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Prognostic Factors for Stage IV Colorectal Cancer after Primary Tumor Resection: A Single-Institutional Retrospective Analysis

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Abstract

Background: The benefits of primary tumor resection without metastasectomy in patients with stage IV noncurative colorectal cancer remain controversial. In our hospital, we perform primary tumor resections to avoid complications related to the tumor, regardless of whether the patients are symptomatic. This study aimed to evaluate the prognostic factors and long-term outcomes after primary tumor resection with or without metastasectomy in patients with stage IV colorectal cancer.

Methods: We retrospectively reviewed 130 consecutive patients with stage IV colorectal cancer who underwent primary tumor resection without metastasectomy (primary resection) or primary tumor resection with metastasectomy (R0 resection) at Juntendo University Hospital between January 2007 and December 2013.

Results: The median duration of observation was 22.5 months (range 30 to 50). The 5-year overall survival rate for all the patients was 13.8%, with a median survival time of 26 months. Of the 130 patients, 59 (45.4%) underwent primary resections, and 71 (54.6%) underwent R0 resections. In univariate analysis, significantly shorter overall survival was associated with age >60 years, peritoneal metastases, palliative resection, poorly differentiated adenocarcinoma, mucinous adenocarcinoma, or signet-ring cell carcinoma (Por/Muc/Sig) histological types, lymphatic invasion, and ≥ 2 metastatic sites. Multivariate analysis suggested that Por/Muc/Sig histological types, lymphatic invasion, and palliative resection were independent prognostic factors for poor survival.

Conclusion: The patients with Por/Muc/Sig histological types or lymphatic invasion, or who underwent palliative resection, showed significantly lower survival rates than other patients with stage IV colorectal cancer. It is possible that preoperative chemotherapy or chemoradiation therapy might contribute to improve their prognosis.

Keywords: Colorectal cancer; Prognostic factor; Primary tumor resection; R0 resection

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Introduction

Despite the many new treatments developed over recent decades, colorectal cancer remains a major cause of death in Japan, where it accounts for the largest number of deaths among women and the third largest number among men [1]. Approximately 20% to 25% of patients with colorectal cancer are diagnosed with synchronous distant metastasis [2,3], but only 20% of these patients can undergo curative resection of the metastatic sites [4,5]. The National Comprehensive Cancer Network and Japanese guidelines recommend chemotherapy for unresectable stage IV colorectal cancer without symptoms [1,6]. Meta-analyses have indicated that resection of an asymptomatic primary tumor increased the risk of major mortality and morbidity, and may have no benefit in term of overall survival [7,8]. In contrast, several reports have advocated resection of the primary tumor to prevent primary tumor-related complications, such as obstruction, bleeding, and perforation, and to avoid emergency operations that could contribute to high mortality and morbidity [9,10]. Thus, the advantages of primary tumor resection without metastasectomy (primary resection) in patients with stage IV colorectal cancer remain controversial. In our hospital, we perform primary tumor resection to prevent these complications caused by the primary tumor, even in asymptomatic patients with metastasis.

Table 1: The patient characteristics.

Characteristics	Values	Number
Age (years)	Median (range)	67 (24-86)
Gender	Male/Female	73/57
Preoperative CEA (ng/ml)	Median (range)	27.5 (0.7-8269)
Tumor location	Colon	94
	Rectum	36
	Left side/Right side	86/44
Depth of invasion	pT1-3/pT4	98/32
Tumor diameter (mm)	Median (range)	53 (14-105)
Metastatic site (overlapping distribution)	Liver	94
	Lung	33
	Peritoneum	30
	Distant node	5
Multiple organ metastases		
Surgical procedure	APR	9
	Hartmann's procedure	12
	Sigmoidectomy	32
	Anterior resection	21
	Left colectomy	13
	Right colectomy	40
	Partial resection	3
curability	R0 resection/Primary resection	59/71
Operation procedure	Laparoscopy/open	30/100
No of dissected lymph node	Median (range)	21 (2-71)
Histology	Well/Mod	112
	Por/Muc/Sig	18
Lymph node metastasis	Absent/Present	36/94
Venous invasion (v)	Absent/Present	31/99
Lymphatic invasion (ly)	Absent/Present	43/87
Complications	≧ 2 (Clavien-Dindo)	14
SSI		8
Leakage		4
Ileus		2
over 3 chemotherapeutic regimens		
Chemotherapy	none	33
	FOLFOX or XELOX	90
	FOLFIRI or IRIS	48
	Targeted agents	76

CEA: Carcinoembryonic Antigen; APR: Abdominoperineal Resection Well differentiated tubular adenocarcinoma; Mod: Moderately Differentiated tubular adenocarcinoma; Por: Poorly differentiated adenocarcinoma; sig: signet-ring cell carcinoma; muc: mucinous adenocarcinoma; SSI: Surgical Site Infection Targeted agent's bevacizumab or cetuximab or panitumumab

Despite the progress in treatments, several studies have reported that the 5-year survival rate for stage IV colorectal cancer can still be as low as 10% to 20% [11,12]. Some studies have reported prognostic factors for colorectal cancer, with several reports that colorectal cancer patients with poorly differentiated adenocarcinoma, mucinous adenocarcinoma, or signet-ring cell carcinoma (Por/Muc/Sig histology) have a poor prognosis [13-15]. However, Pande et al. [16] showed no difference in survival between different histologic types of stage IV colorectal cancer patients. In general, it is difficult to evaluate the prognostic factors because of the wide variations in the backgrounds of stage IV colorectal cancer patients, including their past history, metastatic state, general condition, and paraneoplastic symptoms. In addition, some stage IV colorectal cancer patients undergo curative resection whereas others are unable to do so; Pande et al. [16] study included both groups. Nevertheless, long-term survival of stage IV patients is rare, and the prognostic factors remain unknown. In this study, we analyzed the clinical pathological features and prognostic factors for stage IV colorectal cancer patients

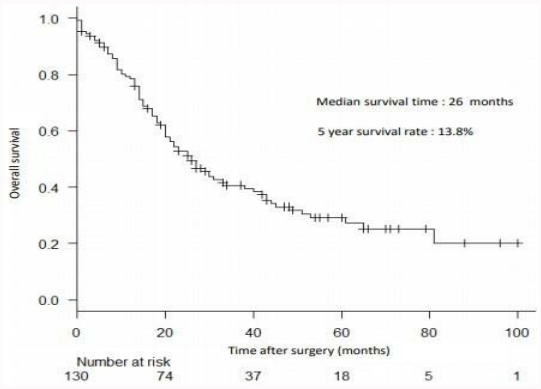

Figure 1:

who underwent primary tumor resection without metastasectomy (primary resection) or curative resection (R0 resection) at our hospital.

Material and Methods

Study population

We evaluated 130 consecutive patients with stage IV colorectal cancer patients who underwent resection of the primary tumor with or without metastasectomy at the Department of Coloproctological Surgery at Juntendo University Hospital between January 2007 and December 2013. Patients were excluded if they had a synchronous colorectal cancer, had previously been treated for a prior colorectal cancer, or had a histologic diagnosis other than adenocarcinoma (e.g., a carcinoid, neuroendocrine tumor, or gastrointestinal stromal tumor). Emergency surgery patients were also excluded. Postoperative complications were classified using the Clavien-Dindo classification [17].

Statistical analysis

Categorical variables were analyzed using Fisher's exact test and continuous variables were analyzed using Student's t test or the Mann-Whitney U test. Descriptive data were reported as the numbers of patients and percentages, or as medians with interquartile ranges. The Kaplan-Meier method was used to estimate overall survival. Differences in survival outcomes were assessed with the log-rank test. Multivariate analyses were performed using the Cox proportional hazards model to identify independent predictors of overall survival. All statistical analyses were performed using the freely available software EZR. Values of P<0.05 were considered statistically significant.

Results

The median follow-up period was 22.5 months (range, 0.2 to 100 months). The general characteristics of the patients are listed in Table 1. The median patient age was 67 years (range, 24 to 86 years), and 73 patients (56.1%) were male. The median level of preoperative Carcinoembryonic Antigen (CEA) was 27.5 ng/ml (range, 0.7 to 8269 ng/ml). Tumors were located in the colon in 94 patients (72.3%) and the rectum in 36 patients (27.7%). The depth of invasion was classified as T4 in 32 patients (24.6%) and the median tumor diameter was 53 mm (range, 14mm to 105 mm). The most common metastatic site was the liver (72.3%), followed by the lung (25.4%), peritoneum (23.1%), and distant lymph nodes (3.8%). Multiple organ metastases were recognized in 31 patients (23.8%). R0 resection was performed in 59 patients (45.4%) and primary resection in the other 71 (54.6%); 100 patients (76.9%) received open surgery and 30 (22.1%) underwent laparoscopic surgery. Of the 30 patients who received laparoscopic surgery, 5 (16.7%) were converted to open surgery because of bulky tumors. Three patients (2.3%) died within 30 days after open surgery, but there were no deaths within 30 days after surgery in the laparoscopic group. The number of dissected lymph nodes was 21 (range, 2 to 71). Histology showed well or moderately differentiated adenocarcinoma in 112 patients (86.2%) and poorly differentiated adenocarcinoma, mucinous adenocarcinoma, or signet-ring cell carcinoma (Por/Muc/Sig) histological types in 18 patients (13.8%). Lymph node metastases were observed in 94 patients (72.3%). Venous invasion and lymphatic invasion were observed in 99 (76.1%) and 87 (66.9%) patients, respectively. According to the Clavien-Dindo classification of complications, 14 patients (10.8%) were classified as Grade II to IV. Following primary resection, 97 patients (74.6%) received chemotherapy. Oxaliplatin-based (FOLFOX or XELOX) and irinotecan-based (FOLFIRI or IRIS) therapies were used in 90 (69.2%) and 48 patients (36.9%), respectively. Finally, 76 patients (58.5%) received bevacizumab, cetuximab, or panitumumab (targeted agents).

The five-year overall survival rate was 13.8%, with a median survival time of 26 months across all the stage IV colorectal cancer patients (Figure 1). The univariate and multivariate analyses of factors associated with overall survival are presented in Table 2. In the univariate analysis, age ≥ 60 years, peritoneal metastases, Por/Muc/Sig pathologies, primary resection, lymphatic invasion, multiple organ metastases, peritoneal metastases, and depth of invasion pT4 were significantly associated with poorer overall survival. In the multivariate analysis, primary resection (Hazard Ratio (HR) = 0.35, 95% confidence interval (CI) 0.20-0.60, P<0.001), lymphatic

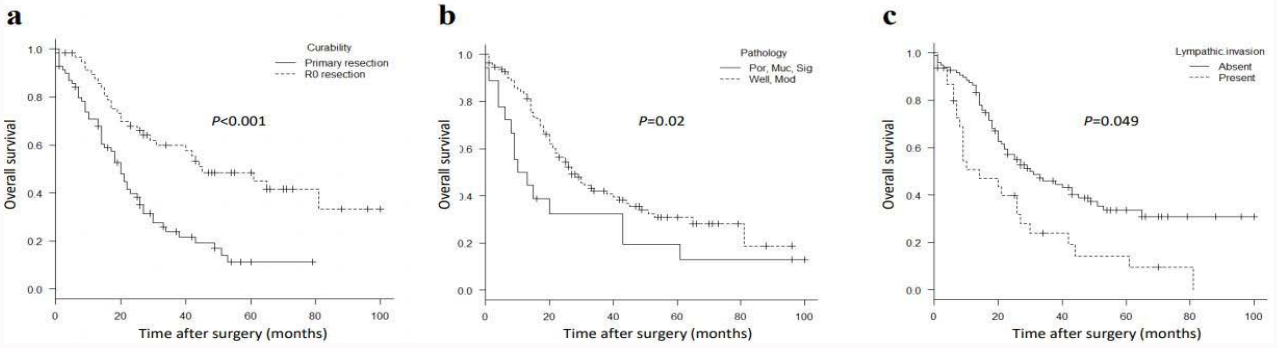

Figure 2:

Table 2: The results of the univariate and multivariate analyses of factors associated with overall survival.

Variable	Univariat analysis		Multivariate analysis	
	n	*P*	HR (95% CI)	*P*
Age ≧ 60 years /60>	90/40	**0.044**	1.5700 (0.92-2.65)	0.093
Male/Female	73/57	0.484	0.8573 (0.55-1.31)	0.481
CEA ≧ 5 ng/mL /5> ng/mL	108/22	0.25	1.4310 (0.77-2.64)	0.253
Depth of invasion pT4/pT1-3	32/98	**0.034**	1.5720 (0.97-2.53)	0.064
Liver metastasis ＋/－	94/36	0.863	1.1520 (0.68-1.93)	0.592
Lung metastasis ＋/－	33/97	0.734	1.1950 (0.70-2.03)	0.512
Peritoneal metastasis ＋/－	30/100	**<0.001**	1.3700 (0.76-2.46)	0.29
Location left side/right side	86/36	0.217	1.3820 (0.86-2.21)	0.179
Open/Laparoscopy	100/30	0.093	1.6010 (0.91-2.80)	0.099
R0 resection/Primary resection	59/71	**<0.001**	0.3496 (0.20-0.60)	**<0.001**
Pathology Por/Muc/Sig /Well/Mod	18/112	**0.033**	2.1190 (1.11-4.01)	**0.02**
Multiple organ metastases/single site	31/99	**0.002**	1.2350 (0.69-2.18)	0.468
Venous invasion ＋/－	51/79	0.652	0.8159 (0.51-1.29)	0.39
Lymphatic invasion ＋/－	33/97	**0.001**	1.6940 (1.00-2.86)	**0.049**
Chemotherapy ＋/－	97/33	0.669	0.6011 (0.34-1.03)	0.068
FOLFOX or XELOX ＋/－	90/40	0.704	0.5874 (0.29-1.16)	0.129
FOLFIRI or IRIS ＋/－	48/82	0.325	1.2660 (0.71-2.23)	0.414
Targeted agents ＋/－	76/54	0.19	1.8550 (0.92-3.72)	0.082
Over 3 chemotherapeutic regimen	36/94	0.729	0.7508 (0.43-1.30)	0.306

HR: Hazard Ratio; CI: Confidence Interval; CEA: Carcinoembryonic Antigen
Well differentiated tubular adenocarcinoma
Mod: Moderately differentiated tubular adenocarcinoma; Por: Poorly differentiated adenocarcinoma; Sig: Signet-ring cell carcinoma Muc: Mucinous adenocarcinoma
Targeted agent's bevacizumab or cetuximab or panitumumab

invasion (HR=1.69, 95% CI 1.00 to 2.86, P=0.049), and Por/Muc/Sig histological types (HR=2.12, 95% CI 1.12 to 4.01, P=0.02) were found to be independent predictors of poor overall survival (Figure 2).

Discussion

This review identified that primary resection, lymphatic invasion, and Por/Muc/Sig histological types were independent prognostic factors for patients with stage IV colorectal cancer after primary tumor resection. Of these, the most significant factor associated with survival was primary resection. The Japanese Society for Cancer of the Colon and Rectum guidelines recommend that if both distant metastases and primary tumor are resectable, curative resection of these should be considered [1]. The patients who underwent primary resection were those for whom R0 resection was not possible, hence accounting for primary resection being a poor prognostic factor. Therefore, R0 resection for stage IV colorectal cancer improves the prognosis.

Although the 5-year overall survival rate for patients with stage IV colorectal cancer has been reported to be 18.5% according to the Japanese Association of Clinical Cancer Centers, patients who received curative resection including the complete resection of metastatic lesions could achieve long-term survival [18]. In this study, primary tumor resection was performed for all patients, with or without unresectable metastatic sites; however, the survival benefits of primary tumor resection with unresectable metastases are controversial. Several studies have demonstrated that surgical resection of the primary tumor improves the survival of patients with stage IV colorectal cancer [19,20]. We believe that the primary tumor should be resected even for patients with unresectable metastases to avoid complications related to the primary tumor, such as bleeding, ileus, and perforation. However, the beneficial results of this have not been confirmed in a randomized controlled trial and previous studies have been retrospective. Currently, several randomized control trials about the benefits of primary tumor resection are in progress: The CAIRO 4, SYNCHRONOUS, GRECCAR 8, and Japan Clinical Oncology Group (JCOG) 1007 studies. Their results are needed to confirm the validity of primary tumor resection in these cases.

Past reports have shown the advantages of laparoscopic procedures compared with open surgery [21-24], and the validity of using laparoscopic surgery for stage IV colorectal cancer patients with unresectable metastases has been sufficiently clarified. Hida et al. [25] and Kim et al. [24] demonstrated that, compared with open surgery, the laparoscopic approach has advantages in the short term and no disadvantages in the long term. Although the difference was not statistically significant, the present study results also suggested that the overall survival rate tended to be better in the patients who underwent laparoscopic surgery than in those who received open surgery, similar to the results of the previous reports. This finding suggested that laparoscopic primary tumor resection may be a reasonable treatment option for certain stage IV colorectal cancer patients with incurable metastases. However, it is possible there was selection bias in the allocation of patients between the laparoscopic and open surgery groups, given that this review was a retrospective study. Currently, a randomized control trial (JCOG1107) about the laparoscopic resection of primary tumors is underway.

In this study, Por/Muc/Sig histological types were found to be an independent predictor of poor overall survival. Poorly differentiated

adenocarcinomas reportedly account for only around 10% of colorectal cancer, with mucinous adenocarcinomas accounting for 10% and signet-ring cell carcinomas 1% [13, 26-28]. Shibata et al. [29] reported that patients with Por/Muc/Sig colorectal cancer synchronous metastasis had significantly shorter survival times than patients with other pathological histologies, even if the metastases were curatively resected. Other reports have provided further supporting evidence that patients with Por/Muc/Sig histological types had poorer prognosis than those with well or moderately differentiated adenocarcinoma [13-15,26]. Conversely, Pande et al. [16] found no difference between histologic types in the survival of patients with stage IV colorectal cancer. However, it should be noted that all these reports were of retrospective studies. Patients with Por/Muc/Sig histological types have a high frequency of microsatellite instability, BRAF and KRAS mutations, or amplification of BLC2, an apoptosis suppressor [13,30-34]. These genetic features may affect the prognosis of Por/Muc/Sig patients.

Lymphatic invasion was also found to be an independent predictor of poor overall survival. Lim et al. [35] reported that lymphovascular invasion was an independent predictor of both disease-free and cancer-specific survival in an analysis of 2,417 patients with colorectal cancer. However, several studies have noted the prognostic influence of lymphatic invasion only in univariable analyses [36-38] or failed to identify a prognostic impact [39]. Unexpectedly, the choice of chemotherapy was not found to be significantly associated with patient outcome in our study.

The limitation of our study was its single-institute retrospective design, which may be associated with a selection bias. Further investigations such as prospective randomized trials are needed to confirm the results of this study.

In conclusion, the patients with Por/Muc/Sig histological types, lymphatic invasion, and palliative resection had significantly lower survival rates than other patients with stage IV colorectal cancer, even though the primary tumor was resected. Randomized control studies are in progress; their results are necessary to confirm the result of this study.

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