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# Preoperative Nutrition Index and Prognosis in Unresectable Pancreatic Cancer Treated with Palliative Bypass Surgery Based on the Intraoperative Diagnosis

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## ABSTRACT

**Introduction:** Pancreatic cancer is often detected at an advanced stage, when patients frequently become malnourished due to obstructive jaundice and poor oral intake. Preoperative nutritional disorders have been determined to result in postoperative complications centered on infectious diseases; therefore, decisions to perform bypass surgery may be difficult.

**Methods:** This study investigated the correlation between the Prognostic Nutrition Index (PNI) and modified Glasgow Prognostic Score (mGPS) and the prognosis among patients with pancreatic cancer scheduled to undergo resection. In total, 20 patients diagnosed with unresectable (UR) pancreatic cancer during laparotomy and who underwent gastrointestinal or biliary bypass surgery (Bp group) were compared to 104 patients who underwent radical surgery during the same period (R group).

**Results:** Six patients in the UR group were determined to have locally advanced disease, whereas 14 patients developed metastasis (UR-M). The PNI of the Bp group was significantly lower than that of the R group. The Bp group (median PNI, 47.1) included several UR-M patients with a short postoperative treatment period and poor prognosis. The Bp group mGPS tended to be abnormal, with a higher rate of cachexia than the R group.

**Conclusions:** Long-term continuation of postoperative treatment in cases where preoperative PNI and mGPS are satisfactory may lead to good prognosis. Although the PNI of the Bp group tended to be lower than that of the R group, few serious complications were noted to occur after palliative bypass for UR pancreatic cancer, which seemed to be feasible in all cases.

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**KEYWORDS:** unresectable pancreatic cancer, palliative bypass, preoperative nutrition, Prognostic Nutrition Index (PNI), modified Glasgow Prognostic Score (mGPS)

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## Introduction

Pancreatic cancer is often detected at an advanced stage, such that it is already unresectable at the time of discovery;<sup>1)</sup> such patients are often malnourished due to obstructive jaundice and poor oral intake. Preoperative nutritional disorders have been determined to result in postoperative complications centered on infectious diseases,<sup>2,3)</sup> and it is possible that the patient's quality of life and prognosis may worsen further without appropriate treatment. Although studies have reported that the preoperative nutritional status contributes to prognosis,<sup>4,5)</sup> few studies have investigated its contribution to the prognosis of unresectable pancreatic cancer.<sup>6)</sup> Therefore, in this study, we investigated the effects of preoperative nutritional status and cancer malignancy on postoperative outcomes in patients who underwent bypass surgery for unresectable (UR) pancreatic cancer.

## Methods

Overall, 156 patients underwent surgery for pancreatic cancer between January 2005 and December 2016 at Toho University Medical Center Omori Hospital. We have retrospectively compared the data concerning preoperative nutritional factors of 20 patients who were diagnosed with UR pancreatic cancer during surgical resection (Bp group) with the medical records of 104 patients who underwent surgical pancreatectomy (pancreaticoduodenectomy, distal pancreatectomy, or total pancreatectomy) (R group). In total, 32 patients were excluded from this study, as they were diagnosed with UR pancreatic cancer before surgery, developed gastrointestinal/biliary obstruction during follow-up, and underwent bypass surgery. There was bias regarding the timing of surgery and nutritional status in some cases; for example, long-term chemotherapy before bypass surgery would evidently lead to poor prognosis, due to the state of metastasis. Therefore, the diagnosis of "UR" was further categorized as "locally advanced" (UR-LA) or metastatic (UR-M), according to the General Rules for the Study of Pancreatic Cancer, 7th edition, by the Japan Pancreas Society.<sup>7)</sup> UR-LA was defined as invasion into the portal vein, hepatic artery, or superior mesenteric artery, whereas UR-M was defined as hepatic metastasis or para-aortic lymph node metastasis; this was diagnosed at the time of laparotomy, as it could not be diagnosed from the preoperative computed tomography image.

The preoperative factors assessed by this study are as

follows: oral intake ability/inability, body mass index, nutritional evaluation, presence/absence of preoperative pancreatic cancer treatment, and tumor markers. Bypass surgery, bleeding volume, and operative time comprised the intraoperative factors. Complications, duration of hospitalization, pancreatic cancer treatment period, and postoperative survival time constituted the postoperative factors. Oral ingestion ability was defined as the ability to ingest solid foods with a consistency thicker than porridge. Preoperative nutritional evaluation involved data obtained immediately before surgery for the measurement of the Prognostic Nutrition Index (PNI) ( $10 \times$  serum albumin +  $0.005 \times$  total lymphocyte count in peripheral blood), as devised by Onodera et al.,<sup>8)</sup> and the modified Glasgow Prognostic Score (mGPS), formulated by Miki et al.<sup>9)</sup> The mGPS was divided into four classes, i.e., A (normal), B (undernutrition), C (pre-cachexia), and D (cachexia), with an albumin level of 3.5 g/dL and C-reactive protein (CRP) concentration of 0.5 mg/dL as the threshold values. These criteria were subsequently used to evaluate the malignancy status.<sup>10)</sup> Postoperative complications were deemed to be positive if their severity was Grade II or higher according to the Clavien-Dindo classification.

### Statistical Analysis

Continuous variables were presented as medians (range). Categorical variables were evaluated using the Fisher's exact test, whereas continuous variables were evaluated using the Mann-Whitney U test. The survival rate was evaluated using the Kaplan-Meier method, and significant differences in these curves were analyzed using the log-rank test. Multivariate analysis was conducted using Cox proportional hazard analysis. P-values < 0.05 were deemed to be statistically significant.

## Results

### Patients' background and disease characteristics

The demographic characteristics of the Bp group were as follows: 13 men and 7 women, with a median age of 68 (45-78) years. The tumor was located in the pancreatic head in 19 patients and in the pancreatic tail in 1 patient. The cause of unresectability was LA disease in six patients (UR-LA) and metastasis in 14 patients (UR-M). None of the patients had undergone preoperative treatment, and preoperative oral intake was possible in 19 patients. Preoperative biliary drainage was performed in 14 (70%) patients due to obstructive jaundice. The types of bypass surgery were as follows: gastrojejunal bypass in 3 pa-

Table 1 Patients' characteristics

	Bypass group	Resectable group	P-values
Male/Female	13:7	52:52	0.23
Age	68 (45–78)	71 (33–85)	0.23
BMI	22.2 (17.1–27.1)	22.7 (15.5–29.3)	0.60
Preoperative oral intake ※	19 (95%)	104 (100%)	0.16
Preoperative biliary drainage	14 (70%)	44 (42%)	0.03
Preope Tx (Chemo and/or RT)	0 (0%)	4 (3.8%)	>0.99
CEA	3.8 (1.5–87.2)	3.2 (0.7–65.3)	0.11
CA19-9	354.8 (0.9–22927)	88.8 (0.6–10690)	0.16
Location of pancreas ca.	Head/body tail = 19:1	Head/body tail = 73:31	0.02
Cause of unresectable	UR-LA:UR-M = 6:14	N/A	-
Surgical procedure	GJ:CJ:GJ + CJ = 3:1:16	PD:DP:TP = 63:29:12	-
Estimate blood loss	430 (50–1020) ml	975 (160–6585) ml	<0.01
Operative duration	295 (142–429) min	493 (150–729) min	<0.01
Postope oral intake	19 (95.0%)	104 (100%)	0.16
Morbidity	3 † (7.5%)	37 (35.6%)	0.11
Mortality	0 (0%)	2 (1.9%)	>0.99
Hospital stay	26.5 (12–97) day	32 (14–193) day	0.18

Tx: therapy. RT: radiation therapy. UR-LA: unresectable locally advanced. UR-M: unresectable metastatic. GJ: gastrojejunal bypass. CJ: choledochojejunal bypass. N/A: not available. PD: pancreaticoduodenectomy. DP: distal pancreatectomy. TP: total pancreatectomy. P-values were determined using Mann-Whitney U test or Fisher's exact test.

※ defined as the ability to ingest solid foods with a consistency harder than porridge. † Morbidity of Bypass group: Clavien-Dindo classified >Grade 2; SSI, Delayed gastric emptying (DGE), bacteraemia

tients; choledochojejunal bypass in 1 patient; and gastrojejunal and choledochojejunal double bypass surgery in 16 patients. All patients were diagnosed by performing laparotomy. The median amount of intraoperative bleeding was 430 (50–1020) mL, and the surgical time was 295 (142–429) min. Postoperative complications were observed in three (15%) patients as follows: surgical site infection, delayed gastric emptying, and bacteremia in one patient each. There were no instances of death during hospitalization after bypass surgery. The median postoperative duration of hospitalization was 26.5 (12–97) days. In total, 19 patients underwent postoperative chemotherapy in the Bp group. The median time interval between surgery and chemotherapy among these patients was 1.0 (0.5–2.7) months, and the median postoperative treatment period was 7.7 (0.5–34.5) months. Postoperative treatment could not be provided in one case, as it was impossible for the patient to resume oral intake. In the R group, there were significantly fewer cases of preoperative biliary drainage, the amount of bleeding was larger, and the operation time was longer, compared to the Bp group. No difference was noted in other background characteristics between the two groups (Table 1). The median survival time of the Bp

group was 10.0 months, with 1-year, 2-year, and 3-year survival rates of 45.6%, 22.8%, and 5.7%, respectively. The prognosis of the Bp group was noted to be significantly poorer than that of the R group (Fig. 1).

### Preoperative nutritional evaluation and postoperative results

#### PNI

The preoperative PNI was 41.7 in the Bp group, which was significantly lower than the corresponding PNI of 45.4 in the R group ( $P < 0.01$ ). Reportedly, the PNI is a risk predictor of perioperative complications, and resection/anas-tomosis is contraindicated in cases with a PNI value  $\leq 40$ .<sup>8)</sup> The percentages of patients with a PNI  $> 40$  were 84.6% and 70% in the R and Bp groups, respectively. Thus, the PNI tended to be lower in the Bp group, but the difference was deemed insignificant (Fig. 2). The Bp group was divided into two subgroups, i.e., good and poor nutrition groups based on the median PNI value of 41.7 in the Bp group; the rate of patients with UR-M was higher in the poor nutrition group. The incidence of postoperative complications did not differ between the good and poor nutrition groups; neither were there differences in the postoperative treatment availability rate. However, the postop-

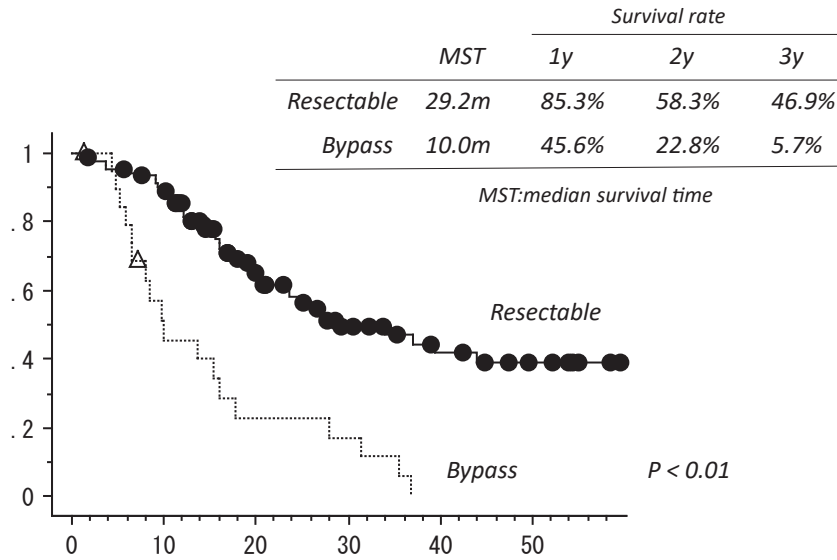


Fig. 1 Kaplan-Meier curves for overall survival. The prognosis of the bypass group was significantly poorer than that of the resectable cancer group as per the log-rank test results.

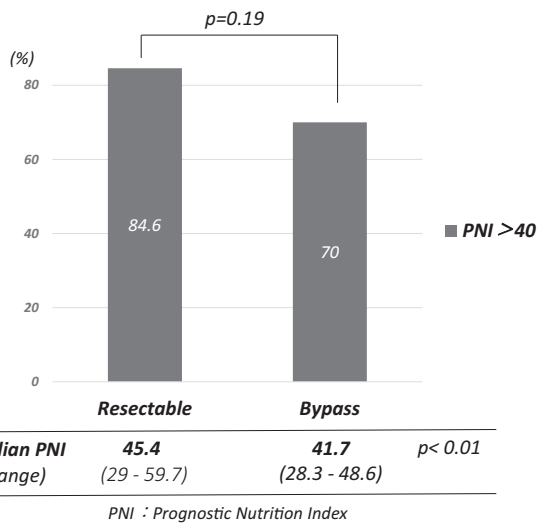


Fig. 2 The preoperative PNI of the bypass group was significantly lower than that of the resectable cancer group as per the Mann-Whitney U test. Additionally, the PNI (measured as the percentage of patients with a PNI > 40) tended to be lower in the bypass group than in the resectable cancer group according to the Fisher's exact test results.

PNI, prognostic nutrition index

erative treatment period and survival times were longer in the good nutrition group than in the poor nutrition group (Table 2).

*Cancer malignancy based on the mGPS*

The distribution of patients into classes A through D in

the Bp group were 5 (25%), 4 (20%), 6 (30%), and 5 (25%), respectively. The proportion of patients in the normal class was significantly lower, and the rate of cachexia and pre-cachexia was higher in the Bp group compared to the R group (Fig. 3). The survival rate of each mGPS class was as follows: in group R, the survival rate was higher in class A and lower in class D. Meanwhile, in the Bp group, the survival rates of classes A and B, which had normal CRP concentrations, were significantly lower than those of classes C and D, whose CRP was > 0.5 mg/dL (Fig. 4). Subsequently, the Bp group was divided into the AB and CD classes according to the mGPS and the patients' background characteristics. When they were compared, the incidence of UR-M was higher, the postoperative treatment period was shorter, and the prognosis was significantly poorer in class AB than in class CD (Table 3).

**Prognostic factors**

Univariate analysis showed that the mGPS, UR-related factors, and postoperative treatment period were prognostic factors after palliative bypass surgery, but the PNI was not a risk factor for pancreatic cancer. Multivariate analysis showed that only the postoperative treatment period was an independent risk factor (Table 4).

**Discussion**

Patients with advanced pancreatic cancer often suffer from malnutrition due to obstructive jaundice and poor oral intake, and preoperative malnutrition has been deter-

Table 2 Patient's characteristics of nutritional comparison

	Good nutrition	Malnutrition	P-values
	PNI $\geq$ 41.7	PNI $<$ 41.7	
Age	64.5	69	0.19
Gender (male)	80%	50%	0.35
BMI	22.5	20.9	0.24
CEA	3.5	5.1	0.06
CA19-9	469.5	50.6	0.85
UR-LA:UR-M	5:5	1:9	0.14
GJ:CJ:GJ + CJ	3:1:6	1:1:8	0.53
Estimate blood loss	453	364	0.80
Operative duration	297	287	0.28
Morbidity	20% (SSI, bacteraemia)	10% (stasis)	$>$ 0.99
Hospital stay	33.5	21.5	0.31
Postoperative Tx rate	100%	90%	$>$ 0.99
Tx duration	12.0 mon	3.7 mon	0.04
Survival time	14.9 mon	6.9 mon	0.04

PNI: prognostic nutrition index. UR-LA: unresectable locally advanced. UR-M: unresectable metastatic. GJ: gastrojejunal bypass. CJ: choledochojejunal bypass. SSI: surgical site infection. Tx: therapy.

P values were determined using Mann-Whitney U test or the Fisher's exact test.

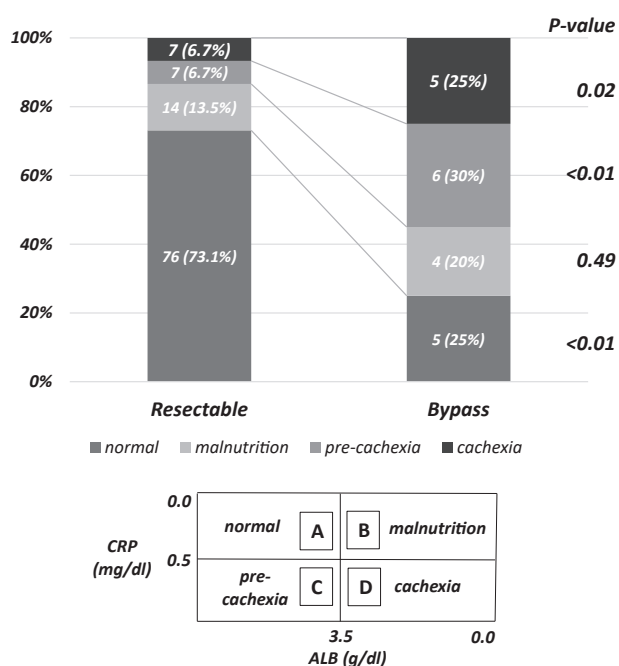


Fig. 3 The proportion of classes A through D of each group. The rate of patients in the normal class was significantly lower, whereas the rate of cachexia and pre-cachexia was higher in the bypass group compared to the resectable cancer group as per the Fisher's exact test.

mined to result in postoperative complications centered on infection. Hence, it can be difficult to determine whether

patients with UR cancer may undergo bypass surgery. Until the publication of the 2016 edition of the Clinical Practice Guidelines for Pancreatic Cancer,<sup>11)</sup> it was recommended that prophylactic bypass surgery should be performed for UR pancreatic cancer if bile duct invasion or duodenal invasion was present or suspected. However, bypass surgery has become less common in recent years, owing to the improvements in endoscopic techniques such as duodenal and biliary stent placement and the need to discontinue chemotherapy administration due to the onset of complications. Therefore, the clinical question concerning prophylactic bypass surgery was removed from the revised 2019 guideline.<sup>12)</sup> Meanwhile, one study has reported<sup>13)</sup> that bypass surgery may be conducted if the general condition is relatively good, because there tend to be fewer complications in such cases. Moreover, it has also been stated that prophylactic bypass surgery may be chosen as a treatment option depending on the situation of the patient and facility.

Onodera et al.<sup>8)</sup> stated that good preoperative nutritional status is deemed desirable<sup>14)</sup> because a nutritional status represented by a PNI of  $\leq$ 40 indicates poor prognosis. There were several cases where a PNI of  $\leq$ 35 was associated with death within 60 days. In this study, the PNI of the Bp group was 41.7, which is higher than the high-risk cutoff of  $\leq$ 40. Although it cannot be stated with absolute

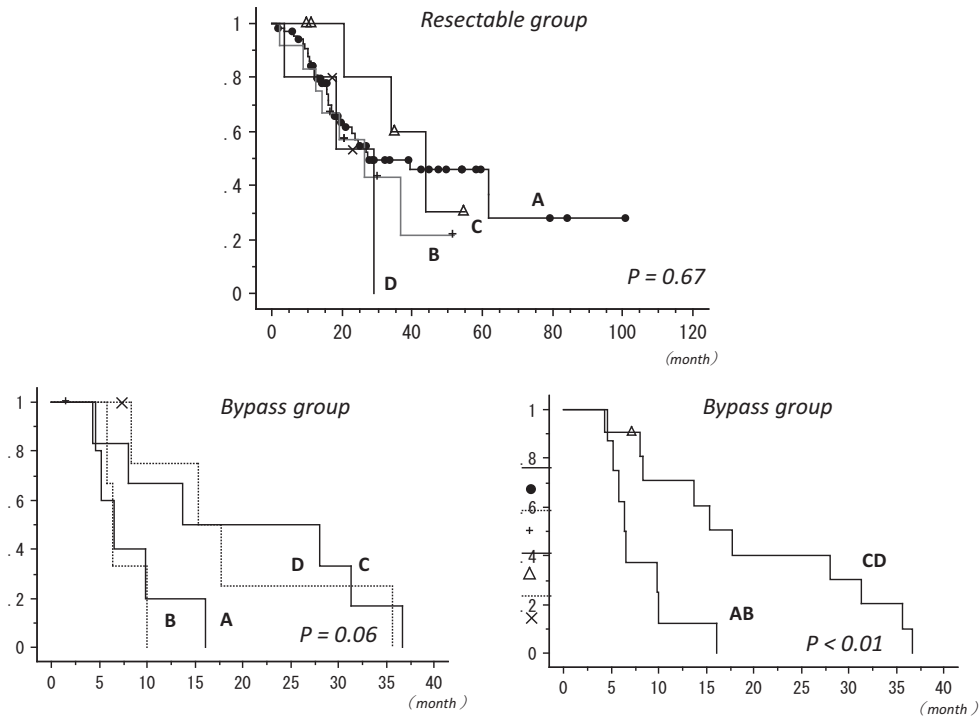


Fig. 4 The survival rate of each mGPS class. The survival rate was higher in class A and lower in class D in the resectable cancer group. Meanwhile, in the bypass group, the survival rates of classes A and B were significantly lower than those of classes C and D via log-rank test.

mGPS, modified glasgow prognostic score

Table 3 Patient's characteristics of nutritional comparison by mGPS

	AB (n = 9)	CD (n = 11)	P-values
Age	69	68	0.70
Gender (male)	55.6%	72.7%	0.64
BMI	22.5	20.9	0.34
PNI	40.4	42.3	0.41
CEA	4.0	3.4	0.40
CA19-9	522	343	0.31
UR-LA:UR-M	0:9	6:5	0.01
GJ:CJ:GJ + CJ	1:0:8	3:2:6	0.21
Estimate blood loss	300	450	0.32
Operative duration	295	295	0.76
Morbidity	11.1% (SSI)	18.2% (stasis, bacteraemia)	>0.99
Hospital stay	22	27	0.62
Postoperative Tx rate	100%	90.9%	>0.99
Duration of post-ope Tx	3.7	13.3	0.08
Survival time	6.4	15.3	0.02

PNI: prognostic nutrition index. UR-LA: unresectable locally advanced. UR-M: unresectable metastatic. GJ: gastrojejunal bypass. CJ: choledochojejunal bypass. SSI: surgical site infection. Tx: therapy.

P values were determined using Mann-Whitney U test or the Fisher's exact test.

confidence because of the low incidence of complications, there may be no need to hesitate to conduct palliative by-

pass surgery, even for patients with UR pancreatic cancer. Meanwhile, the PNI of the Bp group can be noted to be

Table 4 Prognostic factor of palliative bypass surgery

Risk factor	Categories	P-values		Cox proportional hazards analysis
		Univariate	Multivariate	HR (95%CI)
CA19-9	< 350, 350 ≤	0.75		
PNI	< 41.7, 41.7 ≤	0.08		
mGPS	AB, CD	0.01	0.16	2.59 (0.69–9.77)
UR factor	UR-LA, UR-M	0.01	0.10	6.79 (0.68–67.9)
morbidity	+, –	0.23		
Duration of postope Tx	< 3.7 m, 3.7 m ≤	< 0.01	0.01	10.6 (1.80–62.1)

PNI: prognostic nutrition index. mGPS: modified glasgow prognostic score. UR-LA: unresectable locally advanced. UR-M: unresectable metastatic. Tx: therapy. P-values were determined by Log-rank test for univariate analysis, and Cox proportional hazards analysis for multivariate analysis.

significantly lower than that of the R group due to advanced cancer and decreased nutritional status. It should be noted that the cancer may have advanced beyond the findings visible on imaging examinations. Even if the factors related to unresectability, such as intraperitoneal dissemination or distant metastasis, are not manifested, these patients might exhibit a decreased nutritional status prior to radical surgery. Karabicak et al.<sup>15)</sup> have recommended staging laparoscopy for such cases. It is thus necessary to carefully evaluate the indications for bypass surgery for patients who have a poor nutritional status, even if the surgery is for palliative care.

It has been reported that mGPS can serve not only as an index for nutritional status, but also as a prognostic factor for the survival rate and recurrence rate in various cancers.<sup>5)</sup> This index combines the CRP and albumin values to objectively classify systemic metabolic disorders associated with host-tumor interaction<sup>9)</sup> (i.e., “cachexia” and “pre-cachexia”) and was used as a cancer malignancy index in this study. The number of patients with significantly lower albumin values and higher CRP values was noted to be greater in the Bp group than in the R group, and mGPS was thought to be correlated with cancer malignancy. It has been expected that CRP will inevitably be higher in patients with cholangitis; thus, caution is required for patients with obstructive jaundice. In this study, the data were obtained after treatment by biliary drainage of patients with obstructive jaundice. We initially expected prognosis to be good in normal groups with low CRP and high albumin values, such as the R group; however, the rate of UR-M was higher in the group with lower CRP concentration compared to the group with higher CRP, and the prognosis was poor. Matsuda et al.<sup>16)</sup> reported that pancreatic cancer patients with distant metastasis were mal-

nourished and had a poor prognosis. In this study, there were many cases of distant metastasis in the well-nourished group, and the results were deemed inconsistent with the results from the R group; however, it should be noted that, sometimes, the occurrence of well-nourished advanced pancreatic cancer without any inflammatory reaction may be latent in cases of distant metastasis.

In this study, the PNI and mGPS, which were employed as measures of preoperative nutrition evaluation, were not independent risk factors of palliative bypass surgery; instead, the protocol for postoperative pancreatic cancer treatment emerged as a significant factor. The recommended chemotherapeutic regimen includes chemotherapy with gemcitabine or S-1, fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) therapy<sup>17)</sup> or gemcitabine + nab-paclitaxel therapy,<sup>18)</sup> which reportedly can prolong survival.<sup>19)</sup> As these treatments result in increased frequency of side effects compared to treatments with S-1 or gemcitabine alone, it may be advisable to improve the nutritional status of patients with pancreatic cancer. It has been reported that conversion surgery (CS) after multidisciplinary treatment for UR pancreatic cancer improves the prognosis,<sup>20)</sup> but unfortunately, no cases of CS were indicated in this study. When biliary bypass surgery is performed, the jejunal limb might disturb the surgical field of view. The guidelines recommend endoscopic biliary drainage (EBD) for biliary obstruction of UR pancreatic cancer.<sup>12)</sup> EBD may have less effects on CS than bypass surgery, but long-term survival may require repeated drainage treatment due to stent failure.

In this study, the good nutrition group with a PNI of 41.7 and higher underwent postoperative treatment for a significantly longer period of time, which then resulted in significantly prolonged survival compared to the poor nutri-



tion group. Therefore, it is important that the preoperative nutritional status be good in order to conduct postoperative treatment for as long as possible. Preoperative nutritional evaluation using the PNI and mGPS was thought to be an indispensable and useful screening tool that could enable the prediction of not only short-term results, but also long-term prognosis. Patients with UR pancreatic cancer undergoing palliative bypass surgery had a good prognosis, as long-term postoperative treatment is administered in locally advanced/non-metastatic cases; however, patients with distant metastases had a significantly poorer postoperative prognosis. Hence, it is thought that the indications for bypass should be carefully considered.

### Limitations of this study

A limitation of this study was that there were no non-surgical cases among the study population, and no comparisons were made with duodenal stent-treated patients. Therefore, it is thought that sufficiently firm conclusions cannot be drawn based on these data. The duodenal stent is non-invasive and requires a short time interval between stent placement and oral intake;<sup>21)</sup> however, its superiority or inferiority compared to surgical bypass surgery remains to be unclear.<sup>22)</sup> Therefore, prospective clinical trials on UR pancreatic cancer are needed in the future, and it is currently best to choose the treatment based on the patient's current state and desire, as well as the facility conditions. Furthermore, this study was retrospective in design, and the decision to implement chemotherapy (or not) after bypass surgery or parenteral nutrition was not based on definitive criteria. Therefore, this study found that numerous factors are involved in the prognosis of UR pancreatic cancer, and studies with a larger sample size and longer observation periods are warranted to confirm the validity of these prognostic factors.

### Conclusions

As per the findings of this study, the PNI and mGPS were not independent prognostic factors in preoperative nutritional evaluation. However, good prognosis for pancreatic cancer might be obtained by long-term continuation of postoperative treatment in cases where the preoperative PNI and mGPS are deemed good. Even though the PNI of the Bp group tended to be lower than that of the R group, few serious complications were noted after palliative bypass surgery for UR pancreatic cancer diagnosed during surgery; moreover, bypass surgery seemed to be feasible in all cases. Palliative bypass surgery for UR-L pancreatic cancer may improve long-term prognosis, al-

though poor prognosis of UR-M should be noted.

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**Authors' contributions:** M.T. and N.W. designed the study; M.T., T.M., J.L., K.K., Y.M., and R.O. analyzed the data; Y.O., N.W., and K.F. supervised the experiments; M.T. and N.W. wrote the manuscript.

**Ethics statement:** The study protocol was approved by the Ethics Committee of the Toho University Omori Medical Center (26-256, M21298).

**Conflicts of interest:** None declared.

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