the CDC guidelines,[4] monofilament sutures were recommended to reduce SSI.[4] We investigated the use of suture materials during abdominal wound closure, seromuscular approximation, and ligation. In all cases, absorbable sutures were associated with a lower incidence of SSI than non-absorbable sutures in intra-abdominal ligation ($P = 0.047$). This association was also evident in lower alimentary tract operations involving abdominal wound closure ($P = 0.019$), seromuscular suturing ($P = 0.035$), and ligation ($P < 0.001$). Although the differences were not significant, the same tendencies were observed in the upper alimentary tract procedures. Furthermore, multivariate analysis revealed that the odds ratio of absorbable suture material in seromuscular suturing was lower than that of non-absorbable suture material. These facts suggest the superiority of absorbable suture material in gastrointestinal surgical procedures to reduce the risk of SSI. A well-designed randomized controlled trial is needed to prove this assumption.

The development of a suture sinus, which is a superficial incisional SSI, often involves non-absorbable suture material during abdominal wound closure.[20,21] Thus, absorbable suture material is now widely used for abdominal closure in Japan. According to our surveillance protocol, absorbable sutures were used in 86% of the patients. Polydioxanone (PDS-II), an absorbable suture material, was used in 57% of these patients because of its durability and lower wound failure rate in comparison with polygractin 910 (Vicryl), and polyglycoric acid (Dexon).[22–24] However, braided nylon (Surgilon) and silk were still used in 13% of the patients in this study. Surgeons should be made aware of the evidence demonstrating a better surgical outcome associated with the use of absorbable sutures.[25]

In summary, our study showed that cleaner procedures and reduced blood loss can decrease the incidence of SSI following gastrointestinal surgery. The cessation of smoking for more than a month prior to surgery might also reduce the risk of an SSI, especially in patients undergoing elective lower alimentary tract surgery. Moreover, the use of absorbable suture materials might play an important role in reducing the incidence of SSI. Further study is needed to provide evidence on the use of specific types of intra-abdominal suture materials. In conclusion, SSI surveillance should be conducted and maintained in all hospitals to promote better surgical outcomes.

References

1. Emori TG, Gaynes RP. An overview of nosocomial infections, including the role of the microbiology laboratory. Clin Microbiol Rev 1993;6(4):428–42.
2. Smith RL, Bohl JK, McElearney ST, Friel CM, Barclay MM, Sawyer RG, et al. Wound infection after elective colorectal resection. Ann Surg 2004;239(5):599–607.
3. Cruse PJ. The epidemiology of wound infection: a 10-year prospective study of 62,939 wounds. Surg Clin North Am 1980; 60(1):27–40.
4. Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR. Guideline for prevention of surgical site infection 1999. Infection Control Hosp Epidemiol 1999;20(4):247–78.
5. Konishi T, Harihara Y, Morikane K. Surgical site infection surveillance (in Japanese). Nippon Geka Gakkai Zasshi 2004; 105(11):720–5.
6. Cox DR. Regression models and life tables. J R Stat Soc Ser B 1972;34:187–220.
7. Condon RE, Schulte WJ, Malangoni MA, Anderson-Taschendorf MJ. Effectiveness of a surgical wound surveillance program. Arch Surg 1883;118:303–7.
8. Haley RW, Culver DH, White JW, Morgan WM, Emori TG, Munn VP. The efficacy of infection surveillance and control programs in preventing nosocomial infections in US hospitals. Am J Epidemiol 1985;121:182–205.
9. Israelsson LA, Jonsson T. Overweight and healing of midline incisions: the importance of suture technique. Eur J Surg 1997; 163:175–80.
10. Sørensen LT, Hemmingsen U, Kallehave F, Wille-Jorgensen P, Kjægaard J, Møller LN, et al. Risk factors for tissue and wound complications in gastrointestinal surgery. Ann Surg 2005;241(4): 654–8.
11. Morikane K, Konishi T, Nishioka M, Tanimura H, Noguchi H, Kobayashi H. Experience of surgical site infection surveillance following general surgery (in Japanese). Kankyo Kansen 2001; 16(2):163–8.
12. Steichen FM. The use of staplers in anatomical side-to-side and functional end-to-end enteroanastomoses. Surgery 1968;64: 948–53.
13. Hoogendoorn JM, Simmermacher RK, Schellekens PP, van der Werken C. Adverse effects of smoking on healing of bones and soft tissues. Unfallchirurg 2002;105(1):76–81.
14. Belda FJ, Aguilera L, Garcia de la A, Alberti J, Vicente R. Supplemental perioperative oxygen and the risk of surgical wound infection: a randomized controlled trial. JAMA 2005;294(16): 2035–42.
15. Sørensen LT, Karlsmark T, Gottrup F. Abstinence from smoking reduces incisional wound infection: a randomized controlled trial. Ann Surg 2003;238(1):1–5.
16. Bluman LG, Mosca L, Newman N, Simon DG. Preoperative smoking habits and postoperative pulmonary complication. Chest 1998;113:883–9.
17. Pearce AC, Jones RM. Smoking and anesthesia: preoperative abstinence and perioperative morbidity. Anesthesiology 1984;61: 576–84.
18. Yamashita S, Yamaguchi H, Sakaguchi M, Yamamoto S, Aoki K, Shiga Y, et al. Effect of smoking on intraoperative sputum and postoperative pulmonary complication in minor surgical patients. Respir Med 2004;98(8):760–6.
19. B'erard F, Gardon J. Postoperative wound infections: the influence of ultraviolet irradiation of the operating room and of various other factors. Ann Surg 1964;160 Suppl 1:1–192.
20. van't Riet M, Steyerberg EW, Nellensteyn J, Bonjer HJ, Jeekel J. Meta-analysis of techniques for closure of midline abdominal incisions. Br J Surg 2002;89(11):1350–6.
21. Iwase K, Higaki J, Tanaka Y, Kondoh M, Yoshikawa M, Kamiike W. Running closure of clean and contaminated abdominal wounds using a synthetic monofilament absorbable looped suture. Surg Today 1999;29:874–9.
22. Hsiao WC, Young KC, Wang ST, Lin PW. Incisional hernia after laparotomy: prospective randomized comparison between early-absorbable and late-absorbable suture materials. World J Surg 2000;24:747–52.

23. Hodgson NCF, Maithaner RA, Østbye T. The search for an ideal method of abdominal fascial closure: a meta-analysis. Ann Surg 2000;231(3):436–42.
24. Schoelz DJ Jr, Coller JA, Veldenheimer MC. Closure of abdominal wounds with polydioxanone: a prospective study. Arch Surg 1988;123:72–4.
25. Hodgson NCF, Malthaner RA, Østbye T. Current practice of abdominal fascial closure: a survey of Ontario general surgeons. Can J Surg 2001;44(5):366–70.

J Infect Chemother (2009) 15:34–38
DOI 10.1007/s10156-008-0660-x

ORIGINAL ARTICLE

Takeshi Sato · Tadatoshi Takayama · Masashi Fujii
Keio Song · Minoru Matsuda · Tokio Higaki
Shunji Okada

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

Received: August 1, 2008 / Accepted: December 9, 2008

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]

T. Sato (✉) · T. Takayama · M. Fujii · K. Song · M. Matsuda · T. Higaki · S. Okada
Department of Digestive Surgery, Nihon University School of Medicine, 30-1 Oyaguchikamimachi, Itabashi-ku, Tokyo 173-8610, Japan
Tel. +813-3972-8111, (ext. 2471); Fax +813-3957-8299
e-mail: takesato@med.nihon-u.ac.jp

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

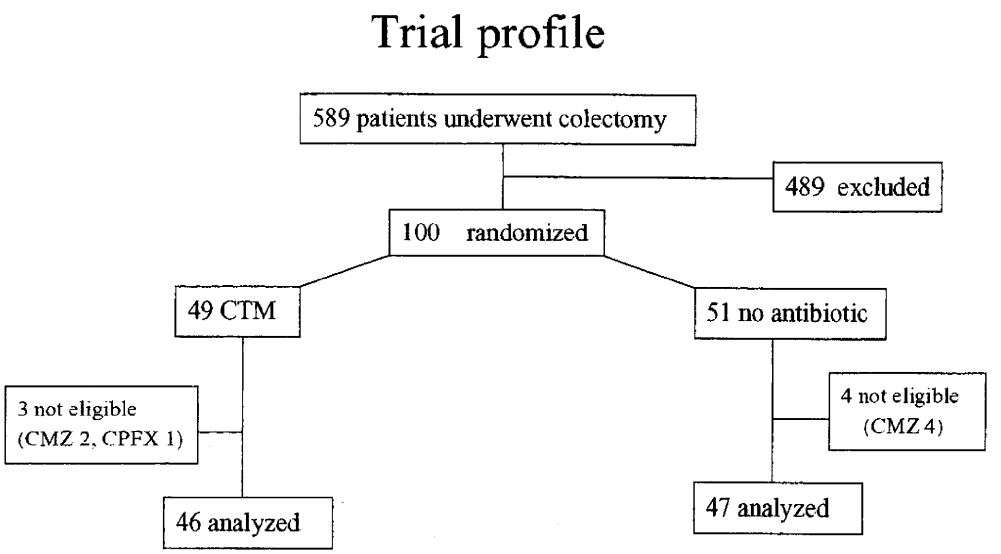

Fig. 1. Analysis was carried out on intention to treat. There were no cases of death during hospitalization

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.

References

1. Utley RJ, Macbeth WAAG. Peroperative cefoxitin. A double-blind prospective study in the prevention of wound infections. J R Coll Surg Edinb 1984;29(3):143–6.
2. Schiessel R, Huk I, Starlinger M, Wunderlich M, Rotter M, Wewalka G. et al. Postoperative infections in colonic surgery after enteral bacitracin–neomycin–clindamycin or parenteral mezlocillin–oxacillin prophylaxis. J Hosp Infect 1984;5:289–97.
3. Gomez-Alonso A, Lozano F, Perez A, Almazan A, Abdel-Lah A, Cuadrado F. Systemic prophylaxis with gentamicin–metronidazole in appendectomy and colorectal surgery: a prospective controlled clinical study. Int Surg 1984;69:17–20.
4. Schoetz DJ Jr, Roberts PL, Murray JJ, Coller JA, Veidenheimer MC. Addition of parenteral cefoxitin to a regimen of oral antibiotics for elective colorectal operations. A randomized prospective study. Ann Surg 1990;212(2):209–12.
5. Finn G, Poul D, Keld S, Soren V, Jorgen O, Ole B. Prophylaxis with whole gut irrigation and antimicrobials in colorectal surgery. A prospective, randomized double-blind clinical trial. Am J Surg 1985;149:317–22.
6. Alicia JM. Guidelines for the prevention of surgical site infection. Hospital Infection Control Practices Advisory Committee, 1999.
7. Takaya S, Keisuke S. Guidelines for antimicrobial use. Japanese Journal of Chemotherapy and Japanese Association for Infectious Disease, 2007.
8. Malhotra-Kumar S, Lammens C, Coenen S, Van Herck K, Goossens H. Effect of azithromycin and clarithromycin therapy on pharyngeal carriage of macrolide-resistant streptococci in healthy volunteers. A randomized, double-blind, placebo-controlled study. Lancet 2007;369:482–90.
9. Lau WY, Chu KW, Poon GP, Ho KK. Prophylactic antibiotics in elective colorectal surgery. Br J Surg 1988;75(8):782–5.
10. Tonelli F. Antimicrobial chemoprophylaxis in colorectal surgery. Chemotherapy 1988;7(4):223–8.
11. Jevtic M, Petrovic M, Stankovic N. Antibiotic prophylaxis in elective colorectal surgery. Vojnosanit Pregl 1993;50(3):251–5.
12. Gul YA, Lian LH, Jabar FM, Moissinac K. Antibiotic prophylaxis in elective colorectal surgery. ANZ J Surg 2002;72(4):275–8.
13. Espin-Basany E, Sanchez-Garcia JL, Lopez-Cano M, Lozoya-Trujillo R, Medarde-Ferrer M, Armadans-Gil L, et al. Prospective, randomised study on antibiotic prophylaxis in colorectal surgery. Is it really necessary to use oral antibiotics? Int J Colorectal Dis 2005;20(6):542–6.
14. Sanderson PJ. Antimicrobial prophylaxis in surgery: microbiological factors. J Antimicrob Chemother 1993;31:Suppl B:1–9.
15. Song F, Glenny AM. Antimicrobial prophylaxis in colorectal surgery: a systematic review of randomized controlled trials. Br J Surg 1998;5:1232–41.
16. Nichols RL. Use of prophylactic antibiotics in surgical practice. Am J Med 1981;70:686–92.
17. Wren SM, Ahmed N, Jamal A, Safadi BY. Preoperative oral antibiotics in colorectal surgery increase the rate of *Clostridium difficile* colitis. Arch Surg 2005;140(8):752–6.
18. National Nosocomial Infections Surveillance (NNIS) System Report. Data summary from January 1992 through June 2004. Issued October. Am J Infect Control 2004;32:470–85.

Original Paper

Digestive Surgery

Dig Surg 2009;26:392–399
DOI: 10.1159/000229973

Received: January 21, 2009
Accepted: July 9, 2009
Published online: November 16, 2009

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

Masaki Ueno Kazuhisa Uchiyama Satoru Ozawa Shinya Hayami
Shigehisa Kiriyama Hiroki Yamaue

Second Department of Surgery, Wakayama Medical University, School of Medicine, Wakayama, Japan

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-

KARGER
Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

0253–4886/09/0265–0392$26.00/0

Accessible online at:
www.karger.com/dsu

Hiroki Yamaue, MD
Second Department of Surgery
Wakayama Medical University, School of Medicine
811-1 Kimiidera, Wakayama 641-8510 (Japan)
Tel. +81 73 441 0613, Fax +81 73 446 6566, E-Mail yamaue-h@wakayama-med.ac.jp

gional therapy, such as radiofrequency ablation therapy or transarterial chemoembolization, instead of surgery.

Major hepatectomy, defined as the resection of 3 or more liver segments by Couinaud's anatomical classification, has been adapted for patients with sufficient functional reserve of the liver. However, high incidences of severe postoperative complications, such as liver failure, are still a problem. Several reports have looked at the risk factors for postoperative complications in major hepatectomy [10, 11], but the selection criteria have not been standardized.

Recently, fibrosis markers such as the type IV collagen 7s domain or hyaluronic acid (HA) have been recognized as predictors of postoperative complications after a resection of HCC [12–15]. HA is expressed by various types of cells, such as fibroblasts [16], and degrades rapidly, mostly in hepatic sinusoidal endothelial cells, with a half-life of 2–5 minutes [17]. Therefore, the concentration of serum HA could be a useful marker for nonparenchymal liver cell function.

In this study, a new discriminant equation was constructed for predicting postoperative complications in patients undergoing a major hepatectomy using various liver functional factors including the preoperative serum HA level and the accuracy of this prediction model was verified.

Methods

Patients

Beginning in 2001, the concentration of serum HA was measured in 192 patients with HCC prior to a liver resection at the Wakayama Medical University Hospital. During this period, major hepatectomies were performed in 52 patients. At the Wakayama Medical University Hospital, hepatectomies were administered to patients based on the previously developed prediction model: liver failure score = 164.8 – 0.58 × (Alb) – 1.07 × (HPT) + 0.062 × (AST) – 685 × (ICGk) – 3.57 × OGTT.LI + 0.074 × (RW), where Alb is albumin (g/dl), HPT is hepaplastin test (%), AST is aspartate aminotransferase (IU/l), ICGk is ICG clearance rate, OGTT.LI is blood sugar at 60 and 120 min after 75 g glucose oral intake, and RW is estimated resection liver volume. A score <25 indicates a safe hepatectomy and a score in the range of 25–50 indicates a marginally safe hepatectomy [9]. Some patients without sufficient remnant liver function or volume underwent a percutaneous transhepatic portal embolization, with the surgical criteria estimated 3–4 weeks later.

Surgical procedures in this study were as follows: a right hepatic lobectomy (S5 + S6 + S7 + S8 according to Couinaud; n = 31), an extended right hepatic lobectomy (S4 + S5 + S6 + S7 + S8; n = 8), a left hepatic lobectomy (S1 + S2 + S3 + S4; n = 8), an extended left hepatic lobectomy (S1 + S2 + S3 + S4 + S5 + S8; n = 3) and a central hepatectomy (S4 + S5 + S8; n = 2).

This study was conducted in accordance with the Helsinki declaration and the guidance of the ethical committee of the Wakayama Medical University Hospital.

Measurement of HA

Peripheral blood samples were collected from every patient early in the morning before surgery when they were in a stable condition during hospitalization. Using the serum of these samples, the HA level was measured using a latex agglutination assay kit (BML, Tokyo, Japan). The reference range of the serum HA concentration was 0–50 ng/ml.

Measurement of the Estimated Ratio of the Remnant Liver Volume

Three-dimensional reconstruction images of the liver volume were obtained from intravenously enhanced multidetector row CT images and several planned surgical procedures were simulated using the AZE Virtual Place system (AZE, Tokyo, Japan) [18]. On the basis of this simulation, the estimated remnant liver volume ratio (remnantVol%) was calculated from the estimated remnant and the resection liver parenchyma volume.

Postoperative Complications

Postoperative complications were analyzed using the classification of Dindo et al. [19]; complications above grade III, including persistent ascites, pleural effusion (unresponsive to diuretics) and/or hyperbilirubinemia (total serum bilirubin concentration >5ml/dl for more than 5 days), were defined as postoperative complications related to hepatectomy and evaluated in the outcome variable of this study. In this study, a complication was defined as the first observed event after hepatectomy, and no complication overlapped with another complication.

Statistical Analysis

For measuring outcome, the predictive variables were initially screened by univariate analysis. The Mann-Whitney U test was used in comparing the difference of continuous variables because the normal distribution was not confirmed in this study. Categorical variables were compared by means of a χ^2 test. Predictive variables with $p < 0.1$ in the univariate analysis were screened and stepwise logistic regression analyses were used to select independent variables and construct a discriminant equation. The goodness-of-fit of the constructed prediction model was evaluated by using the Hosmer-Lemeshow test. The predictive ability was estimated by the receiver operating characteristic (ROC) curve and quantified by the area under the ROC curve (AUC). The optimal cut-off of the logit value was estimated based on the ROC curve. The sensitivity, specificity, accuracy, positive predictive value and negative predictive value of the constructed prediction model were calculated based on the cut-off value. The leave-one-out cross validation method was used to verify the performance of the constructed prediction model and then the cross-validation sensitivity, specificity, accuracy, positive predictive value and negative predictive value were calculated by comparing the predicted response and the observed response.

All the statistical tests were 2-tailed and a significance level of <0.05 was accepted. All the statistical analyses were performed using SPSS program version 13.0J (SPSS, Tokyo, Japan).

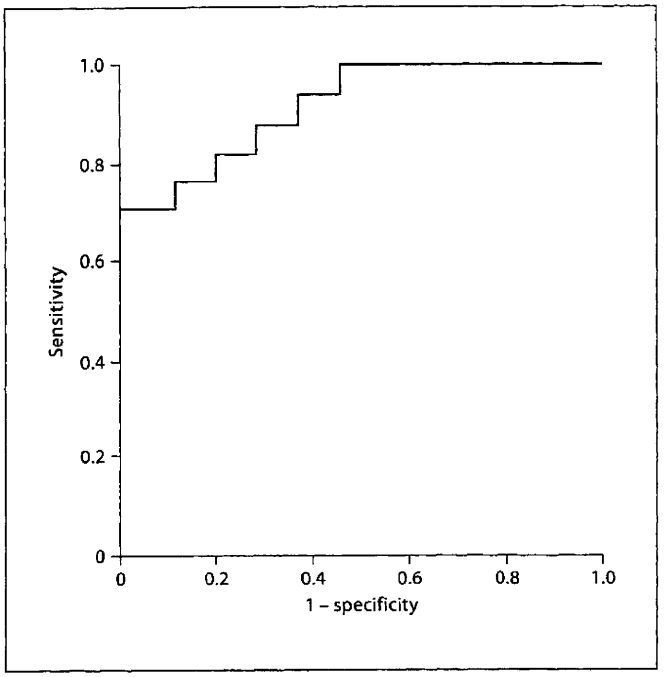

Fig. 1. ROC curve for the constructed prediction model.

Table 1. Clinical outcome after a major hepatectomy

Surgical complications	n
Ileus	2 (3.8)
Gastrointestinal bleeding[1]	2 (3.8)
Pleural effusion	3 (5.8)
Ascites	9 (17.3)
Hyperbilirubinemia	5 (9.6)
Complications related to hepatectomy[2]	17 (32.7)

Values in parentheses represent percentages.
[1] Acute gastric mucosal lesion, ulcer.
[2] Pleural effusion, ascites and hyperbilirubinemia were defined as postoperative complications related to hepatectomy.

Results

The clinical outcomes of all the patients that underwent a major hepatectomy are summarized in table 1. Postoperative complications related to the hepatectomy occurred in 17 patients.

Clinicopathological Backgrounds

The clinicopathological backgrounds of patients with or without postoperative complications are summarized in table 2. Age, gender, proportion of positive hepatitis C virus antibody and cirrhosis defined by METAVIR score [20] were similar in both groups. Although the value of total bilirubin, albumin, alanine aminotransferase, prothrombin test, platelet count and ICG retention rate at 15 min ($ICGR_{15}$) were not different, the values of AST and HA were significantly different between the 2 groups. The median (interquartile range, 95% CI of mean and range) HA values in groups without and with complications were 42.0 (29.0–86.0, 47.6–90.2 and 19.0–236.5) and 149.0 (77.8–332.0, 123.8–318.8 and 37.0–743.0), respectively. The MELD score and the proportion of the Child-Pugh score were not different between the 2 groups. Although the main tumor diameter was similar, the remnantVol% was significantly different between the 2 groups. The median (interquartile range, 95% CI of mean, and range) remnantVol% values in groups without and with complications were 55.7 (44.4–68.3, 51.0–61.1, and 34.2–92.0) and 41.0 (33.4–46.9, 36.6–46.2, and 27.6–61.8), respectively.

Derivation of the Model Predicting Postoperative Hepatic Complications

The potential predictors of postoperative complications were calculated by univariate logistic regression analysis and summarized in table 3. The age and the value of albumin, AST, HA and remnantVol% were selected as useful predictable factors ($p < 0.1$). A logistic stepwise regression analysis was performed from the selected 5 variables and the findings are summarized in table 4. Both the value of HA and the remnantVol% were independent predictors for postoperative complications. The coefficients of HA and remnantVol% are 0.03 and –0.16, respectively. These led to the following prediction model for postoperative complications: $\text{logit} = 4.15 + 0.03 \times (\text{HA}) - 0.16 \times (\text{remnantVol\%})$.

The results of the Hosmer-Lemeshow test, which showed a χ^2 value of 4.76 ($p = 0.78$), indicated that the observed proportion of patients with postoperative complications was similar to the predicted proportion in the derivation group.

ROC analysis to predict postoperative complications (figure 1) reveals that the AUC value (95% CI) is 0.92 (0.84–1.00).

The cut-off value of the logit was determined based on the ROC curve in consideration of an appropriate tradeoff between the sensitivity and specificity. The optimal logit value was 0. At that point in the ROC curve, a cross-tabulation of the predicted and observed postop-

Table 2. Clinicopathological backgrounds of patients with or without complications

Predictor	Postoperative complications		p
	no (n = 35)	yes (n = 17)	
Age, years	69 (61, 74)	70 (65, 78)	0.21
Gender, M/F	31/4	14/3	0.67
HCV antibody, +/–	13/22	6/11	0.90
Cirrhosis, +/–	11/24	6/11	0.78
Total bilirubin, mg/dl	0.7 (0.1, 1.0)	0.8 (0.6, 1.1)	0.84
Albumin, g/dl	4.2 (3.7, 4.4)	3.9 (3.4, 4.3)	0.08
AST, IU/l	38.5 (26.0, 80.0)	60 (22.8, 125.4)	0.04
ALT, IU/l	35.0 (20.4, 83.2)	43 (15.0, 136.4)	0.26
Prothrombin test, %	85.5 (66.6, 107.5)	93.1 (59.9, 111.9)	0.58
Platelet count, $\times 10^4$ μl	19.9 (10.7, 26.1)	21.4 (10.2, 32.4)	0.30
$ICGR_{15}$, %	10.0 (8.3, 13.3)	13.5 (9.0, 18.1)	0.11
MELD score, points	4.4 (1.0, 6.7)	3.6 (–2.2, 5.9)	0.15
Child-Pugh score, A/B	30/5	13/4	0.45
Hyaluronic acid, ng/dl	42.0 (29.0, 86.0)	149.0 (77.8, 332.0)	0.00008
Main tumor diameter, cm	6.3 (4.0, 11.0)	10.0 (4.8, 12.3)	0.22
Remnant liver volume ratio, %	55.7 (44.4, 68.3)	41.0 (34.4, 46.9)	0.0003

Continuous variables are given as median (25th, 75th percentile). Cirrhosis is defined as F4 by METAVIR score. HCV = Hepatitis C virus; ALT = alanine aminotransferase; $ICGR_{15}$ = indocyanine green retention rate at 15 min.

Table 3. Univariate analysis of predictive factors for postoperative complications

Predictor	Coefficient	OR	95% CI	p
Age	0.06	1.06	0.99–1.13	0.10
Gender	–0.51	0.60	0.12–3.06	0.54
HCV antibody	–0.08	0.92	0.28–3.09	0.90
Cirrhosis	0.17	1.19	0.35–4.05	0.78
Total bilirubin	–0.35	0.70	0.08–6.08	0.75
Albumin	–1.00	0.37	0.13–1.03	0.06
AST	0.02	1.02	0.99–1.04	0.08
ALT	0.01	1.01	0.99–1.03	0.15
Prothrombin time	0.01	1.01	0.97–1.05	0.62
Platelet count	0.06	1.06	0.96–1.17	0.26
$ICGR_{15}$	0.06	1.07	0.97–1.18	0.21
MELD score	–0.22	0.80	0.60–1.07	0.13
Child-Pugh score	0.61	1.85	0.43–8.01	0.41
Hyaluronic acid	0.01	1.01	1.01–1.02	0.002
Main tumor diameter	0.09	1.09	0.96–1.25	0.19
Remnant liver volume ratio	–0.11	0.89	0.83–0.96	0.003

Cirrhosis is defined as F4 by METAVIR score. ALT = Alanine aminotransferase.

Table 4. Multivariate analysis of predictive factors for postoperative complications

Predictor	Coefficient	OR	95% CI	p
Intercept	4.15			
Hyaluronic acid, ng/ml	0.03	1.03	1.01–1.06	0.006
Remnant liver volume ratio, %	–0.16	0.85	0.76–0.95	0.006

Table 5. Cross-tabulation of predicted and observed postoperative complications

		Predicted postoperative complications	
		no	yes
Observed postoperative complications	no	34	1
	yes	5	12

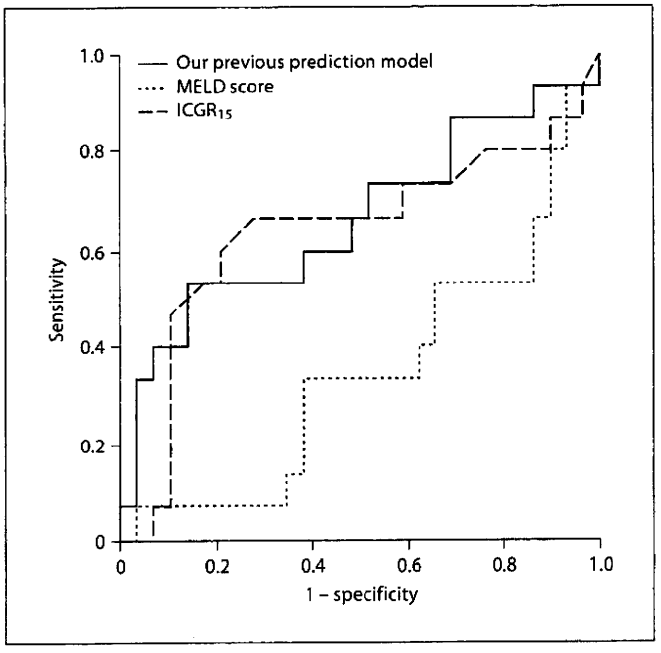

Fig. 2. ROC curves for 3 other prediction models.

Table 6. Cross-tabulation of predicted and observed postoperative complications achieved from cross-validation analysis

		Predicted postoperative complications	
		no	yes
Observed postoperative complications	no	31	4
	yes	5	12

erative complications was made (table 5). The sensitivity, specificity, accuracy, positive predictive value and negative predictive value of this prediction model were 0.71, 0.97, 0.88, 0.92 and 0.87, respectively.

Validation Analysis of the Prediction Model

When this prediction model obtained from the 52 patients was applied to the leave-one-out cross-validation analysis, a cross-tabulation of the predicted and observed postoperative complications was made (table 6). Validation sensitivity, specificity, accuracy, positive predictive value and negative predictive value based on the leave-one-out method were 0.71, 0.89, 0.83, 0.71 and 0.86, respectively. These values were similar to those of the achieved model. This result suggests that the performance of this prediction model for postoperative complications was stable.

Postoperative Mortality

Mortality defined as death within 90 days after the hepatectomy, except for cancer death, occurred in 6 patients in this study, all of whom experienced postoperative complications related to the hepatectomy (table 7). The logit values of all these patients exceeded 1.6. The serum concentrations of albumin, $ICGR_{15}$ and platelet count were distributed over wide ranges.

Comparison of Other Prediction Models

In order to compare the discrimination performance, other prediction models (our previous prediction model [9], MELD score and $ICGR_{15}$) were also analyzed by using the ROC curves shown in figure 2. AUC values (95%CI) of our previous model, MELD score and $ICGR_{15}$ were 0.66 (0.47–0.83), 0.38 (0.21–0.54) and 0.64 (0.46–0.81), respectively.

Discussion

In this study, the preoperative HA concentration and remnantVol% were determined to be independent predictable factors for postoperative complications after a major hepatectomy and produced the prediction model: logit = 4.15 + 0.03 × (HA) – 0.16 × (remnantVol%). AUC values vary from 0 to 1 and an AUC >0.7 is considered to be acceptable to discriminate between the 2 groups [21]. The AUC value of 0.92 in this study reveals that this prediction model has excellent performance for discriminating postoperative complications. Moreover, other prediction models (our previous prediction model [9], MELD score and $ICGR_{15}$) were not statistically significant in this study.

This prediction model was developed from major hepatectomies, but not all hepatectomies, because the risk factors linked to postoperative morbidity differ based on the surgical procedure used [11]. If all hepatectomy patients were analyzed together, then the discriminatory effect may have diminished. Moreover, there were 6 patients who died of postoperative complications in this study. Applying our previous prediction model [9] to major hepatectomy patients resulted in a high rate of mortality and was not suitable in predicting postoperative complications after a major hepatectomy, although there was

Table 7. Results of laboratory tests and index score in the 6 patients who died of postoperative complications

Patient No.	Observed complication	Albumin, g/dl	$ICGR_{15}$, %	Platelet count ($\times 10^4/\mu l$)	Hyaluronic acid, ng/ml	Remnant liver volume ratio, %	Logit value	Cause of mortality
1	ascites	4.0	6.2	16.5	149	44.0	1.6	liver failure
2	ascites	3.1	13.0	31.3	143	41.0	1.9	liver failure
3	ascites	4.3	13.5	18.9	228	37.3	5.0	liver failure
4	hyperbilirubinemia	2.4	26	27.5	290	35.2	7.2	liver failure
5	ascites	3.4	16	22.6	477	41.0	11.9	liver failure
6	ascites	3.3	17.2	10.2	743	35.0	20.8	liver failure

no mortality in minor hepatectomy patients during this period. Therefore, the analysis in this study was limited to major hepatectomy patients.

The ICG clearance test has been recognized, generally, as one of the most discriminatory measures for selecting patients for a hepatectomy and has been included in various algorithms of surgical procedure selection [5, 6, 22]. However, the optimal $ICGR_{15}$ value for a safe major hepatectomy is different in different series [22–24]. Moreover, the ICG clearance test did not reach a significant level as a predictor in some previous reports [12, 13] or in the current study.

There may be several reasons for this result. First, all of the patients in this study had an $ICGR_{15}$ value <30%, with median values around 10%. In patients with well-preserved liver function, the discrimination power of the ICG clearance test is limited. Secondarily, the ICG clearance test reflects the degree of sinusoidal capillarization, intrahepatic portovenous shunt and alterations in liver blood flow [25]. If the tumor size is too large, the need for a major hepatectomy, arterioportal or arteriovenous shunt in liver tumors cannot be ignored. In such cases, ICG recirculates into the systemic or portal circulation and ICG elimination may be delayed and result in underestimation of the liver functional reserve.

The MELD score was originally developed to predict the mortality of cirrhotic patients receiving transjugular intrahepatic portosystemic shunts [26] and subsequently applied as a predictor of the prognosis in patients with liver cirrhosis [27]. It has recently been reported that the MELD score can accurately predict the postoperative morbidity of cirrhotic patients undergoing a hepatectomy for HCC [7, 8]. Although the value of the MELD score in this study was low and not scattered, the MELD score never became a good discriminative factor.

It has also been reported that the remnantVol% is an important predictive factor [5, 6, 9, 24]. Advances in radiological techniques, including 3D hepatic modeling from CT images, provide a detailed hepatic vascular anatomy and a reliable hepatectomy simulation system, as well as easily yield an accurate prediction of liver resection volume or remnant liver volume [18, 28]. In this study the estimated resection or remnant liver volume was also accurate (data not shown) and the ratio of the estimated remnant liver volume per whole liver volume was recognized as a significant predictor for postoperative complications.

The concentration of serum HA reflects hepatic sinusoidal capillarization or the reduction of the HA receptor in hepatic sinusoidal endothelial cells, which is often observed as morphological changes of the sinusoidal endothelial cells in cirrhotic liver tissue [29, 30]. The serum HA level has been recognized not only as fibrosis or a functional marker of an injured liver [31], but also as a predictor of postoperative complications associated with liver surgery [13–15]. Previously, a serum HA level <160 ng/ml was reported to be the discrimination value in a major hepatectomy [15] and >200 ng/ml was reported to indicate an inhibition of liver regeneration after a hepatectomy [32]. In this study, the serum HA level was also a strong predictor for postoperative complications after major hepatectomy.

In this study, preoperative estimation was targeted, which resulted in perioperative factors not being included in the analysis. Perioperative factors, such as operative blood loss, were also recognized as contributors to postoperative complications. The median operative blood loss was 1,990 ml and 1,030 ml in groups with and without complications, and was not significantly different in this study. However, known perioperative factors should be avoided, especially in patients estimated to have marginal safety.

In conclusion, when the $ICGR_{15}$ <30%, the serum HA level and remmantVol% were recognized to be independent significant risk factors for postoperative complications after a major hepatectomy. Moreover, the established prediction model: logit = 4.15 + 0.03 × (HA) − 0.16 × (remnantVol%) had an excellent discrimination performance for prediction of postoperative complications, with logit <0 being the optimal cut-off value for administration of a safe major hepatectomy. In clinical use, the planned surgical procedure could be modified by applying this model if the serum HA level is high.

However, since the validity of the established model was assessed by the cross-validation method in this study, because of the small number of patients, the performance of the validation analysis may be limited. As a result, it has been proposed to do a further external validation study.

References

1 Caesar J, Shaldon S, Chiandussi L, Guevara L, Sherlok S: The use of indocyanine green in the measurement of hepatic blood flow and as a test of hepatic function. Clin Sci 1961;21:43–57.

2 Oellerich M, Raude E, Burdelski M, Schulz M, Schmidt FW, Ringe B, Lamesch P, Pichlmayr R, Raith H, Scheruhn M, et al: Monoethylglycinexylidide formation kinetics: a novel approach to assessment of liver function. J Clin Chem Clin Biochem 1987;25:845–853.

3 Villeneuve JP, Infante-Rivard C, Ampelas M, Pomier-Layrargues G, Huet PM, Marleau D: Prognostic value of the aminopyrine breath test in cirrhotic patients. Hepatology 1986;6:928–931.

4 Ha-Kawa SK, Tanaka Y, Hasebe S, Kuniyasu Y, Koizumi K, Ishii Y, Yamamoto K, Kashiwagi T, Ito A, Kudo M, Ikekubo K, Tsuda T, Murase K: Compartmental analysis of asialoglycoprotein receptor scintigraphy for quantitative measurement of liver function: a multicentre study. Eur J Nucl Med 1997;24:130–137.

5 Yamanaka N, Okamoto E, Kuwata K, Tanaka N: A multiple regression equation for prediction of posthepatectomy liver failure. Ann Surg 1984;200:658–663.

6 Takasaki T, Kobayashi S, Suzuki S, Muto H, Marada M, Yamana Y, Nagaoka T: Predetermining postoperative hepatic function for hepatectomies. Int Surg 1980;65:309–313.

7 Cucchetti A, Ercolani G, Vivarelli M, Cescon M, Ravaioli M, La Barba G, Zanello M, Grazi GL, Pinna AD: Impact of model for end-stage liver disease (MELD) score on prognosis after hepatectomy for hepatocellular carcinoma on cirrhosis. Liver Transpl 2006;12:966–971.

8 Teh SH, Christein J, Donohue J, Que F, Kendrick M, Farnell M, Cha S, Kamath P, Kim R, Nagorney DM: Hepatic resection of hepatocellular carcinoma in patients with cirrhosis: model of end-stage liver disease (MELD) score predicts perioperative mortality. J Gastrointest Surg 2005;9:1207–1215.

9 Uchiyama K, Mori K, Tabuse K, Ueno M, Ozawa S, Nakase T, Kawai M, Tani M, Tanimura H, Yamaue H: Assessment of liver function for successful hepatectomy in patients with hepatocelluar carcinoma with impaired hepatic function. J Hepatobiliary Pancreat Surg 2008;15:596–602.

10 Farges O, Malassagne B, Flejou JF, Balzan S, Sauvanet A, Belghiti J: Risk of major liver resection in patients with underlying chronic liver disease: a reappraisal. Ann Surg 1999;229:210–215.

11 Shimada M, Takenaka K, Fujiwara Y, Gion T, Shirabe K, Yanaga K, Sugimachi K: Risk factors linked to postoperative morbidity in patients with hepatocellular carcinoma. Br J Surg 1998;85:195–198.

12 Kubo S, Tsukamoto T, Hirohashi K, Tanaka H, Shuto T, Takemura S, Yamamoto T, Uenishi T, Ogawa M, Kinoshita H: Correlation between preoperative serum concentration of type IV collagen 7s domain and hepatic failure following resection of hepatocellular carcinoma. Ann Surg 2004;239:186–193.

13 Nanashima A, Yamaguchi H, Shibasaki S, Sawai T, Yamaguchi E, Yasutake T, Tsuji T, Jibiki M, Nakagoe T, Ayabe H: Measurement of serum hyaluronic acid level during the perioperative period of liver resection for evaluation of functional liver reserve. J Gastroenterol Hepatol 2001;16:1158–1163.

14 Mizuguchi T, Katsuramaki T, Nobuoka T, et al: Serum hyaluronate level for predicting subclinical liver dysfunction after hepatectomy. World J Surg 2004;28:971–976.

15 Yachida S, Wakabayashi H, Kokudo Y, Goda F, Okada S, Maeba T, Maeta H: Measurement of serum hyaluronate as a predictor of human liver failure after major hepatectomy. World J Surg 2000;24:359–364.

16 Gressner AM, Schäfer S: Comparison of sulphated glycosaminoglycan and hyaluronate synthesis and secretion in cultured hepatocytes, fat storing cells, and Kupffer cells. J Clin Chem Clin Biochem 1989;27:141–149.

17 Laurent TC: Biochemistry of hyaluronan. Acta Otolaryngol 1987;442:7–24.

18 Masumoto J, Sato Y, Hori M, Murakami T, Johkoh T, Nakamura H, Tamura S: A similarity measure for nonrigid volume registration using known joint distribution of targeted tissue: application to dynamic CT data of the liver. Med Image Anal 2003;7:553–564.

19 Dindo D, Demartines N, Clavien PA: Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205–213.

20 Intraobserver and interobserver variations in liver biopsy interpretation in patients with chronic hepatitis C: the French METAVIR Cooperative Study Group. Hepatology 1994;20:15–20.

21 Hosmer DW, Lemeshow S. Applied Logistic Regression, ed 2. New York, John Wiley & Sons Ltd., 2000.

22 Lau H, Man K, Fan ST, Yu WC, Lo CM, Wong J: Evaluation of preoperative hepatic function in patients with hepatocellular carcinoma undergoing hepatectomy. Br J Surg 1997;84:1255–1259.

23 Lam CM, Fan ST, Lo CM, Wong J: Major hepatectomy for hepatocellular carcinoma in patients with an unsatisfactory indocyanine green clearance test. Br J Surg 1999;86:1012–1017.

24 Kubota K, Makuuchi M, Kusaka K, Kobayashi T, Miki K, Hasegawa K, Harihara Y, Takayama T: Measurement of liver volume and hepatic functional reserve as a guide to decision-making in resectional surgery for hepatic tumors. Hepatology 1997;26:1176–1181.

25 Villeneuve JP, Dagenais M, Huet PM, Roy A, Lapointe R, Marleau D: The hepatic microcirculation in the isolated perfused human liver. Hepatology 1996;23:24–31.
26 Malinchoc M, Kamath PS, Gordon FD, Peine CJ, Rank J, ter Borg PC: A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. Hepatology 2000;31:864–871.
27 Botta F, Giannini E, Romagnoli P, Fasoli A, Malfatti F, Chiarbonello B, Testa E, Risso D, Colla G, Testa R: MELD scoring system is useful for predicting prognosis in patients with liver cirrhosis and is correlated with residual liver function: a European study. Gut 2003;52:134–139.
28 Saito S, Yamanaka J, Miura K, Nakao N, Nagao T, Sugimoto T, Hirano T, Kuroda N, Iimuro Y, Fujimoto J: A novel 3D hepatectomy simulation based on liver circulation: application to liver resection and transplantation. Hepatology 2005;41:1297–1304.
29 Ueno T, Inuzuka S, Torimura T, Tamaki S, Koh H, Kin M, Minetoma T, Kimura Y, Ohira H, Sata M, Yoshida H, Tanikawa K: Serum hyaluronate reflects hepatic sinusoidal capillarization. Gastroenterology 1993;105:475–481.
30 Tamaki S, Ueno T, Torimura T, Sata M, Tanikawa K: Evaluation of hyaluronic acid binding ability of hepatic sinusoidal endothelial cells in rats with liver cirrhosis. Gastroenterology 1996;111:1049–1057.
31 Pares A, Deulofeu R, Gimenez A, Caballeria L, Bruguera M, Caballeria J, Ballesta AM, Rodes J: Serum hyaluronate reflects hepatic fibrogenesis in alcoholic liver disease and is useful as a marker of fibrosis. Hepatology 1996;24:1399–1403.
32 Ogata T, Okuda K, Ueno T, Saito N, Aoyagi S: Serum hyaluronan as a predictor of hepatic regeneration after hepatectomy in humans. Eur J Clin Invest 1999;29:780–785.

J Hepatobiliary Pancreat Surg
DOI 10.1007/s00534-009-0116-4

ORIGINAL ARTICLE

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

Daisuke Hashimoto · Hiroshi Takamori · Yasuo Sakamoto · Yoshiaki Ikuta · Osamu Nakahara · Satoshi Furuhashi · Hiroshi Tanaka · Masayuki Watanabe · Toru Beppu · Masahiko Hirota · Hideo Baba

Received: 24 October 2008 / Accepted: 5 March 2009

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

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

D. Hashimoto · H. Takamori · Y. Sakamoto · Y. Ikuta · O. Nakahara · S. Furuhashi · H. Tanaka · M. Watanabe · T. Beppu · M. Hirota · H. Baba (✉)
Department of Gastroenterological Surgery,
Graduate School of Medical Sciences, Kumamoto University,
1-1-1 Honjo, Kumamoto, Kumamoto 860-8556, Japan
e-mail: hdobaba@kumamoto-u.ac.jp

Published online: 09 May 2009

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).

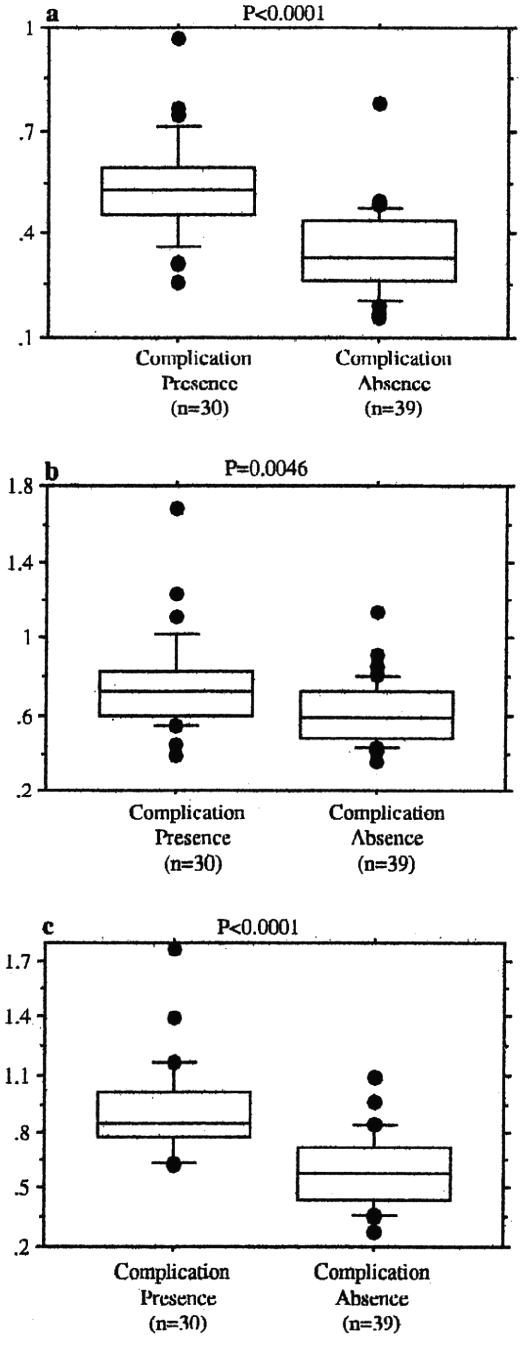

Fig. 1 Relationship between postoperative complications and E-PASS scores (**a** PRS, **b** SSS, and **c** CRS). *Boxes* show 95% confidence intervals

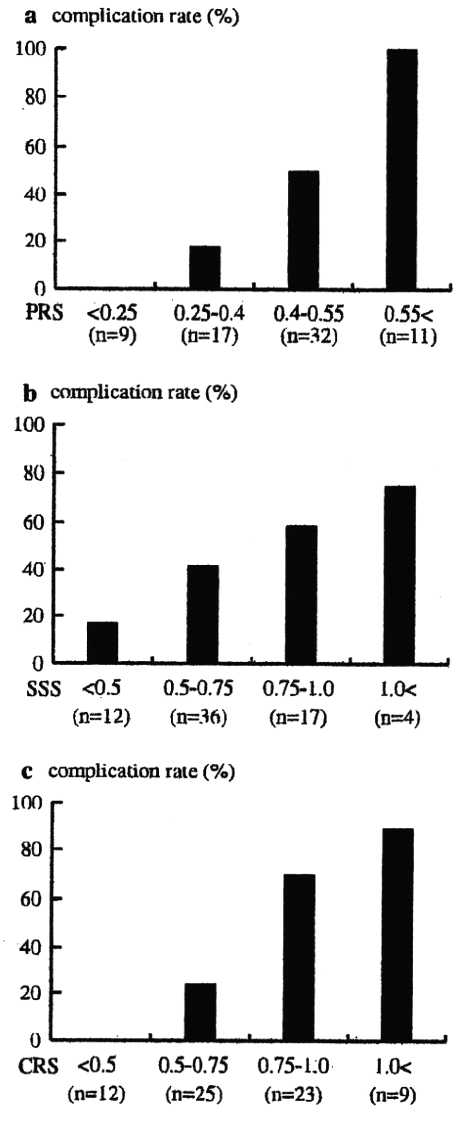

Fig. 2 Incidence of morbidity according to E-PASS scores (**a** PRS, **b** SSS, and **c** CRS)

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

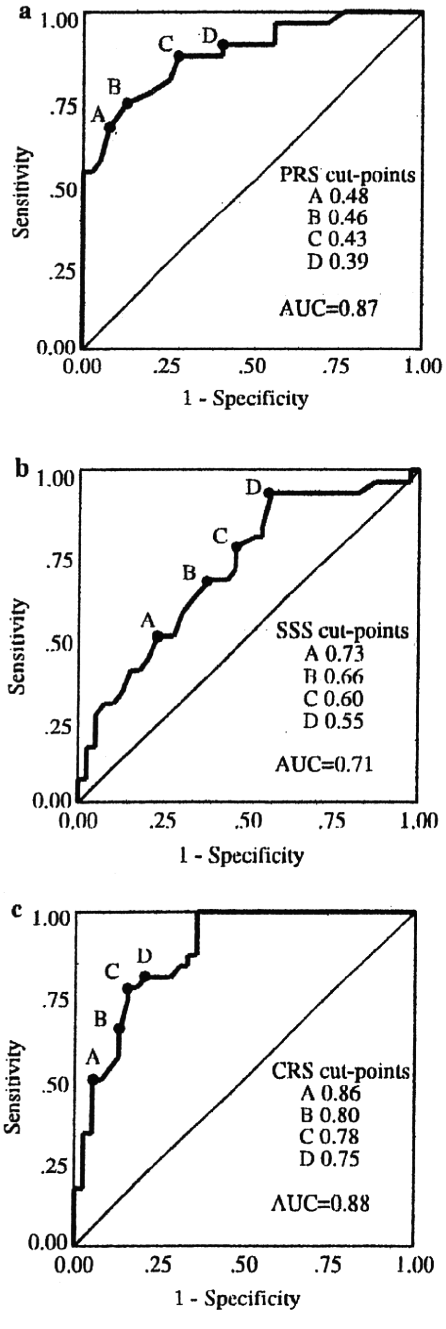

Fig. 3 ROC curves for morbidity, by the E-PASS scores (**a** PRS, **b** SSS, and **c** CRS)

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 post-operative 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