World Journal
of Surgery

Low Nutritional Prognostic Index Correlates with Poor Survival in Patients with Stage IV Colorectal Cancer Following Palliative Resection of the Primary Tumor

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Abstract

Background We retrospectively investigated the prognostic significance of various clinicopathological factors and preoperative nutritional status to select patients with stage IV colorectal cancer (CRC) who will have a poor prognosis after palliative resection of the primary tumor.

Methods A total of 100 stage IV CRC patients who underwent palliative resection were enrolled. Various clinicopathological factors and Onodera's prognostic nutritional index (OPNI) were evaluated to identify any possible relationship with the prognosis.

Results At the time of the analysis, 83 patients had died, and the median survival time was 21 months. Of the 100 patients, 24 had primary tumor-related symptoms such as obstruction or bleeding. No significant correlation was noted between the OPNI and various clinicopathological factors. The multivariate analysis of patients without primary tumor-related symptoms revealed that the OPNI was an independent prognostic factor. The overall survival of the low-OPNI group was significantly worse than that of the high-OPNI group.

Conclusions This retrospective study suggested that patients with a low OPNI may not be candidates for palliative resection, because it provides no survival benefit to these patients.

Introduction

Despite the increasing use of screening strategies, ∼20 % of colorectal cancer (CRC) patients present with stage IV disease at the time of diagnosis [1]. In stage IV disease, complete surgical resection of the primary tumor and distant metastases remains the only potentially curative therapy [2]. For patients with unresectable metastatic disease, the treatment will be mostly palliative, with a goal of prolonging the survival with the best possible quality of life. The median survival time (MST) for the patients with unresectable metastatic disease is ∼8 months when they are given optimal supportive care without chemotherapy [3]. Several studies have shown that palliative resection of the primary tumor leads to prolonged survival, with a reported MST of 11–26 months [4–7]. In contrast, the recent development of chemotherapeutic and molecular targeting agents markedly improved the MST to almost 24 months [8–11]. Therefore, the prognostic benefit of palliative resection of the primary tumor in patients with unresectable metastatic disease remains controversial [12–15].

It has previously been reported that the postoperative prognosis of patients with gastrointestinal malignancies could be reflected by their preoperative nutritional condition [16–19]. Onodera's prognostic nutritional index (OPNI) is thought to be a simple and useful parameter to determine the nutritional and immunological status of patients [20]. Nozoe et al. [18, 21] reported that a low OPNI was significantly associated with a poor prognosis in patients with gastrointestinal cancers.

In the present study, to identify parameters that can be used to select patients who will have a poor prognosis after palliative resection, we retrospectively investigated the correlation between various clinicopathological factors,

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preoperative nutritional status, and prognosis in patients with stage IV CRC who underwent palliative resection of the primary tumor at our institution.

Patients and methods

A total of 1,647 patients with CRC underwent surgical resection in the Department of Surgical Oncology, Osaka University Hospital, between 1 January 2002 and 31 December 2010. From these patients, we identified 129 patients with stage IV CRC. Of these, 25 patients who underwent R0–1 resection and four patients who underwent emergency surgery due to colonic perforation were excluded from the study. The other 100 patients who underwent palliative resection were enrolled in this study. Palliative resection was defined as resection of a primary lesion of the colon and/or rectum, along with regional lymphadenectomy, but no resection of incurable factors, such as peritoneal dissemination or hepatic and distant metastasis. The following parameters were evaluated: age, gender, preoperative performance status, primary tumor-related symptoms (such as constipation, ileus, melena, and anemia), tumor location, histological type, TNM factors, number of incurable factors, serum carcinoembryonic antigen (CEA) level (the cut-off level was 5.0 mg/ml), postoperative complications, peri-operative transfusion, postoperative hospital stay, postoperative chemotherapy, and molecular targeting therapy. Pathological diagnoses and classifications were made according to the 7th edition of the International Union Against Cancer (UICC) *TNM Classification of Malignant Tumors* [22]. None of the enrolled patients had inflammatory or infectious diseases before surgery. The patients who had received preoperative therapy were excluded from the analysis. All blood samples were collected 1 or 2 days before surgery.

The OPNI was calculated using the following formula: $10\times$ serum albumin concentration (g/dl) $+ 0.005 \times$ lymphocyte count (number/mm^2) in the peripheral blood.

The cut-off value of the OPNI was determined to be 40, based on an original investigation by Onodera et al. [20]

Statistical analysis

The statistical analyses were performed using the JMP 10 software program (SAS Institute Japan, Tokyo, Japan). The χ^2 test was used to compare the data. Survival curves were created via the Kaplan–Meier method and analyzed with the log-rank test. The Cox proportional hazards model was used for the multivariate analysis to identify the independent prognostic factors. Values of $p < 0.05$ were considered to be statistically significant.

Results

Patient characteristics

The clinicopathological features of the 100 patients are summarized in Table 1. In total, 24 patients had symptoms associated with the primary tumor; 17 had symptoms associated with obstruction, including constipation, ileus, and abdominal fullness, six patients had symptoms related to tumor bleeding, including melena and anemia, and one patient had anal pain. Of the 24 patients with primary tumor-related symptoms, 23 (95.8 %) experienced relief of these symptoms after palliative surgery. A total of 58 patients had a single incurable factor, and 42 had multiple incurable factors. Postoperative complications were observed in 18 patients. Among these, superficial surgical site infections were observed in six patients, ileus was noted in six patients, anastomotic leakage in three patients, anastomotic bleeding in two patients, and pneumonia developed in one patient. However, all of the patients healed with conservative treatment without the need for surgical intervention. There were no postoperative deaths.

With regard to the administration of postoperative chemotherapy, nine patients refused to receive chemotherapy and six patients were judged to be contraindicated for chemotherapy because of a poor performance status and/or severe co-morbidities. The other 85 patients underwent chemotherapy. Among these 85 patients, 25 were administered a single fluoropyrimidine-based chemotherapy, such as infusional 5-fluorouracil (5FU) or an oral pro-drug, such as capecitabine. The other 60 patients were treated

Table 1 Characteristics of 100 patients with stage IV colorectal cancer who underwent palliative resection

Mean age ± SD (range)	60.4 ± 10.6 (39–87)
Gender (male/female)	55/45
Performance status (0/1/2)	84/12/4
Primary tumor-related symptoms (present/absent)	24/76
Location (rectum/colon)	19/81
Histological type (poorly differentiated/others)	6/94
Depth of tumor invasion (T1–3/T4)	28/72
Lymph node metastasis (N0–1/N2–3/unknown)	51/40/9
Peritoneal metastasis (present/absent)	39/61
Liver metastasis (present/absent)	71/29
Number of incurable factors (multiple/single)	42/58
Postoperative complications (present/absent)	18/82
Transfusion (present/absent)	20/80
Postoperative chemotherapy (present/absent)	85/15
Molecular targeting therapy (present/absent)	32/68

SD standard deviation

Table 2 Relationship between the OPNI and clinicopathological factors

	OPNI		p value
	≧40 (n = 68)	<40 (n = 32)	
Age (years)			
≧70	25	9	0.39
< 70	43	23	
Gender			
Male	36	18	0.33
Female	32	14	
Primary tumor-related symptoms			
Absent	52	24	0.1
Present	16	8	
Performance status			
0	60	24	0.16
1, 2	8	8	
Location			
Rectum	14	5	0.5
Colon	54	27	
Histological type			
Poorly differentiated	4	2	0.7
Others	64	30	
Depth of tumor invasion			
T1–3	20	8	0.65
T4	48	24	
Lymph node metastasis			
N0–1	36	21	0.26
N2–3	28	7	
Unknown	4	4	
Peritoneal metastasis			
Absent	45	16	0.12
Present	23	16	
Liver metastasis			
Absent	22	7	0.28
Present	46	25	
Number of incurable factors			
Single	26	16	0.27
Multiple	42	16	
CEA (ng/ml)			
≧5	61	28	0.10
< 5	7	4	
Postoperative complications			
Absent	55	27	0.63
Present	13	5	
Transfusion			
Absent	55	25	0.09
Present	13	7	
Postoperative hospital stay (days)			

Table 2 continued

	OPNI		p value
	≧40 (n = 68)	<40 (n = 32)	
Mean (range)	20.3 (7–57)	22.1 (8–43)	0.94
Postoperative chemotherapy			
Absent	9	6	0.08
Present	59	26	
Molecular targeting therapy			
Absent	45	23	0.09
Present	23	9	

CEA carcinoembryonic antigen, *OPNI* Onodera's prognostic nutritional index

with a combination of 5FU plus irinotecan or oxaliplatin. Molecular targeting therapy with bevacizumab became available in 2007, and cetuximab was available in 2008 in our country. Therefore, only 32 patients received molecular targeting therapy.

At the time of the analysis, 83 (83 %) patients had died, with a median follow-up of 24.8 months after surgery. The MST was 21 months.

Correlation between the OPNI and clinicopathological factors

The preoperative values of the OPNI ranged from 29.5 to 65, with a mean value ± standard deviation of 44 ± 2.6.

The correlations between the OPNI and clinicopathological factors are shown in Table 2. No significant correlation was noted between the OPNI and any of the various clinicopathological factors examined. Only 11 patients had normal serum CEA levels; the other 89 patients had higher than normal serum CEA values. The serum CEA level was also not associated with the OPNI. According to the postoperative therapy, the administration of the chemotherapy and the targeting therapy tended to be more frequent in the high-OPNI group compared with the low-OPNI group, but statistical significance was not reached.

The correlations between prognosis and various clinicopathological factors were also investigated. In the univariate analysis, a significantly worse prognosis was associated with preoperative performance status, depth of tumor invasion, number of incurable factors, and OPNI (Table 3). A multivariate analysis using Cox's model revealed that both the number of incurable factors and the OPNI were independent prognostic factors.

Because there is a possibility that the value of the OPNI may be lower in patients with primary tumor-related symptoms, such as obstructing or excessively bleeding

Table 3 Results of univariate and multivariate analyses of prognostic factors in 100 patients with stage IV colorectal cancer who underwent palliative resection

Variables	MST (months)	Univariate analysis p value	Multivariate analysis		
			p value	OR	95 % CI
Age, years ($\geqq$ 70 vs. < 70)	22.5 vs. 18.6	0.54			
Gender (male vs. female)	23.9 vs. 19	0.65			
Primary tumor-related symptoms (present vs. absent)	19 vs. 22	0.83			
Performance status (0 vs. 1, 2)	23 vs. 10.5	0.001	0.25	1.32	0.77–2.47
Location (rectum vs. colon)	23 vs. 19	0.45			
Histological type (poorly differentiated vs. others)	18 vs. 21	0.63			
Depth of tumor invasion (T4 vs. T1–3)	18.5 vs. 25	0.025	0.06	1.42	0.99–2.97
Lymph node metastasis (N0–1 vs. N2–3)	27 vs. 19	0.42			
Peritoneal metastasis (present vs. absent)	14 vs. 23	0.2			
Liver metastasis (present vs. absent)	19 vs. 29	0.12			
Number of incurable factors (multiple vs. single)	15 vs. 23	0.042	0.04	1.64	1.02–2.63
CEA, ng/ml ($\geqq$ 5 vs. < 5)	18 vs. 22	0.99			
OPNI (<40 vs. $\geqq$40)	10 vs. 23	0.004	0.005	2.46	1.49–399

CEA carcinoembryonic antigen, *CI* confidence interval, *MST* median survival time, *OPNI* Onodera's prognostic nutritional index, *OR* odds ratio

Table 4 Results of univariate and multivariate analyses of prognostic factors in 76 patients with stage IV colorectal cancer who had no primary tumor-related symptoms

| Variables	MST (months)	Univariate analysis p value	Multivariate analysis		
			p value	OR	95 % CI
Age, years ($\geqq$ 70 vs. < 70)	21 vs. 19	0.13			
Gender (male vs. female)	23 vs. 19	0.99			
Performance status (0 vs. 1, 2)	22.5 vs. 16.3	0.11			
Location (rectum vs. colon)	23 vs. 18	0.76			
Histological type (poorly differentiated vs. others)	19 vs. 23	0.64			
Depth of tumor invasion (T4 vs. T1–3)	17 vs. 27	0.019	0.10	1.73	091–3.53
Lymph node metastasis (N0–1 vs. N2–3)	23 vs. 19	0.32			
Peritoneal metastasis (present vs. absent)	13 vs. 23	0.036	0.46	1.31	0.64–2.80
Liver metastasis (present vs. absent)	18 vs. 30	0.038	0.18	1.53	0.81–3.04
Number of incurable factors (multiple vs. single)	11 vs. 23	0.014	0.32	1.43	0.70–2.88
CEA, ng/ml ($\geqq$5 vs. < 5)	15 vs. 20	0.99			
OPNI (< 40 vs. $\geqq$ 40)	9.5 vs. 23	0.001	0.006	2.77	1.56–4.84

CEA carcinoembryonic antigen, *CI* confidence interval, *MST* median survival time, *OPNI* Onodera's prognostic nutritional index, *OR* odds ratio

tumors, we investigated the correlation between the OPNI and the prognosis of the 76 patients without primary tumor-related symptoms (Table 4). In the univariate analysis, a significantly worse prognosis was associated with peritoneal metastasis, liver metastasis, the depth of tumor invasion, number of incurable factors, and the OPNI. According to the multivariate analysis, the OPNI was the only independent prognostic factor.

The overall survival of the low-OPNI group was significantly ($p = 0.0005$) worse than that of the high-OPNI group (Fig. 1). The MST was 9.5 months for the low-OPNI group and 27 months for the high-OPNI group.

Discussion

Resection of the primary tumor may relieve symptoms and avoid potential complications, such as obstruction or bleeding, in patients with stage IV CRC. However, in the case of resection, the postoperative recovery period and hospital stay may worsen the quality of life for patients and delay the start of systemic chemotherapy, which may be related to a poorer prognosis. In the present study, the MST was 21 months, which was similar to that of patients treated with the current combination chemotherapy and molecular targeting agents [8–11]. Therefore, since the
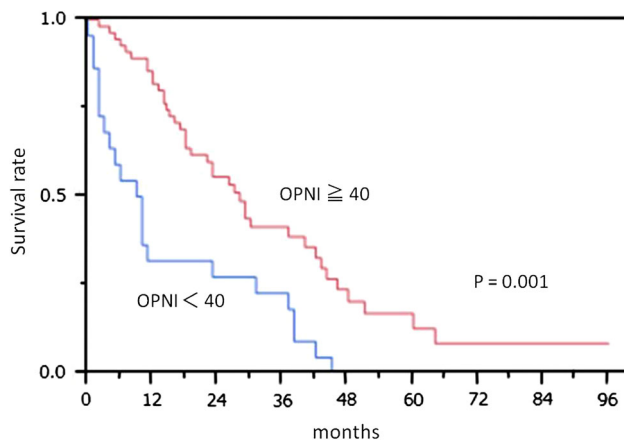
Fig. 1 Overall survival of the 76 patients without primary tumor-related symptoms divided by the Onodera's Prognostic Nutritional Index (OPNI). The overall survival of the low-OPNI group was significantly ($p = 0.001$) worse than that of the high-OPNI group

prognostic benefit of palliative resection for the patients with unresectable metastatic disease remains controversial, it is especially important to identify patients who will have a poor prognosis after palliative resection so that they can receive other treatments.

It is well known that the conventional clinicopathological factors and serum CEA level are important and useful when predicting the prognosis of patients with various gastrointestinal cancers [23]. However, because stage IV is regarded as the final stage of CRC, most of these factors are relatively ineffective for the evaluation of patients with such advanced disease. In fact, our study, using a multivariate analysis, revealed that only the number of incurable factors were associated with survival. Therefore, in stage IV CRC patients, another parameter should be identified to predict the survival of patients.

Although both clinicopathological factors and serum CEA level reflect tumor characteristics, tumor progression is not solely determined by the local characteristics of the tumor, but also by the host systemic immune/inflammatory responses [24]. Furthermore, the presence of an inflammatory response has been proposed to be pathogenic in the development of cancer-associated malnutrition [25]. Several studies have reported that patients with advanced gastrointestinal malignancies are often malnourished, and that preoperative nutrition status is associated with postoperative complications, tumor progression, and a poor clinical outcome [16–19]. Several assessment tools are applied for nutritional status, such as the Malnutrition Universal Screening Tool (MUST), the Nutritional Risk Scoring 2002 (NRS2002), and the mini nutritional assessment [26–28]. These tools are simple, well-validated, and cost-effective tools that are widely utilized to assess the nutritional status of cancer patients. The OPNI is one such

tool and is also a simple index that is calculated using only two parameters: the serum albumin (Alb) and the total lymphocyte count (TLC) [20]. Alb is a main component of the plasma protein that preserves the colloid osmotic pressure, and it reflects nutritional status. The TLC has also been proposed as a useful indicator of nutritional status, as well as host inflammatory status. Both the Alb and the TLC are usually examined in daily clinical practice. Therefore, the OPNI, which reflects the immunonutritional status, is thought to be a useful and convenient index to predict tumor progression and survival in patients with malignancies. With regard to the correlation between the OPNI and clinicopathological factors, Watanabe et al. [17] and Nozoe et al. [18, 21] reported that the OPNI was significantly associated with the depth of tumor invasion. However, almost all of the patients (72 %) in our study had T4 tumors, therefore, we could not find any significant correlation between the OPNI and the depth of tumor invasion. According to prognosis, previous studies [17, 21] have reported that the OPNI was significantly correlated with prognosis of patients with gastrointestinal cancers. These studies examined not only stage IV patients, but also stage I, II, and III patients. Moreover, Nozoe et al. [21] reported that the OPNI was significantly lower in patients with intestinal obstruction, which was one of the primary tumor-related symptoms. Therefore, we investigated the 76 patients without primary tumor-related symptoms. As a result, it was revealed that a low OPNI was an independent predictor of worse prognosis even in the patients limited to stage IV CRC. The MST of patients with a low OPNI was 9.5 months, which was shorter than that reported for patients with stage IV CRC who underwent chemotherapy alone. Although the necessity of palliative resection for patients with asymptomatic primary tumor and unresectable metastatic disease remains controversial, the OPNI may be useful to select patients who will have a survival benefit associated with the palliative resection. Thus, patients with a low OPNI may not be candidates for palliative resection.

Although there were no significant differences in the administration of chemotherapy and molecular targeting therapy in the low-OPNI and the high-OPNI groups, the frequency of postoperative therapy tended to be lower in the low-OPNI group. It has been reported that malnutrition leads to a loss of lean body mass, impaired immune function, a reduced response rate to chemotherapy, and poor survival [29, 30]. Furthermore, it has been reported that nutritional interventions could improve the immuno-nutritional system, response to chemotherapy, and patient survival [31, 32]. Such nutritional interventions should be implemented to improve the survival in patients with low OPNI.

Conclusions

In this retrospective study, the number of incurable factors and the OPNI were found to be significantly associated with prognosis in patients with stage IV CRC who underwent palliative resection. The OPNI was a strong independent prognostic factor in patients without primary tumor-related symptoms. Therefore, patients with a low OPNI may not be candidates for palliative resection due to its lack of a survival benefit. This was a single-arm retrospective study; therefore, a prospective study is required to confirm the present findings by selecting patients who will have a poor survival after palliative resection for stage IV CRC.

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