TABLE 1. Patient Demographics and Tumor-Related Factors for 27 Patients

Characteristics		
Age, y	Median	56
	Range	31–76
Sex, n (%)	Men	14 (51.9)
	Women	13 (48.1)
Location, n (%)	Ph	11 (40.7)
	Pb	12 (44.4)
	Pt	4 (14.8)
Functional tumor, n (%)		1 (3.7)
Maximum diameter, mm	Median	26
	Range	8–92
Diameter, n (%)	<2 cm	16 (59.3)
	≥2 cm	11 (40.7)
Local invasion, n (%)		2 (7.4)
Metastasis, n (%)	—	17 (63.0)
	Lymph node	10 (37.0)
	Liver	1 (3.7)
Mitosis, n (%)	0–1 per 10 HPFs	19 (70.4)
	2–20 per 10 HPFs	8 (29.6)
	>20 per 10 HPFs	0 (0.0)
WHO grading, n (%)	NET G1	19 (70.4)
	NET G2	8 (29.6)
	NEC	0 (0.0)
AJCC stage, n (%)	IA	8 (29.7)
	IB	9 (33.3)
	IIA	0 (0.0)
	IIB	9 (33.3)
	III	0 (0.0)
	IV	1 (3.7)
ENETS stage, n (%)	I	8 (29.7)
	IIa	7 (25.9)
	IIb	2 (7.4)
	IIIa	0 (0.0)
	IIIb	9 (33.3)
	IV	1 (3.7)

NET G1 indicates grade 1 NET; NET G2, grade 2 NET; Pb, pancreatic body; Ph, pancreatic head; Pt, pancreatic tail.

(29.6%) were classified as grade 2. According to the AJCC staging, 17 cases (63.0%), 9 cases (33.3%), 0 cases (0%), and 1 case (3.7%) were classified as stages I, II, III, and IV, respectively. According to the classification proposed by ENETS, 8 cases (29.7%), 9 cases (33.3%), 9 cases (33.3%), and 1 case (3.7%) were classified as stages I, II, III, and IV, respectively.

The median and range of the observation period were 1704 days and 37 to 4206 days, respectively. Three patients died, one of whom had a tumor-related death; the other 2 patients had treatment-related deaths. Recurrence after surgery was observed in 6 patients (22.2%).

Geminin and Ki-67 Expression

The immunohistochemical analysis examined the expressions of geminin and Ki-67 protein in all the cases (Fig. 1). Immunoreactivity was observed exclusively in the nuclei of the tumor cells. Geminin was also immunoreactive in the perichromosomal cytoplasm of mitotic cells in a few cases. The median LIs for geminin and Ki-67 were 1.0% and 1.5%, respectively. The geminin LI was slightly but significantly lower than that of Ki-67. Figure 2 shows the positive correlation between the geminin LI and the Ki-67 LI (Spearman $R_s = 0.757$, $P < 0.001$).

The receiver operating characteristic curves for the geminin LI, the Ki-67 LI, and the mitosis count (all of which were continuous variables), which were used to predict the presence of metastatic lesions, are shown in Figure 3. The curves for the 2 LIs were similar. The area under the curve was calculated to be 0.829 (95% confidence interval [CI], 0.660–0.999) for the geminin LI, 0.776 (95% CI, 0.598–0.955) for the Ki-67 LI, and 0.594 (95% CI, 0.362–0.826) for the mitosis count. The geminin LI seemed to have a slightly superior ability to predict metastasis, compared with the Ki-67 LI. The sensitivity, specificity, positive predictive value, and negative predictive value of a geminin LI greater than 2.0% (n = 4) and of a Ki-67 LI greater than 2.0% (n = 7) for determining metastasis were 33.3%, 90.5%, 50.0%, and 82.6% and 50.0%, 80.0%, 42.9%, and 85.0%, respectively. We defined high-geminin expression cases as those with a geminin LI greater than 2% because this cutoff had the best discriminatory power for the predictive values. According to the current WHO classification, a Ki-67 LI of 2.0% can be used to discriminate G1 tumors, and this cutoff also had the best discriminatory power for the predictive values in the present analysis. Thus, we regarded a Ki-67 LI greater than 2.0% as indicating a high Ki-67 expression level.

Correlations of Geminin and Ki-67 LIs With Prognosis

Because there was only 1 tumor-related death in this series, we examined the predictive values of each LI for the disease-free survival period after surgery. The results of a univariate Cox regression analysis are shown in Table 2. A mitosis count of 2 or more per 10 HPFs (hazard ratio [HR], 10.204; 95% CI, 1.684–61.834; $P = 0.012$), a local invasion (HR, 18.762; 95%

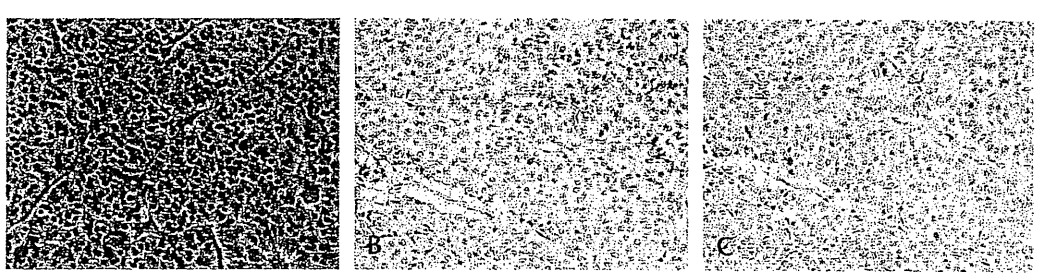


FIGURE 1. Representative photomicrograph of a PNET specimen. Hematoxylin and eosin staining (A) shows a typical trabecular arrangement of uniform tumor cells. The cells have eosinophilic cytoplasm and centrally located, round nuclei. Immunohistochemical staining for geminin (B) and Ki-67 (C) shows brown-stained tumor cell nuclei. The number of geminin-positive cells was smaller than the number of Ki-67–positive cells in most cases (original magnification ×400).

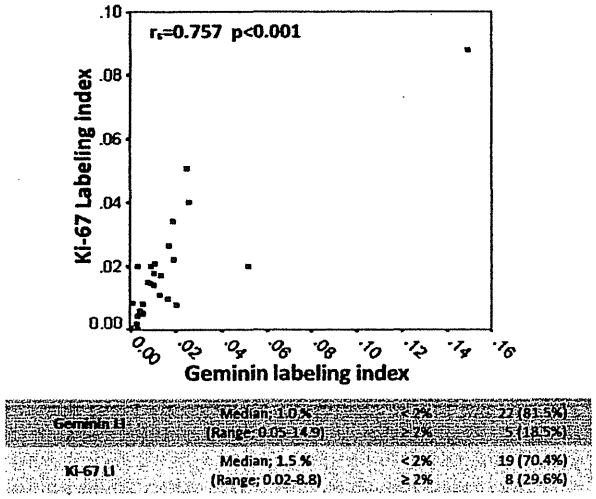


FIGURE 2. Scatterplot of the geminin LI and the Ki-67 LI (top) shows a positive correlation between the 2 LIs (Spearman rank correlation coefficient; $r_s = 0.757$; $P < 0.001$). The geminin expression level was lower than the Ki-67 expression level (bottom).

CI, 1.163–302.6; $P = 0.039$), a metastasis (HR, 10.469; 95% CI, 1.103–102.77; $P = 0.041$), a Ki-67 LI greater than 2.0% (HR, 6.182; 95% CI, 1.221–31.298; $P = 0.028$), a geminin LI greater than 2.0% (HR, 13.709; 95% CI, 1.919–97.739; $P = 0.009$), an AJCC stage of IIA or greater (HR, 8.758; 95% CI, 1.483–51.716; $P = 0.017$), and an ENETS stage of IIb or greater (HR, 16.793; 95% CI, 1.834–153.738; $P = 0.013$) were significantly correlated with recurrence. A multivariate Cox regression analysis revealed that none of these factors were independent prognostic factors. The Kaplan-Meier curves consistently exhibited a more significant relationship with the disease-free survival period after surgery for geminin (log rank, $P < 0.001$) than for Ki-67 (log rank, $P = 0.012$) (Fig. 4).

Concordance of Positivity Between Geminin and Ki-67 Stains

The immunoreactions were quantified using the CIE LAB color system. The color difference quotation was used to evaluate the positivity of the 2 stains. The color difference, ΔE, and a geminin-stained image are shown in Figure 5. The ΔE values

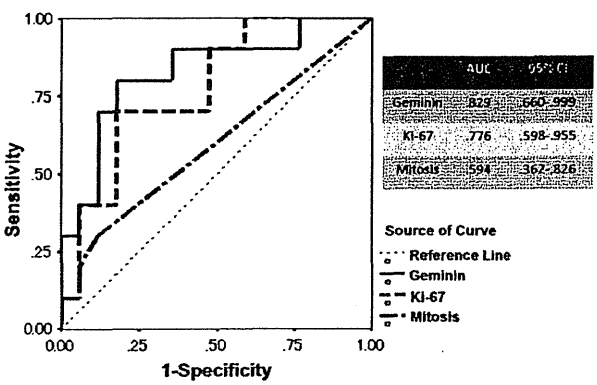


FIGURE 3. Receiver operating characteristic curves comparing the predictive value of the geminin LI to that of the Ki-67 LI or the mitosis count for determining the presence of metastasis.

TABLE 2. Univariate Cox Regression Analysis of Risk of Recurrence After Surgery

Variables	HR	95% CI	*P*
Diameter ≥2 cm	1.209	0.221–6.627	0.827
Mitosis ≥2 per 10 HPFs	10.204	1.684–61.834	0.012
v(+) or ly(+)	0.813	0.114–5.807	0.813
pn(+)	3.615	0.375–34.837	0.266
s(+) or rp(+)	2.068	0.411–10.4	0.378
Local invasion (+)	18.762	1.163–302.6	0.039
Metastasis (+)	10.469	1.103–102.77	0.041
Ki-67 LI >2.0%	6.182	1.221–31.298	0.028
Geminin LI >2.0%	13.709	1.919–97.739	0.009
WHO grade G2	2772.5	0.000–95.889 × 10^7	0.429
AJCC stage ≥IIA	8.758	1.483–51.716	0.017
ENETS stage ≥IIb	16.793	1.834–153.74	0.013

Local invasion indicates (+), presence of local invasion; ly(+), presence of lymphatic invasion; metastasis (+), presence of metastasis; pn(+), presence of peri-neural invasion; rp(+), presence of retroperitoneal invasion; s(+), presence of serosal invasion; v(+), presence of venous invasion.

corresponded with the optical intensity of the positive cells. The same consistency was observed for the images with Ki-67 staining (data was not shown). The distributions of ΔE in the geminin and Ki-67 staining images are shown in Figure 6. $\Delta E = 0$ signified no color difference from negative cells, and the left side of the histogram's distribution indicates the number of cells with equivocal positivity. A larger ΔE reflects a greater color disparity between the positive and negative cells. The medians (ranges) of the ΔE values for geminin and Ki-67 staining were

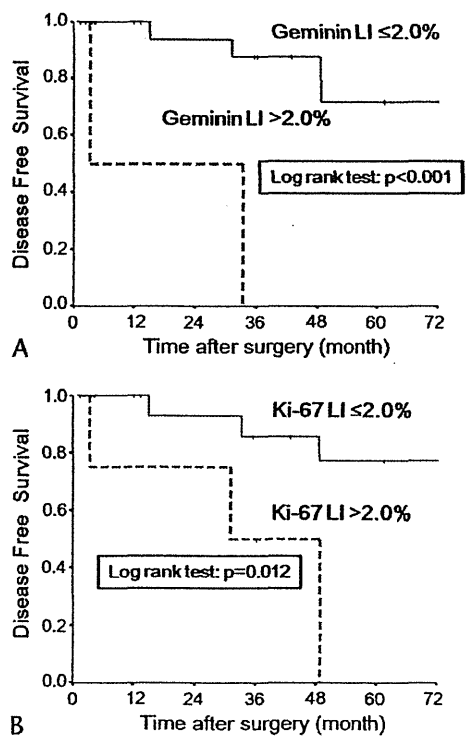
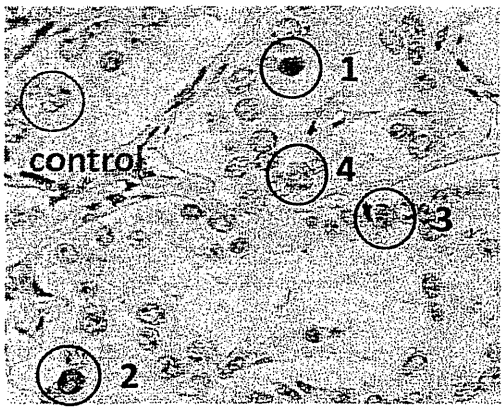


FIGURE 4. Disease-free survival period after surgery according to the geminin LI (A) and the Ki-67 LI (B).



#	L* value	a* value	b* value	ΔE
1	65.17	-1.22	15.30	76.22
2	67.90	7.30	11.63	21.87
3	77.14	5.71	5.74	11.10
4	82.30	3.29	-0.71	2.51
Ctr	83.94	2.82	-2.55	

FIGURE 5. The color difference ΔE in geminin stain is shown. ΔE values were calculated from the difference of L*a*b* values between positive cells (in numbered red circles) and a negative cell (in green circle).

16.12 (5.8–41.8) and 13.17 (3.4–37.9), respectively. The ΔE for the geminin stain was significantly larger than that for the Ki-67 stain ($P < 0.001$).

DISCUSSION

The criteria used to predict the outcome of patients with PNET has been simplified in the 2010 WHO classification.[6] Pancreatic neuroendocrine tumors are divided into well-differentiated NETs and poorly differentiated neuroendocrine carcinoma (NEC). The definition of NEC is the presence of more than 20 mitoses per 10 HPFs. Neuroendocrine tumors were further subcategorized as low-grade NET (G1), characterized by the presence of 0 to 1 mitoses and a Ki-67 LI of 0% to 2%, and intermediate-grade NET (G2), characterized as 2 to 20 mitoses per 10 HPFs and a Ki-67 LI of 3% to 20%. Actually, immunohistochemical staining for Ki-67 has been the most reliable modality for assessing the proliferative activity.[2,3,7] In addition, staging has been noted to be an independent prognostic indicator, and the AJCC staging manual and the staging classification proposed by the ENETS are thought to be useful for predicting the prognosis of patients with PNET. In the present study, 19 and 8 cases were classified as G1 and G2, respectively. No cases of NEC were seen, consistent with the presence of only 1 tumor-related death. Regarding recurrence after radical resection, this grading system is not a reliable prognostic factor (Table 2). Unlike the WHO grading, however, both the AJCC and ENETS stagings are significantly correlated with recurrence; similarly, the superiority of these stagings to anticipate disease-free survival has been previously reported.[25] The present analysis suggested that local spread beyond the pancreas might be a key event.

The usefulness of geminin staining to predict the outcome of several neoplasms has been demonstrated using retrospective analyses.[17–22] The present study also indicated that geminin expression was a more useful indicator of disease-free survival than not only Ki-67 expression but also AJCC and ENETS staging (Table 2). Geminin expression is specifically limited during the S, G2, and early M phases, and it probably reflects the proliferative activity more precisely than these other factors. Indeed, the number of positive tumor cells for geminin was significantly smaller than that for Ki-67. Although the survival analysis using Kaplan-Meier curves suggested that the geminin LI was more associated with the prognosis than the Ki-67 LI (Fig. 4), the present study has a limitation to evaluate the prognosis in accordance with the small number of cases. Further analyses of a larger population is needed to determine the prognostic use of the geminin LI. Moreover, the mechanism by which geminin expression contributes to the aggressiveness of neoplasms remains unknown. The inhibition of Cdt1 by geminin has been regarded as a pivotal event in the licensing of DNA replication, so an increase in Cdt1 inhibition biologically results in cell cycle arrest. This discrepancy between geminin expression and cell proliferation remains to be explained. The predictive superiority of the geminin LI to the Ki-67 LI in the present analysis may depend on some aspect of the malignant potential other than the proliferative activity.

In addition, the immunoreactivity of geminin staining in each tumor cell was relatively clear, whereas weak positivity for Ki-67 staining was observed in some tumor cells (Fig. 1). Thus, fewer intraobserver and interobserver differences between pathologists or institutions can be expected using the geminin LI. Actually, the difficulty in grading PNETs has been attributed to the need for concordance, along with the lower frequencies of proliferative marker positivity in PNETs. In the present study, we performed a color difference quotation analysis using the CIE LAB color system. Several color analyses have reported that the

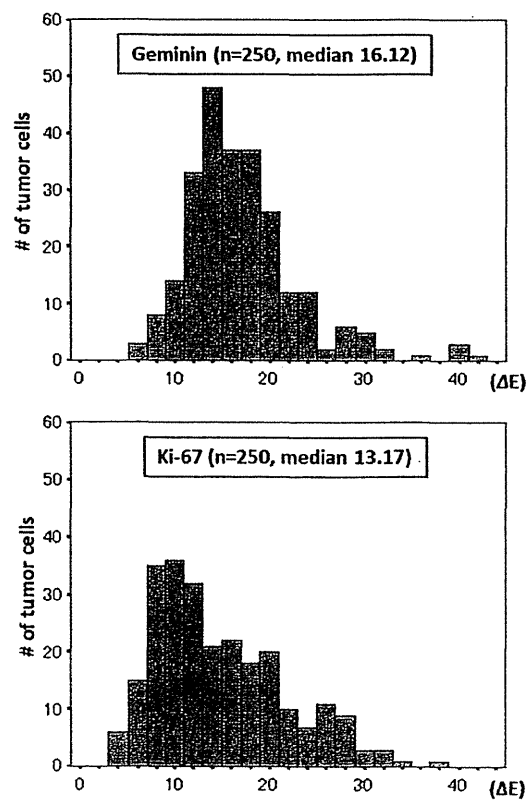


FIGURE 6. The distribution of each ΔE in geminin and Ki-67 stain is shown. The difference of each ΔE was evaluated as statistically significant ($P < 0.001$) using the Mann-Whitney U test.

color parameters of the CIE LAB color system are closely related to the psychophysical characteristics of color perception.[26–28] This analysis was the first application of the CIE LAB color system for the quantification of immunohistochemical positivity. As shown in Figure 5, a precise correspondence between ΔE and the optical color intensities was observed. Furthermore, the ΔE for geminin staining was larger than that for Ki-67 staining. These results suggest that a greater concordance was achieved using the geminin LI rather than the Ki-67 LI. The use of the color difference quotation enabled subjective optical intensities to be measured as absolute values, and no inconsistencies with regard to determining positivity were encountered. Thus, the CIE LAB color system may be a promising tool for making objective histopathologic assessments.

Pancreatic neuroendocrine tumor constitutes a heterogeneous group of rare neoplasms. Recent advances in abdominal imaging techniques have increased the detection of incidental nonfunctional PNET. In particular, endoscopic ultrasound and endoscopic ultrasound–guided fine needle aspiration biopsy procedures have drastically improved diagnostic accuracy.[29] Nowadays, minimally invasive surgery is usually recommended as a pancreas-preserving maneuver.[30] Therefore, accurate estimates of the malignant potential before surgery are becoming increasingly important for optimal patient management. Despite the importance of such estimations, pretreatment evaluations remain difficult. Only microscopic observations are acceptable for tumor grading and staging because PNET can exhibit heterogeneous biological behavior even within the same tumor. In the present study, a heterogeneous expression level was observed throughout the tumor for both geminin and Ki-67 staining. The use of geminin expression for the assessment of biopsy samples or aspirated specimens was not evaluated in the present study. Thus, the establishment of a preoperative classification based on geminin expression will require further research.

In conclusion, the geminin expression level in PNETs was correlated with the disease-free survival period after curative resection. The geminin LI may be more useful than the Ki-67 LI for predicting postoperative outcome.

ACKNOWLEDGMENT

The authors thank Dr Hiroshi Yamaguchi and Dr Toshio Ohmori, Imaging Technology Center, FUJIFILM Corp, Minamiashigara, Japan, for their technical advice.

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J Hepatobiliary Pancreat Sci (2012) 19:249–258
DOI 10.1007/s00534-011-0416-3

ORIGINAL ARTICLE

Compliance with and effects of preoperative immunonutrition in patients undergoing pancreaticoduodenectomy

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Published online: 11 June 2011

Abstract
Background/purpose This study was conducted to ascertain the feasibility and effectiveness of preoperative enteral immunonutrition using an immune-enhanced formula (Impact) in patients undergoing pancreaticoduodenectomy.
Methods Twenty-five patients undergoing an elective pancreaticoduodenectomy were asked to ingest Impact for 5 days (750 mL/day) prior to surgery in addition to their normal diets. We retrospectively compared the early postoperative outcomes of the Impact group ($n = 18$), which consisted of patients who fully complied with the study protocol, and a control group ($n = 13$), which consisted of patients who had not ingested Impact prior to surgery.
Results Overall, 82.6% of the patients complied with the preoperative oral ingestion of Impact; all but four patients tolerated a daily intake of 750 mL. While the clinical backgrounds of the Impact and control groups were not significantly different, the frequency of incisional wound infection was lower (0 vs. 30.8%, $p = 0.012$) and the change in systemic severity as evaluated using the acute physiology and chronic health evaluation (APACHE)-II scoring system was milder ($p = 0.033$) in the Impact group than in the control group.
Conclusion The preoperative oral ingestion of Impact was well tolerated and appeared to be effective for preventing incisional wound infection and reducing the response to surgical stress in patients undergoing a pancreaticoduodenectomy.

Keywords Immunonutrition · Pancreaticoduodenectomy · Surgical site infection · Nutrition

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Introduction

In recent years, pancreaticoduodenectomy (PD) has gained acceptance as an appropriate surgical procedure for selected patients with diseases of the pancreas head and periampullary region. Improvements in surgical techniques and accumulating experience have reduced the complication rate after PD. The postoperative mortality rates after PD are typically 5% or less at major surgical centers [1, 2], although the morbidity rates remain high, ranging from 10 to 50% [3–5]. Thus, postoperative morbidity after PD remains problematic and can lead to delays in the postoperative resumption of adequate oral food intake. Even in series with relatively good rates of postoperative morbidity, about 10% of the patients develop wound infections [1, 3–6]. However, the morbidity rate increases considerably if other complications, such as pancreatic fistula or delayed gastric emptying, are included [7]. Bacteria from the gut, especially Enterococci and *Escherichia coli* [8], translocate into the mesenteric lymph nodes or blood, where they cause the majority of the observed infections. Several conditions before, during, or after surgery can facilitate this bacterial translocation, including a reduction in postoperative intestinal motility, jaundice, the use of antibiotics resulting in small bowel bacterial overgrowth [9], the loss

of mucosal barrier function caused by malnutrition, manipulation of the bowel, and parenteral nutrition [10].

Recently, enteral immune-enhancing formulas supplemented with arginine, omega-3 fatty acids, and ribonucleic acid (RNA) have been suggested to improve the immune response and wound healing in postoperative patients [11, 12]. Arginine, which is classified as a semi-essential amino acid for catabolism, serves as a substrate for the urea cycle and the production of nitric oxide during protein synthesis. Arginine is known to promote T cells and to have a direct enhancing effect on their activities [13], enhancing the phagocytosis of neutrophils. Arginine also reduces the production of inflammatory mediators, such as interleukin (IL)-1beta, tumor necrosis factor alpha (TNF-α), and IL-6 at the site of tissue injury and is capable of enhancing cellular immunity in rat septic models [14]. Finally, arginine accelerates tissue growth after infection [15]. Omega-3 fatty acids compete with omega-6 fatty acids for cyclo-oxygenase metabolism at the cell membrane and for the production of eicosapentanoic acid (EPA). In addition, omega-3 fatty acids increase the production of some prostaglandins (PGs) and leukotrienes, reducing the proinflammatory potential, and inhibit the production of some other PGs (PGE2) and leukotrienes, reducing the cytotoxicity of macrophages, lymphocytes, and natural killer (NK) cells [11]. Supplementation with agents rich in omega-3 fatty acids also decreases prostacyclin and thromboxane (TX)-A2 synthesis and increases the antiaggregatory substance TXA3 [16]. Omega-3 fatty acids and EPA are believed to inhibit excessive inflammatory responses but not to be immunosuppressive. The intravenous administration of omega-3 fatty acids significantly reduced the production of proinflammatory cytokines in a recent clinical trial in patients with sepsis [17]. RNA supplementation is necessary for the proliferation of immune cells or cells involved in wound healing [18].

Several studies have demonstrated that immune-enhancing formulas may improve the postoperative immune response and reduce inflammatory reactions in various groups of postoperative patients, thereby reducing the incidence of serious infectious complications [12, 19–25]. Thus, the preoperative administration of these formulas in patients undergoing gastrointestinal tract surgery has been recommended [15, 24, 26–29]. In Japan, an enteral diet was introduced for immunonutrition in 2002; however, to the best of our knowledge, the utility of preoperative immunonutrition in patients undergoing PD has yet to be examined. The present study was undertaken to determine whether the preoperative oral intake of an immune-enhancing formula may be suitable for patients undergoing elective PD. Furthermore, we attempted to evaluate the effect of a preoperative immune-enhancing formula containing arginine, omega-3 fatty acids, and RNA (Impact Japanese version; Ajinomoto, Tokyo, Japan) on the early postoperative outcomes of patients, comparing outcomes with a historical control group who had received a normal diet alone.

Patients, materials, and methods

From February 2005 to November 2006, 25 consecutive patients (19 men, 6 women; age range, 48–77 years; median age, 64 years) who were candidates for a curative PD for the resection of a lesion in either the pancreatic head or the periampullary region were prospectively enrolled. The study protocol was reviewed and approved by the institutional review board of our hospital. Consenting patients who did not have malnutrition, bowel obstruction, severe cardiopulmonary complications, diabetes, collagen disease, renal failure, ongoing infection, or immune disorders were enrolled in the study. None of the patients had an immunosuppressive condition preoperatively. Patients were required to sign a written informed consent form once the protocol was explained.

The subjects included 5 patients with pancreatic invasive ductal carcinoma (PIDC), 6 with intraductal papillary mucinous neoplasm (IPMN), 9 with biliary tract cancers [bile duct cancer (BDC) in 6 and carcinoma of the papilla of Vater (VC) in 3], 3 with duodenal carcinoma, and 2 with other diseases (a pancreatic solid and pseudo-papillary neoplasm in 1 and a serous cystic adenoma in 1).

First, patient compliance with the preoperative ingestion of Impact was examined. After hospitalization, the patients were instructed to consume 3 packs/day (750 mL) of Impact Japanese version (Ajinomoto) in addition to their normal diets over a 5-day period immediately before surgery. Regarding the timing of the enteral immunonutrition, studies examining gastrointestinal cancer patients without malnutrition have reported that because a sufficient effect could be achieved with 5 days of preoperative administration, the postoperative administration of Impact was not necessary [26, 30]. In the study by Braga et al. [26], 1000 mL/day of Impact was prescribed to patients without malnutrition, but the actual mean intake was 890 mL. Because the mean body size of Japanese is smaller than that of Westerners, the daily intake of Impact Japanese version was set at 3 packs/day (750 mL/day) in the present study. Impact Japanese version is based on Impact (Novartis Consumer Health, Bern, Switzerland), and has been designed to suit the nutritional needs and flavor preferences of Japanese populations. A total of 750 mL of Impact Japanese version contains 9.6 g of arginine, 2.49 g of omega-3 fatty acids, and 0.96 g of RNA. The kilocalorie/milliliter ratio is 1:1. Regular meals of 1800 or 2000 kcal/day, depending on the patient's body size, were served preoperatively.

The patients were admitted at least 1 week before surgery and underwent mechanical preparation, including the oral intake of 2 L of polyethylene glycol electorolyte lavage solution (Niflec; Ajinomoto). Preoperative cultures were performed using nasal and throat swabs from all the patients to test for methicillin-resistant *Staphylococcus aureus* (MRSA). As a preventative antibiotic, 1 g of cefmetazole sodium (CMZ) (Cefmetazone; Daiichi Sankyo, Tokyo, Japan) was administered intravenously via a drip infusion immediately after the induction of anesthesia. A second dose was given 3 h later, followed by doses every 12 h for 2 days after the surgery. Oral feeding was initiated 5 days after the surgery.

Second, we attempted to evaluate the early postoperative outcome after PD by comparing the Impact group, which consisted of patients who fully complied with the ingestion of Impact for 5 days preoperatively, with a control group, which consisted of patients with a similar clinical background and condition who had undergone the same operative procedure in our hospital in 2004 but who had not ingested an immune-enhanced formula preoperatively. The age, sex, body mass index (BMI), serum albumin level, prognostic nutrition index (PNI) [31], preoperative biliary drainage, operative methods, operation times, and intraoperative blood loss of the two groups were compared. Regarding the postoperative course, the surgical morbidity and mortality and the duration of the hospital stay were investigated. The presence of postoperative complications, such as pancreatic fistula and incisional wound infection, and the infection status were described in the medical records. Incisional wound infection was defined based on the evidence of purulent exudate in the wound and the isolation of pathogenic organisms in culture. Surgical site infection (SSI) was diagnosed according to the Centers for Disease Control (CDC) definitions of SSI [32].

During the perioperative period, laboratory blood tests were performed. The white blood cell (WBC) count and the C-reactive protein (CRP), total protein (TP), serum albumin (Alb), total bilirubin (T-Bil), serum amylase (AMY), glutamic oxaloacetic transaminase (GOT), glutamic pyruvic transaminase (GPT), blood urea nitrogen (BUN), and serum creatinine (Cr) levels were routinely measured at 1, 3, and 7 days after surgery. Changes in body weight (BW), and in the acute physiology and chronic health evaluation (APACHE)II scores [33], and the duration of systemic inflammatory response syndrome (SIRS) in the postoperative course were also investigated. The APACHE-II classification includes twelve physiological measures (temperature, mean arterial pressure, heart rate, respiratory rate, oxygenation, arterial pH, serum sodium, serum potassium, serum creatinine, hematocrit, WBC count, and Glasgow Coma Scale score), age, and the presence of severe chronic health problems. The worst value in each patient was used as the physiological score. This index enables the prediction of perioperative events in patients undergoing various surgical procedures [34–39]. The definition of SIRS was adopted from the report by the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference [40]. SIRS was defined as the presentation of two or more of the following criteria: (1) temperature >38°C or <36°C; (2) heart rate >90 beats/min; (3) respiration >20/min or $PaCO_2$ <32 mmHg; (4) leukocyte count >12,000/mm^3, <4000/mm^3, or >10% band cells.

Statistical analysis of the data was performed using an unpaired Student's *t*-test, the χ^2 test, and the Mann–Whitney *U*-test. Variations in some parameters over time and comparisons among the two groups were studied using a repeated measure analysis of variance (ANOVA). Data are shown as means (standard deviation). All statistical analyses were performed using StatView-J 5.0 (Abacus Concepts, Berkeley, CA, USA); all two-sided p values <0.05 were considered statistically significant.

Operation procedures

Five staff surgeons performed all the operations. The operative procedure was a standardized substomach-preserving PD. Reconstruction was achieved using a retrocolic jejunal Roux-en-Y limb with an end-to-side pancreaticojejunostomy, an end-to-side hepaticojejunostomy, and a gastrojejunostomy, according to the child procedure. In all patients, a pancreatic stenting tube was placed in the pancreatic duct and fixed with 2 absorbable suture ligations. The main duct was anchored to the adjacent serosa. A 3-0 polypropylene monofilament thread with curved needle was prepared with a straightened needle at each end. The suture was passed from the ventral to the dorsal surface of the pancreas from the cut end and the serosal surface of the jejunum. All end-to-side pancreaticojejunostomies were performed in two layers. The inner layer comprised the opposition of the pancreatic duct and adjacent pancreatic tissue to a small opening in the jejunum (full thickness), which was made by puncturing the tissues with a thick needle connected to the pancreatic stenting tube and utilizing interrupted stitches of 5-0 monofilament polyglyconate. All pancreaticojejunal anastomoses were stented (decompressed) through 6- or 7.5-F polyvinyl chloride tubes, according to the diameter of the main pancreatic duct, and the tubes were guided externally through the jejunal loop. The pancreatic juice was completely drained via the tube, and the tube was removed 3 weeks or more after the surgery.

Hepaticojejunostomy was performed using interrupted polyglyconate sutures. A stenting tube was not inserted through the anastomosis in any of the patients. Penrose drains were routinely placed on the anterior and posterior

Table 1 List of patients with preoperative Impact consumption

Patient	Age (years)	Sex	Disease	Procedure	Duration of oral intake of Impact (days)	Reasons for discontinuation of Impact
1	79	Female	BDC	SSpPD	5	None
2	57	Female	PIDC	SSpPD	5	None
3	58	Male	IPMN	SSpPD	5	None
4	68	Male	VC	SSpPD	5	None
5	77	Male	BDC	SSpPD	5	None
6	68	Male	DC	SSpPD	1	Diarrhea
7	52	Male	BDC	SSpPD	5	None
8	56	Male	IPMN	SSpPD	5	None
9	62	Female	IPMN	SSpPD	5	None
10	77	Male	VC	SSpPD	2	Nausea
11	57	Male	BDC	EBDR	5	None
12	75	Male	BDC	Not resected	3	Diarrhea
13	64	Female	PIDC	SSpPD	5	None
14	48	Male	IPMN	SSpPD	4	Pancreatitis and cholangitis
15	62	Male	IPMN	SSpPD	5	None
16	57	Female	VC	SSpPD	5	None
17	67	Male	DC	SSpPD	5	None
18	59	Male	SPT	SSpPD	5	None
19	64	Male	PIDC	SSpPD	5	None
20	62	Female	DC	SSpPD	5	None
21	72	Male	BDC	SSpPD	5	None
22	67	Male	PIDC	SSpPD	5	None
23	44	Female	SCT	SSpPD	5	None
24	58	Male	IPMN	SSpPD	3	Changed operation date
25	64	Male	PIDC	Not resected (GJB)	1	Changed operation date

BDC bile duct carcinoma, *PIDC* pancreatic invasive ductal carcinoma, *IPMN* intraductal papillary mucinous neoplasm, *VC* papilla of Vater carcinoma, *DC* duodenal carcinoma, *SPT* solid and pseudo-papillary tumor of pancreas, *SCT* serous cystic tumor of pancreas, *SSpPD* substomach-preserving pancreaticoduodenectomy, *EBDR* extra bile duct resection, *GJB* gastrojejunal bypass

surfaces of the pancreaticojejunal anastomosis and the dorsal side of the hepaticojejunostomy.

Reconstruction was completed before suturing the abdominal wall. Immediately after the opening of the abdomen, the surgical wound was protected by the placement of a drape. Before closing the abdomen, the abdominal cavity was washed using 3000 mL of warm saline, and the drape was removed. The surgeon and assistant changed gloves, and the abdominal muscle and fascia layers were closed using monofilament absorbable sutures. After washing the skin and subcutaneous fat layer with 500 mL of warm saline, the wound was closed using a skin stapler. Postoperatively, the wound was covered using a transparent protective film and was monitored without sterilization until suture removal.

Results

Compliance with preoperative administration of Impact

The amount of the immunonutrition preparation consumed preoperatively was monitored by the doctor in charge of each patient. A total of 25 patients were enrolled in the study (see Table 1). As the scheduled operation date was moved forward for two patients, these 2 patients had to discontinue Impact consumption. Treatment compliance and other reasons for discontinuation are summarized in Table 2. Nineteen patients (82.6%) fully complied with Impact consumption. The mean period of preoperative oral intake was 4.6 ± 1.1 days. The reasons for the discontinuation of Impact consumption were diarrhea in 2 patients, nausea in 1 patient, and pancreatitis and cholangitis caused by the primary disease in 1 patient. The nausea and diarrhea symptoms occurred 3 days after the start of Impact consumption.

Comparison of early postoperative outcome after PD between the Impact and control groups

Of the 25 patients, 18 were able to complete the Impact consumption protocol. These patients (Impact group) were retrospectively compared with a control group consisting of patients treated at our institution in 2004 who had undergone the same surgical procedure for the treatment of

similar conditions but who had not ingested an immune-enhanced formula preoperatively.

The preoperative and intraoperative clinical background characteristics of the two groups of patients are summarized in Table 3. No significant difference was observed in the total numbers of calories served in the daily hospital meals given for 5 days before surgery and until postoperative day (POD) 7 between the two groups (data not shown). In both the Impact and control groups, peripheral parenteral nutritional infusion was used, without using total parenteral nutrition. Moreover, no differences in age, sex, preoperative nutritional status, operative time, or intraoperative blood loss were observed between the groups.

Table 2 Compliance with oral intake of Impact

Duration of oral intake of immunonutrition (days)	4.6 ± 1.1
No. of patients who completed oral intake	19/23[a] (82.6%)
No. of patients who discontinued treatment	4/23[a] (17.4%)
Reasons for discontinuation	
Diarrhea	2 (8.7%)
Nausea	1 (4.3%)
Pancreatitis and cholangitis caused by primary disease	1 (4.3%)

[a] Not including 2 patients (out of a total of 25 patients in this study) who discontinued preoperative Impact consumption because of changed operation dates

Postoperative SIRS duration and complications

The duration and complications associated with postoperative SIRS in each group are shown in Table 4. The duration of postoperative SIRS and the hospital stay were not significantly different between the groups. The incidences of individual complications were also comparable between the groups. The incidence of incisional wound infection was significantly lower in the Impact group than in the control group (0 vs. 30.8%; $p = 0.012$), but no significant differences in the incidences of other postoperative complications were seen between the groups. The operative mortality rate was 0% for each group.

The effects of immune-enhanced nutrition on laboratory and physical data (WBC count, CRP level, TP, Alb, T-Bil, AMY, GOT, GPT, BUN, Cr, BW, and APACHE-II score) during the perioperative period are shown in Fig. 1. No significant differences in the WBC counts, CRP levels, TP, Alb, T-Bil, AMY, GOT, BUN, and Cr results were seen between the two groups. However, the GPT level was significantly higher in the Impact group (Fig. 1h). While the change in BW during the perioperative period also did

Table 3 Baseline patient characteristics

	Impact ($n = 18$)	Control ($n = 13$)	p
Age (years)	62.6 ± 8.5	65.1 ± 10.0	0.466
Sex (male/female)	11/7	7/6	0.686
BMI	21.9 ± 2.1	22.1 ± 3.2	0.821
Serum albumin (g/dL)	3.9 ± 0.3	3.7 ± 0.5	0.296
PNI	46.5 ± 5.8	43.7 ± 5.0	0.176
Biliary drainage	7	8	0.213
PTBD	5 (71.4%)	5 (62.5%)	0.714
ENBD	2 (28.6%)	3 (27.5%)	
Duration of oral intake of Impact (days)	5	None	None
Resection procedure	SSpPD		
Reconstruction method	Modified child method		
Operation time (min)	329 ± 79	308 ± 88	0.488
Intraoperative blood loss (mL)	921 ± 566	947 ± 654	0.905
Pathological diagnosis			
PIDC	4 (22.2%)	2 (15.4%)	
IPMN			
IPMA	3 (16.7%)	1 (7.7%)	
IPMC	0	1 (7.7%)	
SPT	1 (5.6%)	0	
SCA	1 (5.6%)	0	
BDC	5 (27.8%)	3 (23.1%)	
VC	2 (11.1%)	4 (30.8%)	
DC	2 (11.1%)	2 (15.4%)	

BMI body mass index, *PNI* prognostic nutrition index = (10 × serum albumin) + [0.005 × total lymphocyte count (/mm^3)], *PTBD* percutaneous transhepatic biliary drainage, *ENBD* endoscopic naso-biliary drainage, *SSpPD* substomach-preserving pancreaticoduodenectomy, *PIDC* pancreatic invasive ductal carcinoma, *IPMN* intraductal papillary mucinous neoplasm, *IPMA* intraductal papillary mucinous adenoma, *IPMC* intraductal papillary mucinous carcinoma, *SPT* solid and pseudo-papillary tumor, *SCT* serous cystic adenoma, *BDC* bile duct carcinoma, *VC* papilla of Vater carcinoma, *DC* duodenal carcinoma

Table 4 Early postoperative outcome and complications

	Impact (n = 18)	Control (n = 13)	p
Duration of postoperative SIRS (days)	0.8 ± 1.0	0.9 ± 0.8	0.664
Duration of postoperative hospital stay (days)	29 ± 13	26 ± 12	0.516
Morbidity and mortality			
Pancreatic fistula	12 (66.7%)	8 (61.5%)	0.768
Delayed gastric emptying	2 (11.1%)	1 (5.9%)	0.751
Cholangitis	0	1 (5.9%)	0.232
Wound infection	0	4 (30.8%)	0.012
Perioperative death	0	0	

SIRS systemic inflammatory response syndrome

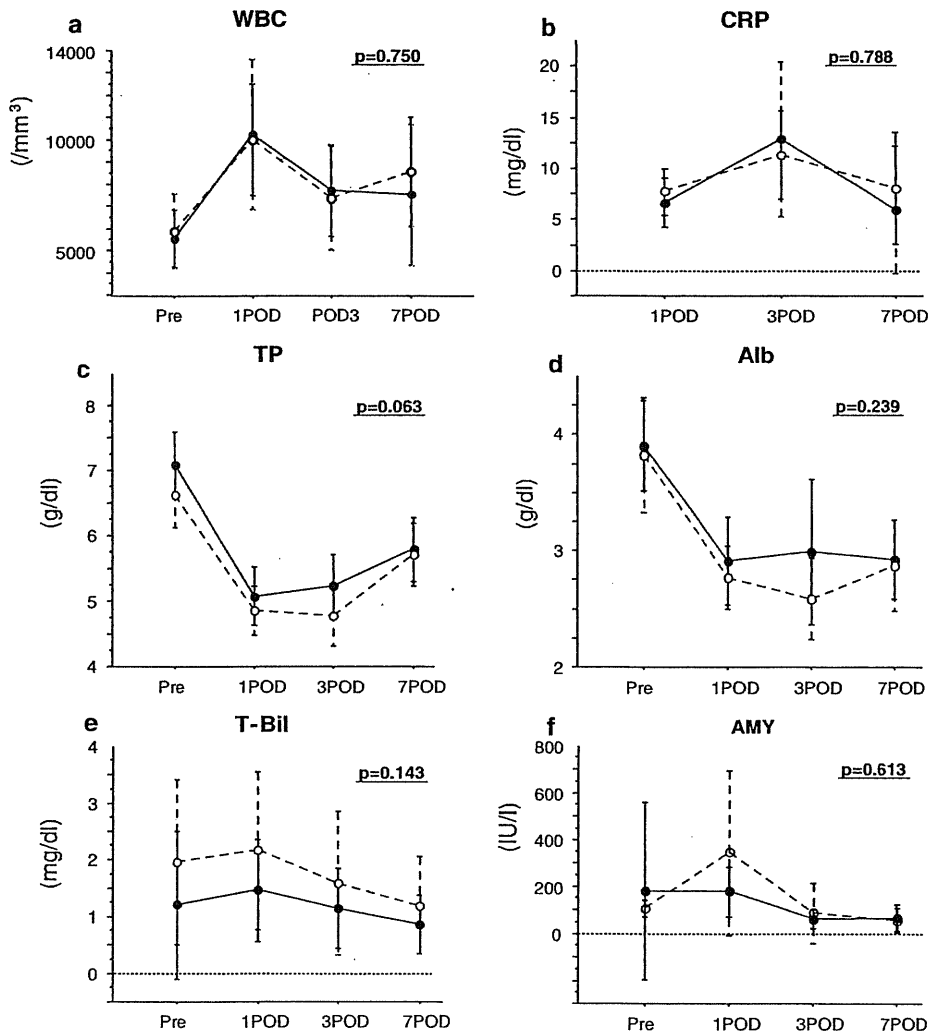
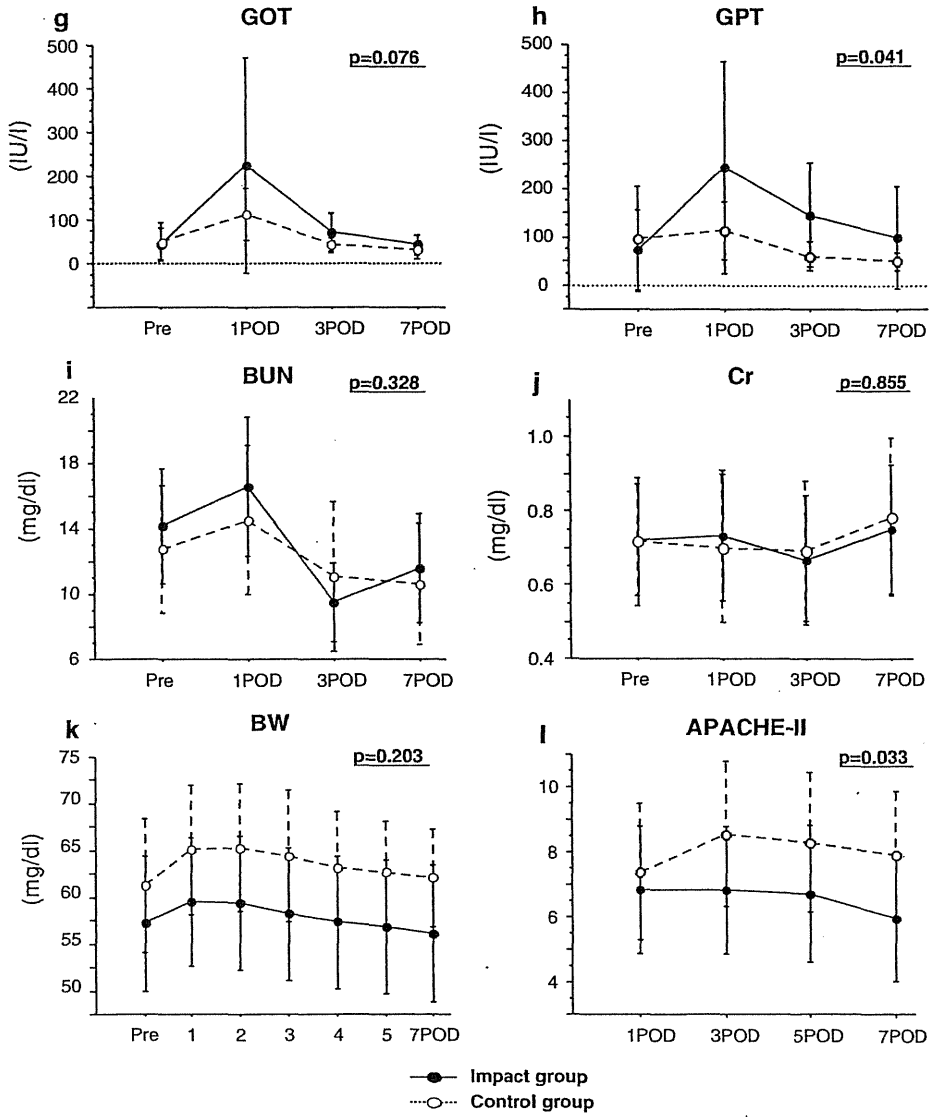


Fig. 1 Laboratory blood test results. *Filled circles* Impact group, *open circles* control group. **a** White blood cell count (*WBC*), **b** C-reactive protein (*CRP*), **c** total protein (*TP*), **d** serum albumin (*Alb*), **e** total bilirubin (*T-Bil*), **f** serum amylase (*AMY*), **g** glutamic oxaloacetic transaminase (*GOT*), **h** glutamic pyruvic transaminase (*GPT*), **i** blood urea nitrogen (*BUN*), **j** serum creatinine (*Cr*), **k** body weight (*BW*), **l** acute physiology and chronic health evaluation score II (*APACHE-II*)

not differ significantly between the two groups, the improvements in the gain or loss of BW after surgery showed a better course in the Impact group than in the control group. To evaluate the systemic severity of patients after surgery, we utilized the APACHE-II classification. A high postoperative APACHE-II score predicts an increased

Fig. 1 continued



risk of a complicated postoperative course [33]. The change in the total APACHE-II score after PD was significantly lower in the Impact group than in the control group ($p = 0.033$). Among the factors measured for the APACHE-II scores, the following factors showed significantly lower scores in the Impact group than in the control group: temperature on POD 1 ($p = 0.008$), mean arterial pressure on POD 1 ($p = 0.048$), heart rate on POD 5 ($p = 0.019$) and POD 7 ($p = 0.049$), and hematocrit on POD 7 ($p = 0.006$).

Discussion

Preoperative oral supplementation with Impact (750 mL/day for 5 days) was well tolerated by patients scheduled to undergo PD. The compliance rate was more than 80%, and the duration and dose of Impact used in this study were suitable. This encouraging result suggests that Impact could also be ingested by outpatients prior to elective PD.

In the present series, one patient with IPMN could not tolerate Impact because of pancreatitis and cholangitis. This patient complained of epigastralgia, fever, and jaundice after beginning to consume Impact. The patient's laboratory data showed elevated serum amylase and bilirubin levels. We suspect that this patient's pancreatitis and cholangitis might have originated from an obstruction caused by a mucinous secretion from the primary tumor, because the pancreatitis and cholangitis occurred simultaneously and progressed synchronously. Actually, the elevated serum bilirubin level consisted predominantly of

direct bilirubin. The patient's condition improved immediately after percutaneous transhepatic biliary drainage.

In the second part of this study, we retrospectively compared the outcomes of patients with and without (control group) the preoperative ingestion of an immune-enhanced formula prior to undergoing PD. In patients without hyperbilirubinemia, laboratory data showed that the postoperative GOT and GPT levels were higher in the Impact group than in the control group; in particular, GPT was significantly higher in the Impact group. In a study examining patients with esophageal cancer who ingested Impact immediately before undergoing a transthoracic esophagectomy with lymph node dissection, Takeuchi et al. [24] also reported an immediate postoperative elevation of transaminases. Although the mechanism remains unclear, a preoperative immune-enhanced diet may impose a load on hepatocytes after invasive surgery such as PD. Immune-enhanced formulas have been suggested to possibly cause a high postoperative BUN level as a result of an overload in nitrogen intake [41]. However, in the present series, we did not observe a marked change in the BUN level, and nitrogen overloading did not appear to be excessive.

Regarding the systemic severity of the patients in this study, the APACHE-II score tended to be lower in the Impact group than in the control group. When measured during the immediate postoperative phase, a high APACHE-II score is thought to be linked to mortality, and the APACHE-II score can be regarded as a summary indicator of an individual's response to surgical injury. The patients who received preoperative immunonutrition had a lower systemic severity score, so it appears that Impact consumption might reduce the severity of systemic damage. Several studies have reported that a supplementary diet rich in omega-3 fatty acids is related to a decrease in PGE2, which is a key fever mediator [42–44]. Our results suggest that the preoperative consumption of an immune-enhanced formula may reduce excess postoperative pro-inflammatory cytokine production (such excess production may result in serious complications or lethal multiple organ dysfunctions in patients who have undergone PD). Additional investigations of the detailed changes in some indicators, such as inflammatory cytokines, are needed.

In the present study, incisional wound infection was significantly less frequent in the Impact group than in the control group. SSI including incisional wound infection is a serious complication following surgery, requiring a prolonged hospitalization period, increased medical costs, and decreased patient satisfaction [45, 46]. SSI is primarily caused by surgical procedures, and performing surgery while minimizing the risk of SSI is important. The preoperative oral intake of immune-enhanced formulas, such as Impact, might also be important for preventing incisional wound infection.

The duration of postoperative SIRS and the length of the hospital stay were not significantly different between the two groups in our study. Thus, the effects of the preoperative ingestion of an immune-enhanced formula on the duration of the hospital stay among patients undergoing PD remain unclear. In this study, pancreatic fistula was the most common and important complication, not wound infection. The length of the hospital stay is likely to be affected by the severity of this complication, as it is regarded as a major unfavorable complication after PD. During this study, an end-to-side dunking anastomosis was used for the anastomosis between the pancreatic stump and the jejunum; however, since 2007 (after the completion of the present study), we have adopted a duct-to-mucosa anastomosis with 5-0 absorbable monofilament using a vinyl tube as a lost stent in pancreaticojejunostomy procedures. As a result, the incidence of pancreatic fistula after PD has decreased (data not shown). This concept has also successfully enabled the duration of the hospital stay after PD to be shortened.

To our knowledge, this is the one of few reports to suggest the feasibility and benefit of using an immune-enhanced formula, Impact, as part of the preoperative management of patients scheduled to undergo PD. To date, several groups have reported on immunonutrition in gastrointestinal cancer surgery patients [11, 12, 15, 47]. Most of these reports have demonstrated that patients receiving immunonutrition before and/or after surgery tended to have fewer postoperative complications. Gianotti et al. [22] reported that patients receiving immunonutrition with an enteral formula after PD had a significantly lower incidence of infectious complications than patients in the standard and parenteral groups. Di Carlo et al. [48] also reported similar results for postoperative enteral feeding in patients with pancreatic head cancer. However, no other reports have described patient compliance with preoperative oral intake, or the clinical significance of the preoperative ingestion of immune-enhanced formulas for patients undergoing PD.

In conclusion, a high rate of compliance with the preoperative oral administration of Impact Japanese version (750 mL/day, for 5 days) was observed in Japanese patients without malnutrition who were scheduled to undergo PD. This treatment appeared to be effective for preventing incisional wound infection and reducing systemic severity. To confirm the clinical benefits of preoperative Impact, a randomized control study including the use of a control group receiving a regular diet alone is needed. Of note, the composition of the commercially available Impact in Japan differs slightly from the original Impact used in Western countries, so we approve the

suggestion from Tsujinaka et al. [29] that such a randomized study should be performed exclusively in Japan. In addition, such a study would require a similar quality of operative procedures and perioperative management in both patient groups.

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J Gastrointest Surg (2012) 16:821–827
DOI 10.1007/s11605-011-1782-5

ORIGINAL ARTICLE

Predictive Factors for Anastomotic Leakage after Simultaneous Resection of Synchronous Colorectal Liver Metastasis

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Received: 15 September 2011 / Accepted: 11 November 2011 / Published online: 29 November 2011

Abstract
Background The optimal surgical strategy for resectable, synchronous, colorectal liver metastases remains unclear. The objective of this study was to determine which patients could benefit from staged resections instead of simultaneous resection by identifying predictive factors for postoperative morbidity and anastomotic leakage after simultaneous resection of synchronous, colorectal liver metastases and the primary colorectal tumor.
Methods This study involved 86 patients with synchronous colorectal liver metastases who underwent simultaneous resection of the primary colorectal tumor and the hepatic tumor. Postoperative mortality, morbidity, and other surgical outcomes, including survival and hospitalization, were assessed. Predictive factors for postoperative morbidity and for anastomotic leakage were evaluated.
Results Postoperative morbidity and anastomotic leakage were found in 55 (64%) and 18 (21%) patients. Predictive factors for postoperative morbidity and for anastomotic leakage were intraoperative blood loss and operation time >8 h, respectively. The overall 5-year survival rate was 45%.
Conclusions The frequency of morbidity and that of anastomotic leakage seemed to be high after simultaneous resection for synchronous colorectal liver metastases, especially when intraoperative blood loss or operation time increased greatly. Staged resections should be considered in cases in which excessive surgical stress from simultaneous resection of synchronous colorectal liver metastases would be expected.

Keywords Colorectal cancer · Hepatic metastasis · Liver metastasis · Morbidity · Anastomotic leakage

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Introduction

For patients with synchronous colorectal liver metastases (SCLM), hepatic resection is considered the best treatment, with reported 5-year survival rates between 23% and 37%.[1–4] Resections of both the primary colorectal lesion and the hepatic metastases are needed for patients with SCLM when they are resectable. However, the optimal surgical strategy for resectable SCLM still remains controversial.

From the perspectives of less operation with less mental stress and simplifying perioperative treatment, simultaneous resection of the primary colorectal and liver tumors is a favorable strategy for patients with SCLM.[5–8] However, several papers reported that the morbidity rate after simultaneous resection of primary and liver tumors was high because of greater surgical stress and a longer

operation time than for single-organ surgery. Staged resection with initial operation for the primary lesion followed by resection of hepatic tumors is regarded as an alternative strategy to avoid excessive surgical stress for patients with SCLM, though the efficacy of this strategy and the patients who could benefit from this strategy are unknown.[4–6,9,10]

Thus, this study was conducted to determine which patients could benefit from staged resections instead of simultaneous resection by identifying predictive factors for postoperative morbidity and anastomotic leakage after simultaneous resection of SCLM.

Patients and Methods

Patient Population

The medical records of all consecutive patients who underwent liver resections for colorectal liver metastases from January 1992 to January 2004 at our institution were analyzed retrospectively, with institutional review board approval. Eighty-six patients had SCLM. During this period, all SCLM patients received simultaneous resection of primary colorectal and hepatic tumors irrespective of the patient's or the tumor's characteristics. Lateral lymph node dissection was routinely performed in patients with advanced lower rectal cancer. All 86 patients underwent contrast enhanced computed tomography (CT) of the chest, abdomen, and pelvis, as well as hepatic MRI, preoperatively.

As a control, the morbidity of 167 patients who underwent hepatectomy for metachronous liver metastasis from colorectal cancer from January 1992 to January 2004 and that of 1,728 patients who underwent only resection for colorectal cancer with colorectal reconstruction during the same period were also reviewed. Of the 1,728 colorectal cancer patients, 1,319 had colon cancer and 409 had rectal cancer.

Postoperative Morbidity

Incidences of the following postoperative complications were analyzed: anastomotic leak, rectovaginal fistula, intraperitoneal or pelvic abscess, wound infection, wound dehiscence, ileus, enteroparesis, postoperative delirium, urinary tract infection, dysuria, empyema thoracis, pleural effusion, atelectasis, cholecystitis, perihepatic or subphrenic abscess, bile leak, liver failure, and others. Anastomotic leakage was defined as follows: peritonitis and a dehiscence in the anastomosis, discharge of pus from the anus, vaginal fistula, or feces from the abdominal drain. Leakage was confirmed by CT scan, contrast enema, re-operation, or digital rectal examination. All complications were graded according to the classification proposed by Clavien et al.[11] Postoperative mortality was defined to include any death during postoperative hospitalization or within 30 days.

Assessment of Predictive Factors for Postoperative Morbidity

Correlations between postoperative morbidity and the following patient, tumor, and surgical factors were analyzed: age, sex, body mass index (BMI), preoperative comorbidity, site of primary tumor, intestinal obstruction by tumor, size of primary tumor, differentiation of tumor, distribution of hepatic tumors, number of hepatic tumors, hepatic tumor size, operative methods, operation time, intraoperative blood loss, and blood transfusion.

Survival

Patients were followed regularly at 3-month intervals with blood testing and CT. Survival and follow-up were calculated from the time of the operation to the date of death or last available follow-up. The survivors' median follow-up time after surgery was 73 months.

Statistical Analysis

Statistical comparisons of baseline data were performed using the chi-square test. Continuous variables were compared with the independent t test. Multivariate analyses to evaluate the independent predictive factors for postoperative complications or anastomotic leakage were done by multiple logistic regression analysis. The survival rate was calculated by the Kaplan–Meier method.[12] A difference was considered significant when p was less than 0.05.

Results

Patients and Operative Details

From 1992 to 2004, 86 patients were treated with simultaneous resection of primary and hepatic tumors for SCLM. There were 37 female and 49 male patients, with a median age of 59 years (range, 40 to 85 years). The site of the primary tumor was colon in 48 and rectum in 38. The primary tumor was staged as T3 in 54 (63%) and T4 in 32 (37%) according to the TNM classification. Metastatic lymph nodes were found in 65 patients (76%). The mean diameter of the primary tumor was 55 mm (range, 26–140 mm).

Liver metastases were solitary in 29 patients and multiple in 57 patients. In 47 patients (55%), the hepatic

tumor showed a unilobar distribution, while a bilobar tumor distribution was observed in 39 (45%). The mean diameter of the hepatic tumor was about 43 mm (range, 5–200 mm). The mean resected liver volume was 380 g (range, 10–1,660 g).

The operation for primary colorectal cancer was right (hemi) colectomy in 17 patients, transverse colectomy in 1, left (hemi) colectomy in 4, sigmoidectomy in 24, high anterior resection in 7, low anterior resection in 20, very low anterior resection in 6, inter-sphincteric resection in 2, Hartmann's operation in 1, and abdomino-perineal resection in 4 (Table 4). A diverting stoma to prevent anastomotic leakage was made in 22 (26%) patients at the surgeon's discretion, and lateral lymph node dissection was performed in 20 (23%). In terms of liver tumor resection, lobectomy was performed in 11 patients, segmentectomy in 22, bisegmentectomy in 1, trisegmentectomy in 2, subsegmentectomy in 3, and partial resection in 47.

Adjuvant therapy was given to only 17 patients (19.8%) because adjuvant chemotherapy for colorectal cancer in stage III or more was performed since January 2003. Neoadjuvant chemoradiation targeting for rectal cancer was given to three patients (3.5%).

Morbidity

No patients died within 30 days of the operation, but 55 (64%) patients developed complications (Table 1). Eighteen patients (21%) experienced leakage, of whom 6 needed urgent re-operation with ileostomy and drainage of an intra-abdominal collection caused by leakage. Postoperative bleeding, wound dehiscence, and ileus were the reasons for the three other re-operation cases. The most frequent complication was wound infection.

The morbidity rate of the 167 patients who underwent hepatectomy for metachronous colorectal liver metastasis during the same period was 19.8%, and that of 1,728 patients who underwent only resection for colorectal cancer was 32.1%. Anastomotic leakage occurred in 123 (7.1%) of the aforementioned 1,728 patients.

Factors Affecting Complications, Especially Anastomotic Leakage

Postoperative complications were significantly correlated with presence of diverting stoma ($p<0.01$), duration of operation greater than 8 h ($p<0.01$), amount of intraoperative blood loss ($p<0.01$), and intraoperative blood transfusion ($p<0.01$). The aforementioned factors were entered into multivariate analysis. Only a greater amount of blood loss had a predictive value for increased occurrence of postoperative complications.

Then, the correlations between anastomotic leakage and clinicopathological factors were examined to identify risk factors for anastomotic leakage after simultaneous resection for SCLM. Patients who underwent abdomino-perineal

Table 1 Postoperative complications after simultaneous resection for SCLM according to Clavien grade

Complications	No. of patients	Gr I	Gr II	Gr IIIa	Gr IIIb	Gr IVa
Colon and rectum						
Anastomotic leakage	18 (21%)		12		6	
Intrapelvic abscess	6 (7%)	1	4		1	
Intraperitoneal abscess	5 (6%)	1	0	3	1	
Rectovaginal fistula	4 (5%)		1		3	
Liver						
Bile leakage	7 (8%)	6	1			
Hepatic abscess	7 (8%)		5	1	1	
Liver failure	3 (3%)	1	1			1
Postoperative bleeding	1 (1%)				1	
Other organs						
Wound infection	25 (29%)	23	2			
Pleural effusion	12 (14%)	1		11		
Wound dehiscence	6 (7%)	3	2		1	
Enteroparesis	5 (6%)	5				
Postoperative delirium	4 (5%)	1	3			
Dysuria	4 (5%)		4			
Urinary tract infection	3 (3%)		3			
Pneumonia	2 (2%)		2			
Others	7 (8%)	1	4		2	

resection (n=4) or Hartmann's operation (n=1) were excluded from the analysis. Anastomotic leakage was significantly correlated with lateral lymph node dissection (p<0.01), primary site of rectum (p=0.01), duration of operation greater than 8 h (p<0.01), and amount of intraoperative blood loss (p=0.02). Neither serum levels of TP and ALB, steroid usage, nor neoadjuvant therapy showed correlation with occurrence of anastomotic leakage (data not shown). Multivariate analyses revealed operation time greater than 8 h (p<0.01) as the only independent predictive factor for anastomotic leakage after simultaneous resection of SCLM (Table 2). Extent of hepatectomy, timing of anastomosis and hepatectomy, and usage of Pringle maneuver did not correlate with occurrence of complication or anastomotic leakage.

Table 3 showed the rates of complication ≥ IIIa and anastomotic leakage according to operative procedures of the primary and hepatic resections which were performed in the same patient. Complication ≥ IIIa and anastomotic leakage were more frequently observed in patients with rectal resection; however, extent of hepatectomy did not seem to affect occurrence of complication ≥ IIIa or anastomotic leakage.

Hospitalization was significantly longer in the 55 patients with postoperative morbidity (32.2 days) than in the 31 patients without postoperative morbidity (17.6 days) (p<0.01). In addition, hospitalization was significantly longer in the 18 patients with anastomotic leakage (43.5 days) than in the 63 patients without anastomotic leakage (22.2 days) (p<0.01).

Survival

The overall survival rate after simultaneous resection for SCLM of the 86 patients was 61% at 3 years and 45% at 5 years, with MST of 47 months.

Discussion

For patients with resectable SCLM, both primary tumor resection and hepatectomy for liver metastasis could lead to long-term survival, with a 5-year survival rate of 23–37%. However, the optimal strategy, including surgical resection and perioperative treatment, remains controversial for resectable SCLM. In terms of surgical resection for SCLM, it has not been resolved whether simultaneous resection or staged resections would be preferable.

There are several rationales for simultaneous resection of SCLM. In simultaneous resection, the treatment strategy would become simpler. In the staged resections, a series of neoadjuvant chemotherapy or chemoradiotherapy, resection of primary tumor, chemotherapy between two operations, hepatectomy, and adjuvant chemotherapy could be the maximal total treatment for SCLM, while simultaneous resection could simplify and shorten the treatment schedule by eliminating one operation. Completion of the two resections and initiation of adjuvant chemotherapy occur earlier with simultaneous resection than with staged resections. Considering survival, comparable survival for simultaneous resection was shown in comparison with that for staged resections.[13] Furthermore, simultaneous resection could relieve patients from a considerable degree of mental and physical stress and decrease total treatment cost by preventing a second resection for hepatic metastases. Recent advances in colorectal and hepatic surgery have enabled simultaneous resection to be performed more safely. Martin et al. reported the safety and efficacy of simultaneous resection. By avoiding a second laparotomy, the overall complication rate was reduced, and length of hospital stay was shortened, with no change in operative mortality.[7,8]

However, at present, staged resections with initial resection of the primary tumor followed by hepatic resection have been frequently performed in patients with SCLM for several reasons.[4,5,9,10] First, the perioperative risk of staged resections has been thought to be less than that of simultaneous resection.[4,13,14] Sheele et al. reported 13 anastomotic leakages of 90 simultaneous procedures in their series, and two of them led to death.[4] Thelen et al. proposed the criteria for simultaneous liver resection according to the age and extent of liver resection, because death after simultaneous liver resection (n=4) occurred after major hepatectomies, and three of these four patients were 70 years of age or older.[15] Second, staged resections might offer a chance to evaluate liver or extrahepatic metastases between the two operations. Lambert et al. reported that staged resections of synchronous hepatic metastases with an interval of 3 to 6 months might allow occult disease to become clinically detectable and could potentially identify patients for whom a hepatic resection would offer no survival benefit.[10] Fujita recommended an interval resection to assess the metastatic status of the regional lymph nodes, because the presence of six or more lymph node metastases was an independent poor prognostic factor in patients with resected SCLM and a relative contraindication for hepatic resection.[9] Some authors proposed chemotherapy between primary tumor resection and liver resection to select patients that could benefit from hepatectomy.[13,16] Alternatively, a liver-first approach of doing liver resection first and primary resection second was newly proposed as a strategy for SCLM.[17,18] The liver-first approach might avoid needless radical colorectal surgery by confirming curability of hepatic metastases first and also might increase resectability compared with the ordinary staged resections especially in patients with progressive hepatic metastases.

Table 2 Correlation between anastomotic leakage and clinicopathological factors in patients who underwent simultaneous resection for SCLM

		Leakage (−) (n=63)	Leakage (+) (n=18)	Univariate analysis p value	Multivariate analysis p value, RR (95%CI)
Patient characteristics					
Median age (range) (years)		59 (40–85)	59 (41–73)	0.81	
Male/female		33/30	12/6	0.42	
BMI (mean±SD)		21.9±2.9	22.5±2.2	0.44	
Preoperative comorbidity					
Absent		44	12	0.78	
Present		19	6		
Primary colorectal tumor					
Site	Colon	42	6	0.01	N.S.
	Rectum	21	12		
Stenosis	Absent	56	0	0.34	
	Present	7	18		
Tumor size, mm		52.0	58.0	0.25	
pT stage	pT3	41	9	0.25	
	pT4	22	9		
pN stage	pN0	17	2	0.22	
	pN+	46	16		
Histology	Well, mod	60	15	0.12	
	Poor	3	3		
Liver metastasis					
Distribution	Unilobar	38	9	0.43	
	Bilobar	25	9		
Number of tumors (range)		2.3 (1–8)	2.6 (1–8)	0.57	
Tumor size, mm		47	33	0.06	
Operative factors					
Lateral lymph node dissection					
Absent		55	10	<0.01	N.S.
Present		8	8		
Diverting stoma					
Absent		48	11	0.24	
Present		15	7		
Liver resection					
Partial Hx, segmentectomy		51	16	0.72	
≥Lobectomy		12	2		
Timing of anastomosis					
Colectomy→anastomosis→Hx		20	4	0.20	
Colectomy→Hx→anastomosis		7	5		
Hx→colectomy→anastomosis		36	9		
Pringle maneuver					
Absent		10	1	0.44	
Present		53	17		
Operation time					
<8 h		53	8	<0.01	<0.01, 6.63 (2.09–20.9)
≥8 h		10	10		
Blood loss, g (range)		1,345 (162–6,000)	2,487 (430–6,560)	0.02	N.S.
Transfusion					
Absent		39	9	0.37	
Present		24	9		
Blood transfusion, ml		343	1,212	0.05	

RR relative risk, *CI* confidence interval, *Hx* hepatectomy, *N.S.* non-significant (p>0.05)

Table 3 Rates of complication ≥ Gr IIIa and anastomotic leakage according to the site of primary colorectal resection and extent of hepatectomy

Primary colorectal resection	Hepatectomy	Complication ≥ Gr IIIa	Anastomotic leakage
Colectomy	<Lobectomy	4/40 (10%)	5/39[a] (13%)
	≥Lobectomy	0/7 (0%)	1/7 (14%)
Rectal resection	<Lobectomy	11/32 (34%)	11/28[b] (39%)
	≥Lobectomy	2/7 (29%)	1/7 (14%)

[a] One patient who underwent Hartmann's operation was excluded from the analysis

[b] Four patients who underwent abdomino-perineal resection were excluded from the analysis

This study evaluated morbidity, especially anastomotic leakage, after simultaneous resection for SCLM in order to assess the safety of simultaneous resection. Anastomotic leakage is sometimes fatal and can cause a difficult situation with physical and mental discomfort or pain. The morbidity rate of patients who underwent simultaneous resection for SCLM seemed to be higher than that of patients with resected metachronous colorectal hepatic metastasis or that of patients who underwent only resection for colorectal primary cancer. Predictive factors for postoperative morbidity and for anastomotic leakage were intraoperative blood loss and operation time greater than 8 h, respectively. The overall morbidity rate and the rate of anastomotic leakage were 91% and 50%, respectively, in patients with operation time greater than 8 h, and 54% and 13%, respectively, in patients with operation time less than or equal to 8 h. Blood loss and operation time usually represent the amount of surgical stress. Excessive surgical stress was possibly correlated with postoperative morbidity. Hospitalization of patients with complications was significantly longer than that of patients without complications. In particular, the average hospitalization of the 18 patients with anastomotic leakage was more than 43 days. Retrospective studies have also indicated that the occurrence of anastomotic leakage is associated with increased morbidity, mortality, and prolonged hospital stay. Additionally, anastomotic leakage may be associated with an increased risk of local recurrence.[19]

Various risk factors for anastomotic leakage have been analyzed by several investigators. Age, sex, obesity, level of anastomosis, smoking, blood transfusion, tumor diameter, preoperative (chemo) radiotherapy, physical status, obstruction, and coronary heart disease have been shown to be significant risk factors for leakage.[20–24] In simultaneous resection for SCLM, not only the factors related to the tumor, the patient, or the colorectal operation, but factors related to the hepatectomy could affect the occurrence of anastomotic leakage. However, the extent of hepatic resection, sequence of colectomy, hepatectomy, anastomosis, use of the Pringle maneuver, and total time of the Pringle maneuver were not predictive factors for anastomotic leakage or postoperative complications in patients with resected SCLM.

Recently, a diverting stoma has been often used to prevent anastomotic leakage in patients who undergo low anterior resection by diverting the fecal stream and keeping the anastomosis free of material.[19,25,26] In this study, the presence of a diverting stoma was not a predictive factor for absence of postoperative anastomotic leakage. However, the analysis estimating efficacy of a diverting stoma in this study was not accurate, because a diverting stoma was basically used in patients whose risk for anastomotic leakage was considered to be high by the surgeons. The site of primary tumor that has been reported as a strong predictive factor in previous studies was not a predictive factor for anastomotic leakage in this series. Use of diverting stoma might affect the result of analyses of predictive factors for anastomotic leakage. A randomized, controlled trial is needed to elucidate the efficacy of a temporary diverting stoma.

Although several rationales for the simultaneous resection for SCLM are clear, staged resections should be selected to prevent anastomotic leakage or serious complications when the scheduled operation would result in considerable surgical stress, i.e., predicted operation time greater than 8 h according to the results of the present study. Predicted operation time should be calculated by considering various factors, such as characteristics of the patient, primary and metastatic tumor, extent of operation, difficulty of the procedure, and so on. Based on the results of this study, we now select staged resections when operation time is expected to be greater than 8 h; otherwise, we select simultaneous resection. A prospective study of SCLM to evaluate the efficacy and safety of the operation time-based decision model is in progress.

Currently, adjuvant chemotherapy is one of the key factors which could affect prognosis. Then, comparison of ratio of patients who could receive adjuvant chemotherapy will be essential when comparing the efficacy of simultaneous resection and that of staged resections in a future study of SCLM. Furthermore, in staged resections, there is a risk that some patients could not undergo a second resection after the first resection due to tumor progression or complication of first surgery. Resection rate of patients who could undergo both primary and hepatic resections