatectomy for hepatocellular carcinoma (HCC). ***Methods:*** Serum HA concentrations and other conventional liver function tests were measured prior to major hepatectomies in 52 patients. Independent predictors for postoperative complications were analyzed and the discriminant equation was established and validated. ***Results:*** Postoperative complications occurred in 17 patients. Serum HA concentrations and the estimated remnant liver volume ratio (remnantVol%) were recognized as independent predictors for postoperative complications (OR 1.03, 0.85; CI 95% 1.01–1.06, 0.76–0.95; p = 0.006, 0.006; respectively) and produced the discriminant equation: logit = 4.15 + 0.03 × (HA) −0.16 × (remnantVol%). The value of the area under the curve of a receiver operating characteristic analysis was 0.92. If the cut-off of the logit value was set to 0, then the predictive accuracy was 0.88. The validation accuracy performed by a leave-one-out cross-validation method was 0.83. ***Conclusions:*** The constructed discriminant equation model consisting of the preoperative serum HA concentrations and estimated remnantVol% could be useful for predicting postoperative complications in a major hepatectomy for HCC.

Introduction

It is important to assess functional reserve of the liver when selecting treatment modalities for hepatocellular carcinoma (HCC) because most of the patients have underlying liver fibrosis or cirrhosis. Previously, various methods have been advocated to evaluate the functional reserve of the liver [1–4] and various algorithms based on the indocyanine green (ICG) retention test [5, 6] or the model for end-stage liver disease (MELD) score [7, 8] have been established to select surgical procedure. Our group has also reported on selection algorithms using various parameters [9]. According to these algorithms, patients without sufficient functional reserve have received locore-

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