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ORIGINAL ARTICLE

Surgical treatment of lymph node metastases from hepatocellular carcinoma

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Abstract
Background No consensus has been reached on the feasibility and efficacy of surgery for lymph node metastases (LNM) from hepatocellular carcinoma (HCC).
Methods Of 2189 patients with HCC treated at our hospital between July 1992 and March 2008, we retrospectively reviewed the medical dossiers of the 18 patients (0.8%) who underwent lymph node resection and were pathologically diagnosed to have LNM from HCC. The surgical procedure for LNM was selective lymphadenectomy of those lymph nodes suspected to harbor metastasis. The feasibility and efficacy of selective lymphadenectomy was examined, and clinicopathological factors were analyzed with the aim of determining which patients would most benefit from surgery.
Results Eighteen patients underwent surgery without mortality or liver failure. Morbidities were found in four patients (22.2%). The median survival time (MST) after surgery was 29 months [95% confidence interval (CI) 21–38 months). The 1-, 3-, and 5-year overall survival rates were 85, 42, 21%. The median progression-free survival (PFS) after surgery was 6 months (95% CI 1–11 months), and the median extrahepatic PFS was 16 months (95% CI 13–18 months). Single LNM was the only favorable prognostic factor after surgery (Hazard ratio 0.082, 95% CI 0.008–0.83).
Conclusion Selective lymphadenectomy of LNM from HCC was a feasible and efficacious procedure. Survival rates can be expected to improve after selective lymphadenectomy of single LNM.

Keywords Hepatocellular carcinoma · Lymph node metastases · Surgery

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Introduction

Lymph node metastases (LNM) are rare and generally associated with poor prognosis in hepatocellular carcinoma (HCC) [1, 2]. No consensus has yet been reached on the treatment strategy for LNM from HCC [3–5]. A few case reports have been published on the surgical treatment of LNM from HCC. Abe et al. [6] described two patients who survived for more than 4 years after the resection of an isolated metastatic lymph node followed by transarterial embolization (TAE). Togo et al. [7] also described a patient who survived for 7 years without recurrence after single node resection and simultaneous hepatectomy. In contrast, Uenishi et al. [8] reported that the resection of multiple LNM led to a poor prognosis, and they questioned the efficacy of regional lymphadenectomy in HCC. Their poor results are partly attributable to the deterioration of cirrhotic liver function due to altered portal or lymphatic drainage caused by extensive LN dissection [9]. Based on these findings, it is possible that selective lymphadenectomy of suspected metastatic lymph nodes instead of regional lymphadenectomy would be an effective treatment for LNM from HCC.

The aims of this study were to present our surgical experiences on LNM from HCC and to discuss the feasibility and efficacy of selective lymphadenectomy. We also

examined prognostic factors to determine who might most benefit from surgical resection.

Patients and methods

From July 1992 to March 2008, 2189 patients with HCC were treated at the National Cancer Center Hospital East in Kashiwa, Japan. Among those 2189 patients with HCC, 75 patients (3.4%) were clinically diagnosed to have LNM from HCC and 21 patients (1.0%) actually underwent surgery. Eighteen patients (0.8%) who underwent lymph node resection and in whom LNM were pathologically diagnosed were included in this and their medical histories retrospectively examined.

The staging and resectability of tumors were assessed by contrast-enhanced computed tomography (CT) scans, magnetic resonance imaging (MRI), hepatic arterial angiography, ultrasounds, and chest X-rays. The clinical diagnosis of LNM was based on the following findings from the contrast-enhanced CT, MRI, or ultrasound scans: (1) the short axis diameter of the lymph node was minimally >1 cm; (2) the lymph node showed hypervascularity in the arterial phase and washout of enhancement in the venous phase; (3) the liver tumor had been pathologically or clinically diagnosed as HCC according to the guidelines issued by American Association for the Study of Liver Diseases [10]. A typical case of LNM from HCC is depicted in Fig. 1. Indications of surgery for LNM from HCC were: (1) isolated LNM; (2) metachronous LNM without any tumor in the liver or synchronous LNM with intrahepatic tumor that was potentially resectable or controllable by non-surgical treatments, such as TAE or radiofrequency ablation (RFA); (3) no extrahepatic metastases except lymph nodes; (4) sufficient liver function (Child–Pugh grade [11]: A or B) and performance status [Eastern Cooperative Oncology Group Performance Status (ECOG PS) [12]: 0 or 1] to undergo surgery. Liver function was assessed by liver biochemistry tests, the Child–Pugh grade, and the indocyanine green retention rate at 15 min [13]. The patients' data were reviewed by hepatic surgeons, medical oncologists, and interventional radiologists during a conference to determine if the patients met the aforementioned criteria.

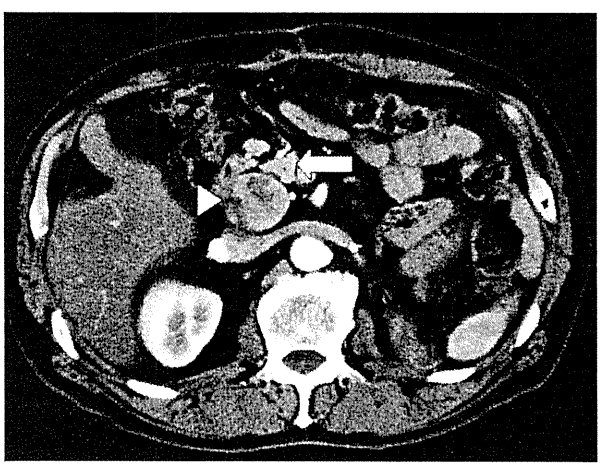

Fig. 1 Computed tomography findings of a solitary lymph node metastasis from hepatocellular carcinoma (HCC). A round-shaped, large lymph node (*arrowhead*) was found on the posterior surface of pancreas head (*arrow*). The lymph node was 6.0 cm in diameter and showed early enhancement in the arterial phase of the dynamic study

The surgical treatment procedure for LNM was, in principle, selective lymphadenectomy in which only lymph nodes suspected of metastasis were resected. With this approach, potential deterioration of liver function caused by altered lymphatic drainage after extensive LN dissection was avoided. Thin vessels around the lymph nodes were ligated whenever possible to prevent lymphatic leakage. Resected lymph nodes were pathologically examined with hematoxylin–eosin (HE) stain. When the results from the HE stain were not definitive, we also performed immunohistochemistry tests to confirm the diagnosis. Patients were followed-up every 3 months after surgery and were assessed for recurrence by CT examination and tumor marker level (alpha fetoprotein and protein induced by vitamin K absence-II).

Survival time was calculated from the date of operation. Clinicopathological findings and survival were compared among the 18 patients who underwent resection for LNM. The correlation between survival and clinicopathological findings was also examined. Survival analyses were performed using the Kaplan–Meier method, and differences between the curves were tested using the log-rank test (SPSS ver. 11.0J for Windows; SPSS, Chicago, IL). Factors related to survival were analyzed with the Cox proportional hazards regression model. p values <0.05 were considered to be statistically significant.

Results

Patient characteristics

Patient characteristics of the 18 patients are listed in Table 1. Sixteen and two patients were Child–Pugh grade A and B, respectively. The LNM was solitary in 13 patients and multiple in five patients. The mean diameter of the metastatic lymph nodes was 5.1 cm. Thirteen patients had received previous treatments that consisted of hepatectomy ($n = 8$), TAE ($n = 3$), percutaneous ethanol injection ($n = 1$), and proton-beam therapy ($n = 1$). Median

Table 1 Patient characteristics

Patient characteristics	Patients ($n = 18$)
Male, *n* (%)	16 (88.9)
Age (years)	65.2 ± 2.1
Performance status (0/1/2/3), *n*[a]	17/1/0/0
HCV Ab (+), *n* (%)	9 (50)
Child–Pugh grade (A/B/C), *n*	16/2/0
Albumin (g/dl)	3.9 ± 0.1
T.Bil (mg/dl)	0.9 ± 0.1
ICG15R (%)	17.3 ± 2.6
PT (% standard)	82.6 ± 3.9
Platelet ($\times 10^4$/mm^3)	15.3 ± 1.1
AFP (ng/ml)	1200 ± 750
PIVKA-II (mAU/ml)	410 ± 270
Previous treatments, *n* (%)	13 (72.2)
Simultaneous intrahepatic lesion, *n* (%)	13 (72.2)
Portal vein invasion, *n* (%)[b]	8 (44.4)
Multiple intrahepatic lesions, *n* (%)[b]	7 (38.9)
T-stage of intrahepatic lesions (T1/T2/T3/T4), *n*[b,c]	3/5/5/5
Size of LNM (cm)	5.1 ± 1.0
Multiple LNM, *n* (%)	5 (27.8)
Extrahepatic metastasis except LNM, *n* (%)	0 (0)
JIS score (3/4/5), *n*[d]	16/2/0

All values are given as the standard error of the mean (SEM) unless otherwise indicated

HCV Ab Hepatitis C virus antibody, *T.Bil* total bilirubin, *ICG15R* indocyanine green retention rate at 15 min, *PT* prothrombin time, *AFP* alpha fetoprotein, *PIVKA-II* protein induced by vitamin K absence-II, *LNM* lymph node metastases, *JIS score* Japan Integrated Staging score

[a] Performance status was evaluated according to the ECOG (Eastern Cooperative Oncology Group) criteria [11]

[b] When LNM was metachronous and the hepatic lesion did not exist simultaneously, the findings were evaluated for the most recently treated hepatic lesions

[c] T-stage was evaluated according to the TNM staging by the Liver Cancer Study Group of Japan [14]

[d] Japan Integrated Staging score can be obtained by combining the TNM stage score by the Liver Cancer Study Group of Japan and the Child–Turcotte-Pugh stage score [18]

duration from the primary treatment for HCC to LN recurrence in these 13 patients was 36 months (range 4–124 months). In 13 patients, LNM were accompanied by simultaneous hepatic lesions, and five of the 13 patients had multiple hepatic lesions. Of the five patients without simultaneous hepatic lesions, two had multiple hepatic lesions previously while three patients had only single lesions. The underlying liver pathology in three patients was normal, while seven patients had chronic hepatitis and eight patients had cirrhosis.

Locations of LNM

The metastatic lymph nodes in the 18 patients were located along the left gastric artery ($n = 4$), on the posterior surface of the pancreas head ($n = 4$), around the abdominal aorta ($n = 3$), above the diaphragm ($n = 3$), in the hepatoduodenal ligament ($n = 3$), and along the common hepatic artery ($n = 1$).

Surgery for LNM

Selective lymphadenectomy was performed in 17 patients, while one patient underwent regional lymphadenectomy along the left-gastric artery, common hepatic artery, and hepatoduodenal ligament. Among the 13 patients with simultaneous hepatic lesions, nine patients underwent simultaneous hepatectomy (3 lobectomies, 3 partial resections, 1 segmentectomy, 1 central bisegmentectomy, and 1 extended lobectomy), three patients received non-operative treatments (2 TAE and 1 RFA), and one patient received careful follow-up without treatment because the lesion became obscure in severely cirrhotic liver and could not undergo TAE. During the same period, one patient underwent surgery for LNM, but the lymph node could not be resected due to involvement of main portal vein. Two other patients underwent surgery for LNM, but the pathological findings revealed that one was benign reactive lymphadenopathy and the other was metastasis from a neuroendocrine tumor. These three cases were not included in the present study. There was no postoperative mortality. Six postoperative complications occurred in four patients: transient pleural effusions ($n = 2$), cholecystitis ($n = 1$), bile leak ($n = 1$), intestinal obstruction ($n = 1$), and wound infection ($n = 1$). No patients developed liver failure or refractory ascites. Transient pleural effusions were treated with single thoracocentesis.

Survival

The median survival time (MST) of 18 patients was 29 months after surgery [95% confidence interval (CI) 21–38 months) and 32 months after clinical diagnosis (95% CI 23–41 months). The 1-, 3-, and 5-year overall survival rates after surgery were 85, 42, 21%, respectively. The median progression-free survival (PFS) after surgery for LNM was 6 months (95% CI 1–11 months), and the median extrahepatic PFS was 16 months (95% CI 13–18 months) (Fig. 2).

Recurrence after resection of LN metastasis from HCC

Among the 12 patients with disease progression after surgery, four patients developed only intrahepatic lesions that were treated by TAE ($n = 2$) or RFA ($n = 2$). The other

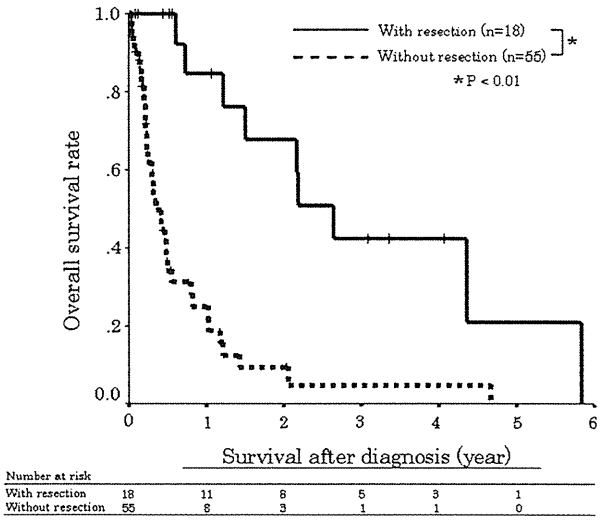

Fig. 2 Cumulative survival curves of patients with or without resection of lymph node metastases (LNM). The median survival time after clinical diagnosis was 32 months with resection (95% CI 23–41 months) and 4 months without resection (95% CI 3–6 months)

eight patients developed both intra- and extrahepatic lesions. The extrahepatic recurrences occurred in LN ($n = 6$), lung and LN ($n = 1$), and peritoneum ($n = 1$). One patient with lung and LN recurrence was treated with repeated selective lymphadenectomy and partial lung resection each time. The remaining seven patients with extrahepatic recurrences received the best supportive care ($n = 4$) or chemotherapy ($n = 3$).

Correlation between clinicopathological factors and overall survival

The correlation between clinicopathological factors and overall survival of the 18 patients is shown in Table 2. The survival rate of the patients with resection of single LNM was statistically higher than that of multiple LNM (MST: 52 vs. 14 months after surgery, $p < 0.01$) (Fig. 3). Liver functions, status of viral hepatitis, history of previous treatments, presence of intrahepatic lesions, curability of simultaneous intrahepatic lesions, regions of metastatic LNs, and other factors were not statistically significant. In order to eliminate the effect of possible confounding factors and small sample size, factors with p values <0.2 by univariate analysis were analyzed with the Cox proportional hazards regression model: the single LNM was found to be the only favorable prognostic factor (hazard ratio 0.082, 95% CI 0.008–0.83).

Non-surgical treatments

During the same period, 55 patients were clinically diagnosed to have LNM, but did not undergo lymphadenectomy due to the following reasons: (1) poor control of intrahepatic lesions ($n = 18$); (2) regional or systemic LNM ($n = 16$); (3) extrahepatic metastasis other than LNM ($n = 9$); (4) poor liver function (Child–Pugh grade C) ($n = 5$); (5) poor performance status (ECOG PS ≥ 2) ($n = 4$); (6) patients' preference ($n = 2$); (7) involvement of main portal vein ($n = 1$). The MST of 55 patients without lymphadenectomy was 4 months after clinical diagnosis (95% CI 3–6 months) and was significantly shorter than that of patients with lymphadenectomy (32 months; 95% CI 23–41 months) ($p < 0.01$) (Fig. 2). Non-operative treatments included the best supportive care ($n = 19$), systemic chemotherapy ($n = 13$), TAE ($n = 8$), external beam radiation therapy ($n = 5$), transarterial infusion chemotherapy ($n = 5$), immunotherapy ($n = 3$), and hepatic arterial continuous infusion chemotherapy ($n = 2$). Four patients developed complications that were directly related to the LNM from HCC, namely, obstructive jaundice ($n = 2$), esophageal obstruction ($n = 1$), and obstruction of inferior vena cava ($n = 1$) (Fig. 4).

Discussion

Lymph node metastases from HCC are rare. The feasibility and efficacy of surgical treatment for LNM from HCC has not been fully evaluated. Several case studies have reported mortality cases and high morbidity rate after surgery [8, 9]. In our study, however, there was no mortality or liver failure associated with surgery for LNM, although eight cases were complicated by liver cirrhosis. These results demonstrate the safety of selective lymphadenectomy for LNM from HCC in selected patients and are in contrast to the high rate of liver failure previously reported following regional lymphadenectomy [8, 9]. The favorable outcomes of selective lymphadenectomy may be attributable to the maximum conservation of the lymphatic and portal flow around the liver. Selective lymphadenectomy of LNM might be a safer and feasible procedure in patients with liver cirrhosis, although the indication for selective lymphadenectomy should still be carefully considered, especially in terms of liver function.

Considering the survival benefit of selective lymphadenectomy for patients with LNM, the MST was 29 months after lymphadenectomy and the 1-, 3-, and 5-year OS were 85, 42, and 21%. Survival more than 3 years was achieved in five patients after surgery, and two of these patients are still alive without a recurrence. These results indicate the survival benefit of selective lymphadenectomy for LNM from HCC in selected patients. The efficacy of lymphadenectomy was recently questioned by Sun et al. [3]. However, the methods and patient backgrounds were different between two studies. In Sun's study, the evaluation

Table 2 Correlation between clinicopathological factors and overall survival after lymph node resection of HCC (the log-rank test)

Patient characteristics	*n*	Univariate analysis				Multivariate analysis		
		3-year OS (%)	5-year OS (%)	MST (months)	*p* value	Hazard ratio	(95% CI)	*p* value
Age (years)								
<70	12	34.3	0	24.5	0.15	0.09	(0.005–1.62)	0.29
≧70	6	66.7	66.7	68.3				
Serology of viral hepatitis								
HBs Ag (−) and HCV Ab (−)	5	100	0	52.3	0.13	0.02	(0.00–1.12)	0.19
HBs Ag (+)/HCV Ab (+)/both (+)	13	22.2	22.2	24.5				
Child–Pugh grade								
A	16	40.9	0	29.4	0.48			
B	2	50	50	24.5				
AFP (ng/ml)								
≥400	5	50	50	14.5	0.97			
<400	13	38.1	19.1	29.4				
PIVKA-II (mAU/ml)								
≥100	9	40	40	29.4	0.77			
<100	9	41.7	41.7	24.5				
Liver cirrhosis								
Yes	8	57.1	57.1	68.3	0.18	0.04	(0.00–5.73)	0.07
No	10	22.2	0	25.6				
Simultaneous hepatic lesions								
Absent	5	75	75	68.3	0.08	0.57	(0.00–88.8)	0.21
Present	13	25.9	0	25.6				
Number of intrahepatic lesions[a]								
Single	12	37.5	37.5	24.5	0.6			
Multiple	6	50	25	25.6				
T-stage of intrahepatic lesions[b]								
T1/2	8	33.3	33.3	24.5	0.67			
T3/4	10	51.4	25.7	52.3				
Portal vein invasion[a]								
Present	8	62.5	0	52.3				
Absent	10	28.6	28.6	25.6	0.77			
Number of LNM								
Single	13	55.6	27.8	52.3	<0.01	0.082	(0.008-0.83)	0.03
Multiple	5	0	0	14.5				
Size of metastatic LN (cm)								
≥4.0	12	33.3	16.7	25.6	0.48			
<4.0	6	66.7	66.7					
Differentiation of metastatic LNs								
Well or moderately differentiated	3	50	50	25.6				
Poorly differentiated	15	40.9	20.5	29.4	0.68			
JIS score[c]								
3	16	40.9	0	29.4	0.48			
4 or 5	2	50	50	24.5				

HCC Hepatocellular carcinoma, *OS* overall survival, *MST* median survival time, *CI* confidence interval, *LN* lymph node, *HBs Ag* hepatitis B surface antigen

[a] Metachronous intrahepatic lesions were evaluated in the absence of simultaneous intrahepatic lesions

[b] T-stage of intrahepatic lesions was evaluated according to the TNM staging by the Liver Cancer Study Group of Japan [14]

[c] Japan Integrated Staging score can be obtained by combination of the TNM stage score by the Liver Cancer Study Group of Japan and the Child-Turcotte-Pugh stage score [18]

of LNM and decision whether lymphadenectomy should be done or not were mostly based on the palpation of surgeons during surgery. The preoperative evaluation of LNM was not performed precisely in most of the patients. In comparison, in our study, the diagnosis of LNM was made by preoperative imaging diagnosis. Selective lymphadenectomy was performed only for lymph nodes which were clinically diagnosed for metastasis. Patients' backgrounds were also different because the present study included many recurrent cases and cirrhotic cases. Based on these aspects, we consider that the efficacy of resection for LNM from HCC was not fully evaluated in Sun's study and that selective lymphadenectomy is a safe and beneficial procedure in selected patients.

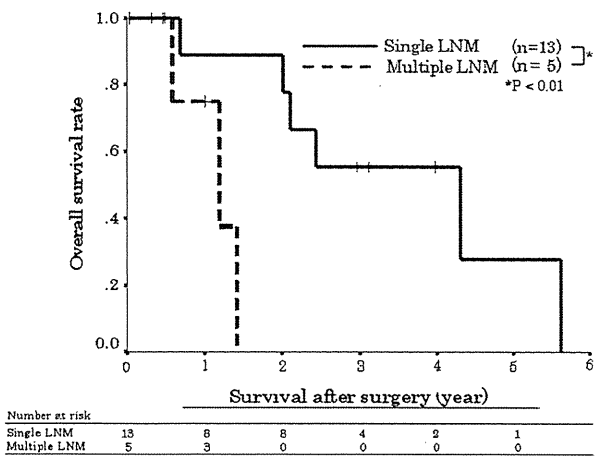

Fig. 3 Cumulative survival curves after surgery according to the number of MLN. The survival rate of the patients with resection of single LNM was statistically higher than that of multiple LNM (mean survival time 52 vs. 14 months; $p < 0.01$)

The possible candidates for selective lymphadenectomy are not many. In the present study, among 2189 patients with HCC who were treated in our institution, 75 patients (3.4%) were clinically diagnosed to have LNM from HCC, and 21 patients (1.0%) actually underwent surgery according to the aforementioned criteria. Among those 21 patients, 19 patients were pathologically diagnosed to have LNM from HCC while benign reactive lymphadenopathy was identified in resected lymph nodes in one case and metastasis from neuroendocrine tumor in the other. The positive predictive value of our diagnostic criteria of LNM from HCC was 90.5%. Among 19 patients with pathologically proven LNM, 18 patients underwent successful lymphadenectomy while it was abandoned due to invasion of the main portal vein in one patient. Thus, selective lymphadenectomy might be indicated in 24.0% (18/75) of cases with clinical diagnosis of LNM from HCC.

A comparison of surgical and non-surgical treatments suggests that external beam radiation therapy can be considered as a possible alternative modality for the treatment of LNM from HCC. However, median survival following this therapy has been found to be only 7–9.4 months, while the incidence of gastrointestinal bleeding was fairly high (9.4–22.0%) [4, 15]. A newer molecular targeting agent, Sorafenib (Nexavar; Bayer HealthCare Pharmaceuticals, Basel, Switzerland/Onyx Pharmaceuticals, Emeryville, CA), has been recently shown to prolong survival in patients with advanced HCC [16, 17]. However, a survival benefit was not demonstrated in the sub-group analysis of patients with extrahepatic metastasis. Long-term survival was rarely seen after those non-surgical treatments. Although candidates for resection are limited, and multimodal treatment might be necessary after resection, surgery for LNM seems to play an important role in achieving

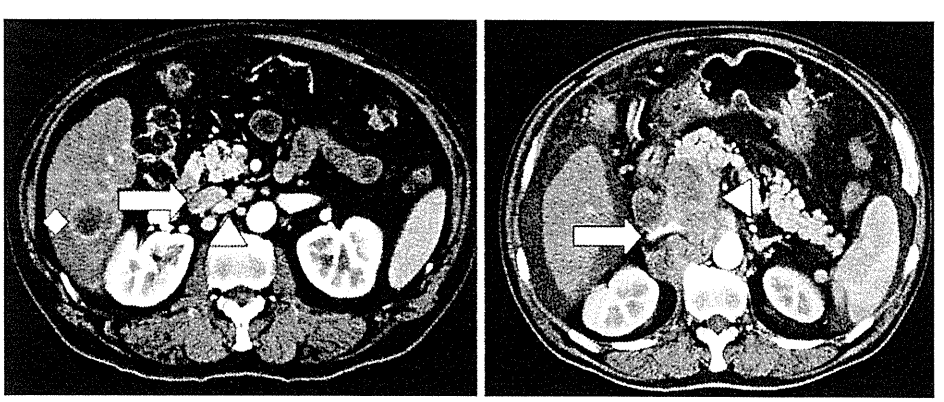

Fig. 4 Computed tomography findings of inferior vena cava obstruction by huge metastatic lymph nodes from hepatocellular carcinoma. *Left* A 57-year-old female underwent proton beam therapy for her solitary HCC (*diamond*). The slightly enlarged lymph nodes (*arrowhead*) around the inferior vena cava (IVC) (*arrow*) were at first judged equivocal as metastases (short axis diameter <1.0 cm). *Right* Only 2 months later, the patient developed IVC obstruction (*arrow*) by the rapidly growing lymph nodes (*arrowhead*)

long-term survival in the treatment strategy for LNM from HCC.

Evaluating the correlation between clinicopathological factors and prognosis after selective lymphadenectomy, single LNM was the only favorable prognostic factor after surgery (hazard ratio 0.082, 95% CI 0.008–0.83). The MST of patients with single and multiple LNM after surgery were 52 and 14 months, respectively ($p < 0.01$). All five patients who survived >3 years had single LNM and four of them did not develop extrahepatic metastasis within 3 years. On the contrary, three of the five patients with multiple LNM developed intra- and extrahepatic recurrences within 6 months after surgery. Therefore, multiple LNM indicated its advanced and systemic nature of the disease, while single LNM might be considered to be a localized disease. The MST of patients with resection of multiple LNM was not significantly longer than that of patients without resection (15 vs. 4 months after diagnosis, respectively; $p = 0.12$). Patients with single LNM appear to be the best candidates for selective lymphadenectomy. On the other hand, efficacy of selective lymphadenectomy for multiple LNM seemed equivocal due to its advanced and systemic nature of the disease.

The LNM from HCC might also cause severe complications, such as obstructive jaundice, pyloric obstruction, and inferior vena cava obstruction [15]. The resection of LNM might prevent these complications. In our institution, there were four complications directly related to LNM during the same period as that covered by our study. One patient developed inferior vena cava obstruction due to rapidly growing lymph nodes while receiving proton beam therapy for her solitary intrahepatic lesion (Fig. 4). Another patient developed esophageal obstruction due to large metastatic lymph nodes in the mediastinum. Two other patients developed obstructive jaundice due to metastatic lymph nodes in the hepatoduodenal ligament, which were treated with percutaneous transhepatic biliary drainage. Although selective lymphadenectomy should be performed with curative intent, it might additionally be beneficial as a preventative and palliative measure against these life-threatening complications.

The present study has several limitations. It is a single institutional study with a small patient population. Also, this study was not performed as a randomized controlled trial (RCT). However, RCTs are very difficult to conduct in this disease group due to the small number of patients scattered over diverse facilities. Our future perspective is to conduct a prospective observational study in a multi-institutional setting focusing on selective lymphadenectomy for patients with single LNM.

Conclusion

Selective lymphadenectomy of LNM from HCC is a feasible and efficacious procedure. Long-term survival can be expected after selective lymphadenectomy, especially in patients with a single LNM.

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ORIGINAL ARTICLE

Compliance with and effects of preoperative immunonutrition in patients undergoing pancreaticoduodenectomy

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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

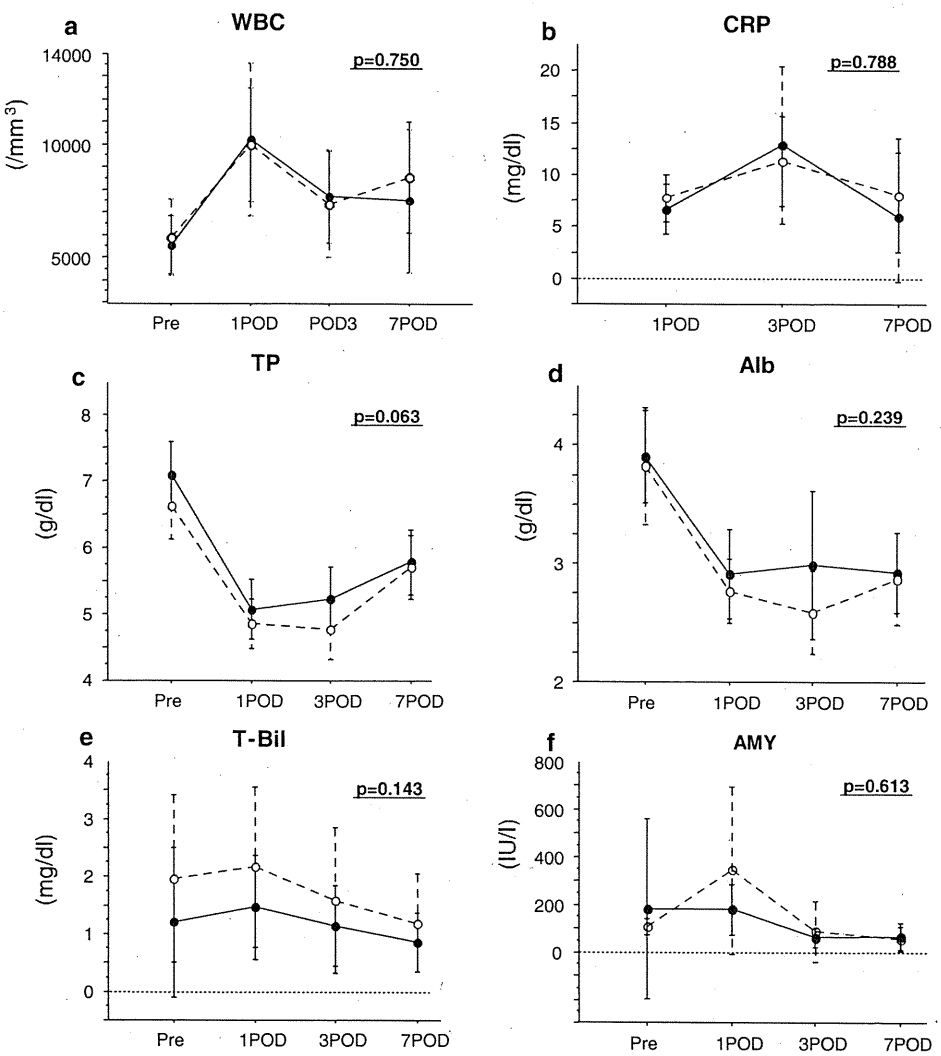
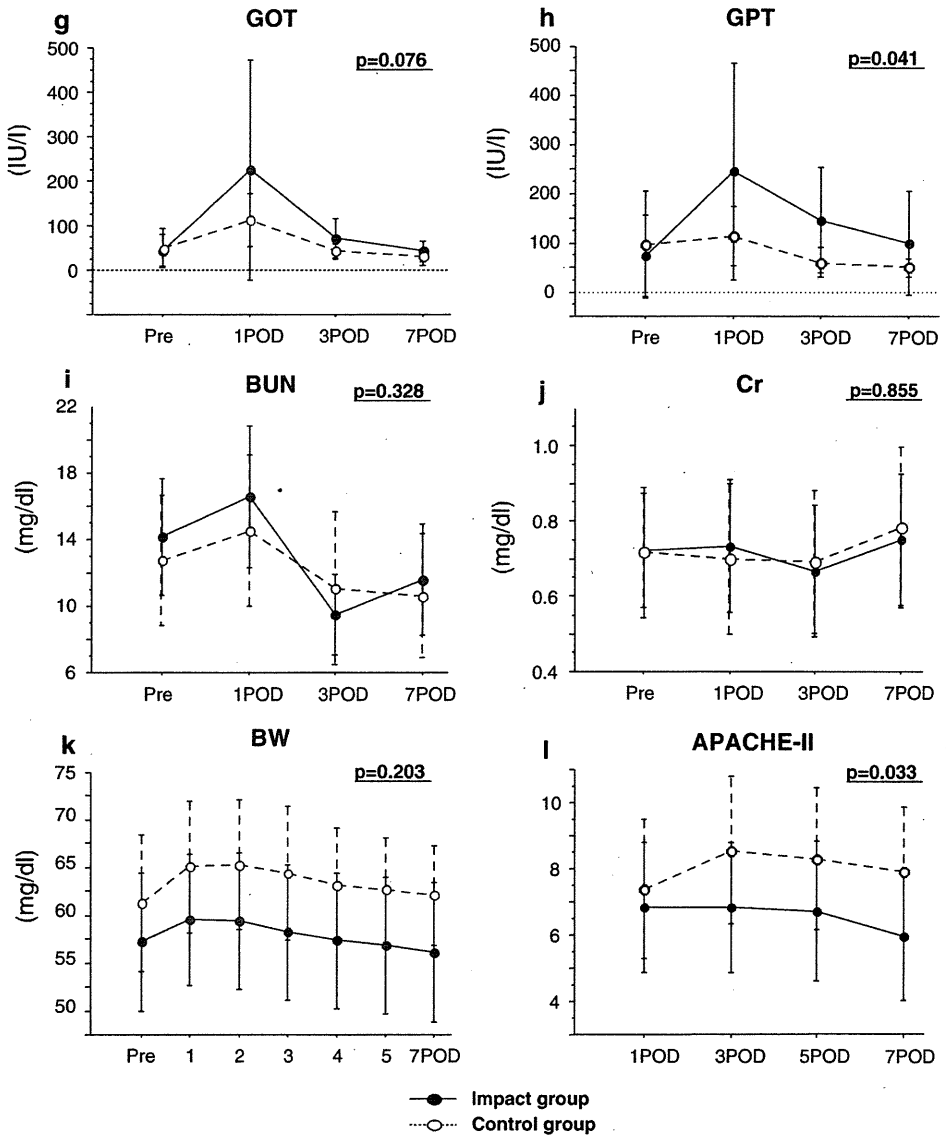


Fig. 1 Laboratory blood test results. *Filled circles* Impact group, *open circles* control group. **a** White blood cell count (*WBC*), **b** C-reactive protein (*CRP*), **c** total protein (*TP*), **d** serum albumin (*Alb*), **e** total bilirubin (*T-Bil*), **f** serum amylase (*AMY*), **g** glutamic 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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Pancreatic Ductal Adenocarcinoma Derived From IPMN and Pancreatic Ductal Adenocarcinoma Concomitant With IPMN

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Objectives: Pancreatic ductal adenocarcinoma (PDAC) may derive from an intraductal papillary mucinous neoplasm (IPMN) of the pancreas or may develop in the pancreatic duct apart from IPMN. The purpose of this study was to define the clinicopathological features of these 2 entities and compare them with those of ordinary PDAC.

Methods: Of 765 patients who had surgical resection for IPMN, 122 were diagnosed as having PDAC derived from IPMN and 31 with PDAC concomitant with IPMN. In addition, 7605 patients with PDAC who were registered in the Japan Pancreas Society pancreatic cancer registry were compared with the above patients.

Results: Pancreatic ductal adenocarcinomas derived from IPMN and concomitant with IPMN were significantly smaller, less invasive, and less extensive than ordinary PDAC. The median survival of patients with the 2 conditions was significantly longer than for those with ordinary PDAC when compared overall or when limited to TS2 (2.0 cm < tumor size ≤ 4.0 cm) or TS3 (4.0 cm < tumor size ≤ 6.0 cm) cases.

Conclusions: These findings suggest that PDAC concomitant with IPMN and PDAC derived from IPMN may have more favorable biological behaviors or be diagnosed earlier than ordinary PDAC.

Key Words: IPMN, PDAC concomitant with IPMN, PDAC derived from IPMN

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Intraductal papillary mucinous neoplasm (IPMN) is characterized by papillary proliferation of atypical mucinous epithelium in the pancreatic ductal system, and the affected pancreatic ducts are often cystically dilated.[1,2] Intraductal papillary mucinous neoplasm is a spectrum of diseases ranging from adenoma, to in situ carcinoma, to invasive carcinoma (minimally invasive carcinoma and invasive carcinoma derived from IPMN).[3] On the other hand, pancreatic ductal adenocarcinoma (PDAC) develops independently of IPMN in the pancreatic duct.[4,5] When PDAC originates in the vicinity of IPMN, the distinction between PDAC derived from IPMN and PDAC concomitant with IPMN is sometimes difficult to make. In this collective series, we developed a definition of the 2 conditions and analyzed the incidence of the conditions in patients with IPMN. In addition, we compared the clinicopathological features between (1) ordinary PDAC and PDAC derived from IPMN and (2) ordinary PDAC and PDAC concomitant with IPMN.

MATERIALS AND METHODS

The Japan Pancreas Society (JPS) formed a committee to solve the clinical and pathological problems associated with PDAC derived from IPMN and PDAC concomitant with IPMN. The committee (Drs H. Maguchi, K. Hanada, Y. Noda, M. Tada, and A. Nakaizumi as internists; Drs K. Yamaguchi, T. Hatori, Y. Shimizu, and T. Nakagori as surgeons; and Drs Y. Kato, T. Furukawa, B. Nobukawa, and S. Ban as pathologists) discussed the definition of PDAC derived from IPMN and PDAC concomitant with IPMN and proposed a new definition of 3 categories (PDAC derived from IPMN, PDAC concomitant with IPMN, and PDAC of undetermined relationship with IPMN) based on the topological relationship of the 2 conditions and the presence or absence of a histological transition (Fig. 1) between the conditions as follows:

PDAC Derived From IPMN

Pancreatic ductal adenocarcinoma is evidently derived from IPMN, based on the findings of radiologic images and macroscopic or microscopic findings, and a histological transition is present between IPMN and PDAC.

PDAC Concomitant With IPMN

Intraductal papillary mucinous neoplasm is obviously different from PDAC, according to the radiologic images and macroscopic or microscopic findings.