

ORIGINAL RESEARCH ARTICLE

## Prognostic Nutritional Index Predicts Treatment Outcomes following Palliative Surgery for Colorectal Adenocarcinoma

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### Abstract:

**Objectives:** Palliative surgeries such as stoma creation and bypass are effective for relieving symptoms related to incurable abdominal malignancies; however, these methods are controversial in patients with severe metastatic disease or poor pre-surgical health. The aim of this study was to examine the clinical significance of the prognostic nutritional index (PNI) in evaluations for palliative surgery. **Methods:** We retrospectively analyzed data from 37 patients who underwent palliative surgery for histologically-proven colorectal adenocarcinoma from 2009 to 2015. We investigated both risk factors for postoperative complications and prognostic factors. We used a PNI cutoff value of 40, as defined by previous studies. **Results:** The reason for surgery was stenosis in 18 patients, obstruction in 12, fistula in 5, and bleeding in 2. Bypass was performed in 10 cases, ileostomy in 5, and colostomy in 22. Postoperative morbidity and mortality occurred in 9 and 2 patients, respectively. Median overall survival time was 8.9 months. Only low PNI correlated with postoperative complications at trend-level ( $p=0.07$ ), and the 2 patients with mortality were classified as PNI-low. The presence of ascites ( $p=0.003$ ) and PNI ( $p=0.02$ ) were identified as independent prognostic factors. **Conclusions:** PNI could be used as an objective marker for deciding whether to proceed with palliative surgery, independent of the extent of metastatic disease.

### Keywords:

colorectal adenocarcinoma, palliative surgery, prognostic nutritional index

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### Introduction

Acute and subacute intestinal obstruction, pain, fistula, and bleeding are common occurrences among patients with incurable, advanced abdominal malignancies<sup>1)</sup>. These symptoms have a significant impact on the quality of life of patients and their families. Malignant bowel obstruction (MBO) is the most frequent of these conditions, and is estimated to occur in 10-28.4% of cases of colorectal cancer (CRC)<sup>2)</sup>.

Palliative surgical procedures, such as stoma creation and bypass, are effective treatment methods to relieve these symptoms; however, these approaches are controversial in cases of severe metastatic disease or poor patient health. In

cases of MBO, recent studies have reported the efficacy of alternative treatments such as self-expandable metallic stents (SEMS)<sup>3)</sup> or medical management with agents such as octreotide<sup>1)</sup>. The establishment of a marker that can identify an optimal group for surgical intervention will help to minimize the risks of unnecessary surgery and allow for the application of less-invasive alternative therapies.

The prognostic nutritional index (PNI), which is calculated based on the serum albumin concentration and total lymphocyte count in the peripheral blood, was initially proposed by Onodera and colleagues to assess the nutritional and immunological status (and thus surgical risk) of patients undergoing gastrointestinal surgery<sup>4)</sup>. Previous studies have reported the predictive potential of the PNI on prognosis of

several malignancies, including CRC<sup>5</sup>). However, there have been no investigations to date of whether the PNI predicts treatment outcomes after palliative surgery for CRC.

In the present study, we investigated both risk factors for postoperative complications and prognostic factors following palliative surgery. The aim of this study was to examine the clinical significance of the PNI in evaluations for palliative surgery.

## Methods

We retrospectively analyzed data from 37 patients with histologically-proven colorectal adenocarcinoma who underwent palliative surgery from 2009 to 2015 at the Higashihiroshima Medical Center. Patient characteristics and treatment outcomes were obtained from an established database, and we subsequently evaluated treatment outcomes of palliative surgery. We investigated risk factors for postoperative complications as well as prognostic factors, and determined the clinical impact of the PNI after palliative surgery. Patients who underwent curative surgery after palliative surgery or gastrojejunostomy were excluded. During the study period, there were no cases of stent placement because of issues pertaining to instruments and technical difficulties.

The following clinicopathological variables were investigated: sex (male/female), age (low/high), operative method (stoma/bypass), presence of bowel obstruction (present/absent), presence of metastatic disease (present/absent), presence of peritoneal dissemination (present/absent), extent of peritoneal dissemination (P0-P2/P3), positivity of peritoneal lavage (positive/negative), preoperative carcinoembryonic antigen (CEA) serum level (low/high), presence of primary tumor resection (yes/no), presence of preoperative chemotherapy (yes/no), Eastern Cooperative Oncology Group Performance Status (ECOG PS; 0, 1/2, 3), preoperative body mass index (low/high), albumin level (low/high), lymphocytes count (low/high), and PNI (low/high). The cutoff values for the continuous variables, with the exception of the PNI, were determined by median value. The cutoff value of the PNI was determined to be 40, as defined by Onodera and colleagues<sup>4</sup>.

The study was approved by the local ethics committee. Survival time was calculated from the date of palliative surgery.

## Surgery

Cytology was performed if ascites was present at the time of laparotomy. If ascites was absent, peritoneal lavage was performed. We aimed to conduct bypass operations if possible, in cases where no stenotic lesions were observed in the pelvic cavity. When it was inappropriate to perform bypass surgery, we aimed to perform a colostomy if there were stenotic lesions in the distal colon. When it was inappropriate to perform colostomy, we aimed to perform a ileostomy.

## Definition

The extent of peritoneal dissemination was defined according to the Japanese Classification of Colorectal Carcinoma<sup>6</sup>: P0 (absence of dissemination), P1 (localized dissemination in peritoneum near primary tumor), P2 (localized dissemination in peritoneum distant from primary tumor), and P3 (diffuse dissemination).

Postoperative complications were reviewed for at least 30 days after surgery. The complications were graded according to the method described by Dindo and colleagues<sup>7</sup>. Complications with a grade above 2 were classified as morbid. Postoperative mortality was defined as any death that occurred within 30 days of surgery.

## Statistical analyses

The differences between the two groups were analyzed using the chi-square test and the Mann-Whitney U-test. Survival curves were plotted using the Kaplan-Meier method, and univariate analyses were estimated using the log-rank test. The Cox proportional hazards model was used for multivariate analyses. In all analyses, statistical significance was set at a *p* value less than 0.05. All statistical analyses were performed using the IBM SPSS Statistics 20.0 software package (IBM Corp., Armonk, NY, USA).

## Results

### Patient characteristics

23 male and 14 female patients with a median age of 75 years (range, 48-92 years) were included in the study. The reason for surgery was stenosis in 18 cases, obstruction in 12, fistula in 5, and bleeding in 2. Bypass was performed in 10 cases, ileostomy in 5 cases, and colostomy in 22 cases. Prior to the present surgery, primary tumor resection had been performed in 6 cases, and chemotherapy had been administered in 7 cases. Distant metastases were present in 26 cases, and ascites was observed in 16 cases during surgery. Peritoneal cytology (including lavage) was performed in 31 cases, and cytology was positive in 7 cases. The median serum CEA level was 25.3 ng/mL (1.6-5749). Median PNI was 39.6 (range, 32.1-53.2). Patient characteristics are shown in Table 1. The median follow-up time was 7.4 months (range, 0.2-76.8).

### Treatment outcomes

Morbidity was observed in 8 patients (22.0%), while mortality occurred in 2 patients (5.4%). Specifically, pneumonia occurred in 4 patients, intraabdominal abscess in 2 patients, ileus in 1 patient, and disseminated intravascular coagulation in 1 patient. Oral intake was enabled in 36 cases (97%), and discharge was possible in 25 cases (68%). Recurrent bowel obstruction within the survival time was observed in only 1 case (2.7%). Postoperative chemotherapy was performed in 21 cases (57%), and median overall survival time was 8.9

**Table 1.** Patient characteristics (n=37).

Sex	Male/Female	23/14
Median age (range)		75 (48-92)
Diagnosis		
	Colon cancer	20
	Rectal cancer	17
Reason for operation		
	Stenosis	18
	Obstruction	12
	Fistula	5
	Bleeding	2
Operative methods		
	Bypass	10
	Ileostomy	5
	Colostomy	22
Preoperative chemotherapy		7
Primary tumor resection		6
Distant metastasis		26
Ascites	Present	16
Peritoneal cytology (Including lavage)	Positive	7
Histological type	Well, Mod	34
	Poorly	3
The extent of peritoneal dissemination	P0	23
	P1	4
	P2	2
	P3	9
Median serum CEA levels (ng/ml) (range)		16.2 (1.6-5749)
ECOG Performance Status	0-1	28
	2-	9
Median Body Mass index (range)		19.9 (14.2-35.5)
Median albumin (g/dl) (range)		3.4 (2.3-4.4)
Median lymphocytes (/ $\mu$ l) (range)		1420 (430-2170)
Median PNI (range)		41.1 (31.2-53.2)

*Well* well differentiated adenocarcinoma, *Mod* moderately differentiated adenocarcinoma, *Poorly* poorly differentiated adenocarcinoma, *CEA* carcinoembryonic antigen, *ECOG* Eastern Cooperative Oncology Group, *PNI* prognostic nutritional index

months (Figure 1A).

### Risk factors for postoperative complications

To investigate risk factors for postoperative complications, univariate analyses were performed for each variable. There were no significant risk factors, however, low PNI correlated with postoperative complications at trend-level ( $p=0.07$ ) (Table 2). The 2 patients who experienced mortality were classified as PNI-low.

### Prognostic factors

To investigate prognostic factors, univariate analyses were performed for the variables, including postoperative complications. The extent of peritoneal dissemination (P3,  $p=0.04$ ), the presence of ascites ( $p=0.006$ ), poor ECOG PS (2 or more,  $p=0.02$ ), and PNI (low,  $p=0.02$ ) were identified as significant prognostic factors (Table 3). In a multivariate analysis of the variables found to be significant in the univariate analyses, the presence of ascites ( $p=0.003$ ) and PNI ( $p=0.02$ ) were identified as independent prognostic factors (Ta-

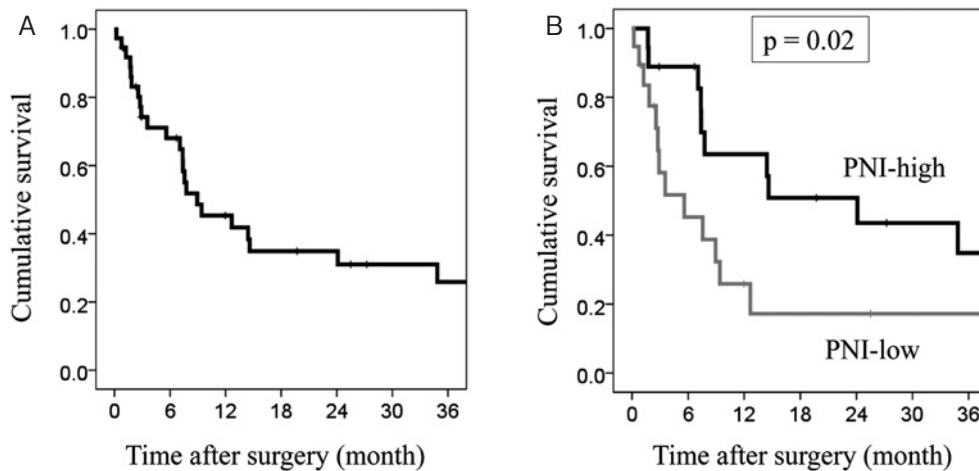
ble 3).

The median survival time of patients classified as PNI-low was 5.6 months, whereas patients classified as PNI-high had a median survival time of 24.1 months ( $p=0.02$ , Figure 1B). Long-term outcomes were not expected in patients classified as PNI-low.

## Discussion

In the present study, we demonstrated that palliative surgeries are effective treatment methods that enable most patients to achieve oral intake within their remaining lifetimes. Moreover, we showed that the PNI predicted short- and long-term outcomes, independent of the extent of metastatic disease.

Palliative surgeries have been reported to be effective treatment approaches for the relief of malignant symptoms in the abdominal cavity; however, high morbidity and mortality have also been reported due to poor patient health pre-surgery. Blair and colleagues reported a treatment-related



**Figure 1.** A: Overall survival after palliative surgery. Median overall survival time was 8.9 months.

B: Prognostic utility of the prognostic nutritional index (PNI). The median survival time of patients with low PNI was 5.6 months, whereas that of patients with high PNI was 24.1 months.

morbidity rate of 44% and a mortality rate of 15% in 63 cases after palliative surgery for gastrointestinal malignancies<sup>8</sup>). Previous studies also reported a limited median survival time of about 4 to 7 months after surgery<sup>9,10</sup>. The process of surgical decision-making relies upon an assessment of the likely benefits and risks to the patient of the proposed procedure<sup>1</sup>). Despite the important role of palliative surgery in maintaining the quality of life of patients with incurable diseases, few reports have examined the outcomes of palliative surgical procedures. A previous study examined patients who had ascites and cancer, which first presented with MBO, and found that patients with noncolorectal primary tumors had inferior survival<sup>8</sup>). Higashi and colleagues reported that the presence of more than 100 mL of ascetic fluid was related to short symptom-free survival<sup>10</sup>); however, objective criteria for palliative surgery have not been determined. Therefore, the actual indications for surgery have been dependent on the judgement of surgeons at each institution, and the establishment of selection criteria to improve treatment outcomes for palliative surgery is sorely needed. In the present study, we demonstrated that the PNI predicted short- and long-term outcomes following palliative surgery. These results indicated that the PNI could be used as an objective marker for deciding whether to proceed with palliative surgery, independent of the extent of metastatic disease.

The presence of ascites was also identified as an independent prognostic factor in the present study; therefore, careful decision-making should take this factor into consideration when relevant for a patient, along with the PNI. Ascites in patients with advanced cancer likely develops in the following manner: cancer cells produce excessive fluid, but the lymph glands in the abdomen are blocked and cannot drain away the excess fluid adequately. Additionally, the liver cannot synthesize sufficient quantities of blood proteins. Low nutritional status and a past history of heart, liver, and renal failure in the patient can also contribute to

the presence of ascites. Therefore, the causes of ascites in patients with advanced cancer could be attributed to a number of etiological factors<sup>11</sup>). This suggests that a single cause of ascites does not have significant prognostic value, as multiple factors including low nutrition, cancer cachexia, and organ failure influence the prognosis.

Determinants of cancer progression and prognosis are multifactorial, and the important role of cancer-associated malnutrition has been increasingly recognized<sup>12</sup>). Over the past decades, it has become well-accepted that malnutrition is associated with poorer response to therapy, greater impairment of quality of life, increased risk of chemotherapy-induced toxicity, and worse outcomes<sup>13-15</sup>). Assessment of the systemic immunonutritional status has been refined by the introduction of the PNI, and many studies have reported the significant prognostic role of this variable for several malignancies. The PNI can be calculated from the serum albumin concentration and lymphocyte count, which are standard parameters assessed in a clinical setting. Cancer progression worsens nutritional status and can cause subsequent hypoalbuminemia. Poor nutritional status also causes lymphopenia, which is associated with a pre-existing state of immunosuppression, suggesting that the patient has an inadequate anti-tumor immunological reaction<sup>16</sup>). That indicated that cancer progression was correlated to the decline in the PNI. The present study provides the first description of the clinical significance of the PNI following palliative surgery. The significance of the other nutritional markers, such as the modified Glasgow prognostic score<sup>17</sup>), should be evaluated in future studies. In addition, the question of whether preoperative nutritional therapy can lead to improved treatment outcomes—including survival—after palliative surgery should also be investigated.

Recent studies have reported the efficacy of other palliative interventions, such as SEMS, for the treatment of malignant colonic obstruction<sup>3</sup>). It has been reported that the

**Table 2.** Risk Factors for Postoperative Complications.

		Postoperative complication		P-value
		no	yes	
Sex	Male	16	7	0.27
	Female	12	2	
Age	low	14	3	0.38
	high	14	6	
Operative method	ileostomy	3	2	0.67
	colostomy	17	5	
	bypass	8	2	
Bowel obstruction	absent	18	7	0.45
	present	10	2	
Distant metastasis	absent	9	2	0.57
	present	19	7	
Peritoneal dissemination	absent	16	6	0.61
	present	12	3	
The extent of peritoneal dissemination	P0-2	22	6	0.47
	P3	6	3	
Ascites	absent	16	5	0.93
	present	12	4	
Peritoneal cytology	negative	18	6	0.85
	positive	5	2	
Serum CEA levels	low	13	3	0.49
	high	15	6	
Resection of the primary tumor	no	23	8	0.63
	yes	5	1	
Previous treatment	no	21	9	0.10
	yes	7	0	
Infectious disease	absent	19	6	0.95
	present	9	3	
ECOG Performance Status	0-1	23	5	0.11
	2-	5	4	
Body mass index	low	14	4	0.77
	high	14	5	
Albumin	low	17	6	0.75
	high	11	3	
lymphocytes	low	13	7	0.10
	high	15	2	
PNI	low	12	7	0.07
	high	16	2	

CRC colorectal cancer, CEA carcinoembryonic antigen, ECOG Eastern Cooperative Oncology Group, PNI prognostic nutritional index

technical success rate of this procedure ranges from 88-100%, whereas the migration rate is 11% and the perforation rate is 4.5% in the palliative setting. Although the initial clinical relief of obstruction was higher after palliative surgery (100%) compared with stent placement (93%), a significantly lower 30-day mortality rate and shorter duration of hospitalization were reported with SEMS<sup>18</sup>. European Society of Gastrointestinal Endoscopy (ESGE) guidelines recommend SEMS placement as the preferred treatment for palliation in selected patients with malignant colonic obstruction<sup>3</sup>. Despite the high success rate of SEMS, however, long-term patency is not guaranteed; the median patency time has been reported to be 106 days (68-288 days) and the patency rate was found to be 80% (53-90%) until

death<sup>19</sup>. In addition, chemotherapy with antiangiogenic agents, which is usually used for gastric cancer and CRC, has been found to be a risk factor for perforation after SEMS insertion<sup>20</sup>. In the present study, the median survival time of patients classified as PNI-high was 24.1 months, whereas that of patients classified as PNI-low was 5.6 months. These findings suggest that patients with high PNI and a life expectancy of more than 1 year should undergo palliative surgery even in cases in which SEMS insertion is possible.

For patients with bleeding, pain, or fistula, medical palliation is not expected to be effective. Only surgical palliation could improve the quality of life for such patients, despite the high morbidity and mortality rates. We believe, there-

**Table 3.** Prognostic Factors.

		n	median OS (month)	univariate			
				P-value	multivariate		
				P-value	Odds ratio	95% Confidence interval	
Sex	Male	23	14.6	0.11			
	Female	14	7.8				
Age	low	17	12.3	0.62			
	high	20	7.8				
Operative method	stoma	31	12.3	0.65			
	bypass	10	7.6				
Bowel obstruction	absent	25	8.9	0.37			
	present	12	9.4				
Distant metastasis	absent	11	14.4	0.50			
	present	26	7.6				
Peritoneal dissemination	absent	22	14.4	0.09			
	present	15	7.4				
The extent of peritoneal dissemination	P0-2	28	12.7	0.04	0.94	1.05	0.34-3.23
	P3	9	7.4				
Ascites	absent	21	14.4	0.006	0.003	5.68	1.83-17.5
	present	16	3.6				
Peritoneal cytology	negative	26	14.4	0.25			
	positive	9	15.2				
Serum CEA levels	low	16	7.6	0.28			
	high	21	14.6				
Resection of the primary tumor	no	31	7.6	0.17			
	yes	6	24.1				
Previous treatment	no	30	9.4	0.45			
	yes	7	7.4				
Infectious disease	absent	25	8.9	0.87			
	present	12	12.7				
Postoperative complication	absent	28	9.4	0.36			
	present	9	5.6				
ECOG Performance status	0-1	28	12.7	0.02	0.25	2.15	0.58-7.87
	2-	9	2.9				
PNI	low	19	5.6	0.02	0.02	3.75	1.23-11.36
	high	18	24.1				

OS overall survival, CRC colorectal cancer, Well well differentiated adenocarcinoma, Mod moderately differentiated adenocarcinoma, Poorly poorly differentiated adenocarcinoma, CEA carcinoembryonic antigen, ECOG Eastern Cooperative Oncology Group, PNI prognostic nutritional index

fore, that the indications for surgical palliation should not be determined only by the PNI in such cases.

The limitations of the present study include the fact that it is a retrospective study with a relatively small sample size.

In conclusion, the preoperative PNI predicted short- and long-term outcomes following palliative surgery. The PNI could be used as an objective marker for deciding whether to proceed with palliative surgery, independent of the extent of metastatic disease.

#### Conflicts of Interest

There are no conflicts of interest.

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