Treatment Outcome of Resection of Disseminated Peritoneal Metastases from Colorectal Cancer

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Abstract. *Aim: To show the treatment outcomes of disseminated nodule resection for peritoneal metastasis of colorectal cancer and describe the details of cured cases. Patients and Methods: From January 2001 to December 2016, patients who underwent disseminated nodule resection of colorectal adenocarcinoma with no macroscopic residual tumor in our institution were retrospectively analyzed for clinicopathological factors associated with prognosis. Results: Forty-one cases were included in this study. The 3-year relapse-free survival was 12.5%, and the 5-year overall survival was 38.4%. In a multivariate analysis, lack of post-operative adjuvant chemotherapy and pre-operative carbohydrate antigen 19-9 over 100 IU/l were extracted as independent factors associated with short relapse-free survival, respectively. Among 41 cases, 32 were followed-up 5 years after surgery and five (15.6%) survived without relapse and were regarded as 'cured'. Conclusion: More than a few cases of colorectal peritoneal metastasis, which is thought to be difficult to cure, were cured by resection of disseminated nodules without resorting to highly invasive treatment.*

Peritoneal metastasis (PM) of colorectal cancer is regarded as an incurable condition compared with that to the liver or lung, due to its unfavorable treatment outcome (1). Recently, cytoreductive surgery (CRS) and perioperative intraperitoneal chemotherapy (POIC), including hyperthermic intra-peritoneal chemotherapy, have been reported to be associated

with a good treatment outcome for PM of colorectal cancer, mostly by Sugarbaker *et al.* (2, 3). Such advancements have suggested that a cure can now be achieved. However, POIC is not covered by the national insurance system of Japan and has been performed at only a few institutions. Furthermore, these treatments were reported to cause severe adverse events, therefore the potential pool for such therapy may be limited (4, 5).

Several reports have described a potential benefit of resection of disseminated PM of colorectal cancer (6-8). Although nodule resection itself is not a curative treatment for PM in theory, the outcome of this treatment has been dramatically improved by combining it with systemic chemotherapy, in light of recent advances in systemic chemotherapy.

We herein report the treatment outcomes of nodule resection for PM of colorectal cancer and describe the details of cured cases.

Patients and Methods

Patients. From January 2001 to December 2016, patients who underwent resection of visible disseminated nodules leading to no macroscopic residual tumor for PM of pathologically proven colorectal adenocarcinoma at Chiba University Hospital, Chiba, Japan were included in this study. This study was approved by the Institutional Review Board of Chiba University School of Medicine and was registered in UMIN Clinical Trials Registry (UMIN000035807).

Study items. The details of patient age, sex, side of the primary site, timing of PM (synchronous or metachronous), pathological type, peritoneal carcinoma index (PCI), metastasis other than PM, tumor marker [carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9)] before surgery, number of resections, intra-operative lavage cytology, and peri-operative systemic chemotherapy were investigated. The rates of relapse-free survival (RFS) and overall survival (OS) from the time of resection were calculated by the Kaplan-Meier method, and the factors affecting RFS and OS were analyzed by univariate and multivariate analyses.

Patients who survived for more than 5 years without any relapse of colorectal cancer after surgery were defined as 'cured cases', and the details of these cases were studied.

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Key Words: Colorectal cancer, peritoneal metastasis, nodule resection.

Table I. Background characteristics of 41 cases of peritoneal metastases (PM) from colorectal cancer.

	Value
Age, years	Median (range) 66 (30-87)
Gender, n (%)	Male 17 (41.5%) Female 24 (58.5%)
Site of primary tumor, n (%)	Right side 19 (46.3%) Left side 22 (53.7%)
Histology, n (%)	Well/moderate 34 (82.9%) Poor/mucinous 7 (17.1%)
Degree of PM, n (%)	P1 13 (31.7%) P2 28 (68.3%)
PCI, n (%)	>5 7 (17.1%) ≤5 30 (73.2%) Unknown 4 (%)
Pre-operative serum CEA, n (%)	>10 ng/ml 16 (39.0%) ≤10 ng/ml 25 (61.0%)
Pre-operative serum CA19-9, n (%)	>100 U/ml 10 (24.4%) ≥100 U/ml 30 (73.2%) NA 1 (%)
Diagnostic interval	Synchronous 20 (48.8%) Metachronous 21 (51.2%)
Distant metastases other than PM, n (%)	Yes 14 (34.1%) None 27 (65.9%)
Number of resections, n (%)	1 28 (68.3%) 2 9 (22.0%) 3 3 (7.3%) 4 1 (2.4%)
Intraperitoneal lavage cytology, n (%)	Positive 12 (29.3%) Negative 16 (39.0%) Not done 13 (31.7%)
Neo-adjuvant chemotherapy, n (%)	Yes 9 (22.0%) No 32 (78.0%)
Postoperative chemotherapy, n (%)	Yes 24 (58.5%) No 17 (41.5%)

PCI: Peritoneal carcinoma index; CEA: carcinoembryonic antigen; CA19-9: carbohydrate antigen 19-9.

Statistical analyses. The log-rank test was used in the univariate analysis, and Cox's proportional hazard model was used in the multivariate analysis. A *p*-value less than 0.05 was regarded as significant. Data were statistically analyzed using JMP software, version 12 (SAS Institute Inc., Cary, NC, USA).

Results

Forty-one cases were retrospectively identified and included in this study. The patients' background characteristics are shown in Table I. There were 20 case of synchronous PM and 21 cases of metachronous PM. Over half of the cases underwent single surgery, while 13 underwent multiple resection. Intra-operative lavage cytology was performed in 28 cases (68.3%), and 16 cases were negative for cytology despite PM.

The survival curves of the RFS and OS are shown in Figure 1. The median observation period was 27.8 months.

Table II. Univariate and multivariate analysis of the relapse-free survival of 41 cases of peritoneal metastasis (PM) from colorectal cancer.

	No. of patients	Median-RFS (months)	<i>p</i> -Value	
			Univariate analysis	Multivariate analysis
Age				
>70 Years	27	5.4	0.4957	
≤70 Years	14	11		
Gender				
Male	17	7.45	0.1561	0.2897
Female	24	12.6		
Site of primary tumor				
Right side	19	10.1	0.8303	
Left side	22	12.1		
Histology				
Well/moderately	34	10.9	0.2891	
Poorly/mucinous	7	11		
Degree of PM				
P1	13	10.9	0.5862	
P2	28	10.9		
PCI				
>5	7	10.9	0.914	
≤5	30	13.4		
Pre-operative CEA				
>10 ng/ml	16	10.1	0.7934	
≤10 ng/ml	25	11.35		
Pre-operative CA19-9				
>100 U/ml	10	5.55	0.0065	0.1519
≤100 U/ml	30	13.2		
Diagnostic interval				
Synchronous	20	10.9	0.3872	
Metachronous	21	10.9		
Distant metastases other than PM				
Yes	14	5.85	0.8158	
No	27	10.95		
Intraperitoneal lavage cytology				
Positive	12	8.6	0.1136	0.1434
Negative	16	15.7		
Neo-adjuvant chemotherapy				
Yes	9	9.1	0.419	
No	32	10.9		
Postoperative chemotherapy				
Yes	24	13.45	0.0101	0.0259
No	17	5.1		

PCI: Peritoneal carcinoma index; CEA: carcinoembryonic antigen; CA19-9: carbohydrate antigen 19-9. Bold values show significance.

The median RFS of all cases was 10.9 months, and the 3-year RFS was as low as 12.5%. The median OS was 38.7 months, and 5-year OS was 38.4%.

Results of the univariate and multivariate analyses of the RFS are shown in Table II. Those patients without post-

Figure 1. Relapse-free survival curve (A) and overall survival curve (B) for 41 patients who underwent resection of disseminated nodule of colorectal peritoneal metastases with no macroscopic residual tumor.

operative adjuvant chemotherapy (POAC) or CA19-9 over 100 IU/l had a significant shorter RFS in the univariate analysis than others. A multivariate analysis was performed for factors with $p \leq 0.2$ in the univariate analysis, and no POAC was extracted as an independent factor associated with a short RFS (hazard ratio=3.22, $p=0.0259$). Regarding OS, those without POAC, CA19-9 over 100 IU/l, or poorly differentiated or mucinous carcinoma had a significantly poor prognosis in the univariate analysis. A multivariate analysis was performed for factors with $p < 0.1$ in the univariate analysis, and only pre-operative CA19-9 over 100 IU/l was extracted as an independent factor associated with a poor prognosis (hazard ratio=3.02, $p=0.0254$) (Table III).

Among 41 cases, 32 were followed-up 5 years after surgery. Of those 32 cases, five (15.6%) survived without relapse for more than 5 years and were regarded as 'cured'. The details of these cases are shown in Table IV. Four cases had metachronous PM, and all cases had well- or moderately differentiated adenocarcinoma. All five cases had a PCI of 4 or less. Only one case had distant metastasis without PM (port site recurrence). Four cases underwent POAC, and two of them also received neo-adjuvant chemotherapy (NAC). Four cases were negative for intra-operative lavage cytology.

Discussion

PM is regarded as the worst form distant metastasis of colorectal cancer, and patients with PM are classified as

stage IVC in the eighth edition of the TNM classification (9). CRS and POIC for PM of colorectal cancer are reportedly associated with an excellent treatment outcome (2) but the severe surgical stress and high post-operative complication rate have kept them from becoming standard therapies (4, 5). Some reports of resection for disseminated PM of colorectal cancer have noted improved treatment outcomes when combined with advanced systemic chemotherapy (6-8). Although the 3-year RFS in this study was relatively low at 12.5%, several cases were able to tolerate nodule re-resection (13 cases, 31.7%), and the 5-year OS was comparable to the OS after hepatectomy for hepatic metastasis of colorectal cancer reported in the literature.

In this study, patients who achieved a 5-year RFS were defined as cured, and 15.6% of cases survived for more than 5 years after nodule resection were cured. Goere *et al.* reported that 16% of cases treated with CRS and POIC were cured (10), which is comparable to our findings. However, the study of Goere *et al.* included cases with relatively higher PCI scores (up to 36), so nodule resection cannot be said to be equivalent to CRS and POIC. The present findings indicate that there are some cases of reportedly difficult-to-cure PM of colorectal cancer in which a cure can be achieved by nodule resection.

In general, metachronous metastasis has milder malignancy and a better prognosis than synchronous metastasis (11, 12). However, for colorectal cancer, metachronous PM has largely been reported to have equivalent malignancy to synchronous

Table III. Univariate and multivariate analysis of the mean overall survival (MST) of 41 cases of peritoneal metastasis (PM) from colorectal cancer.

	No. of patients	MST (months)	p-Value	
			Univariate analysis	Univariate analysis
Age				
>70 Years	27	28.6	0.1792	
≤70 Years	14	49.2		
Gender				
Male	17	25	0.3405	
Female	24	41.5		
Site of primary tumor				
Right side	19	27.8	0.0613	0.1513
Left side	22	88.8		
Histology				
Well/moderately	34	41.5	0.0196	0.0563
Poorly/mucinous	7	23.2		
Degree of PM				
P1	13	23.2	0.1601	
P2	28	49.2		
PCI				
>5	7	23.2	0.1977	
≤5	30	41.5		
Pre-operative CEA				
>10 ng/ml	16	57	0.3465	
≤10 ng/ml	25	30.1		
Pre-operative CA19-9				
>100 U/ml	10	17.3	0.0045	0.0254
≤100 U/ml	30	49.2		
Diagnostic interval				
Synchronous	20	25	0.3872	
Metachronous	21	60.65		
Distant metastases other than PM				
Yes	14	28.6	0.9262	
No	27	38.7		
Intraperitoneal lavage cytology				
Positive	12	41.5	0.1648	
Negative	16	116.7		
Neo-adjuvant chemotherapy				
Yes	9	NA	0.2305	
No	32	27.8		
Postoperative chemotherapy				
Yes	24	64.3	0.0104	0.2194
No	17	20		

PCI: Peritoneal carcinoma index; CEA: carcinoembryonic antigen; CA19-9: carbohydrate antigen 19-9. Bold values show significance.

PM (13-15). Synchronous PM is often detected incidentally during an operation. In contrast, metachronous PM can be difficult to detect in the early stage and therefore tends to be diagnosed late, which may be one reason for the unfavorable

treatment outcomes associated with metachronous PM. However, no significant differences between metachronous and synchronous PM were noted in the RFS or OS in the present study, although the median OS of those with metachronous PM was much longer than that of synchronous PM (60.7 vs. 25 months). Among the five cured patients, four suffered from metachronous PM, and the above results indicate that resectable metachronous PM has a better prognosis than synchronous PM.

In the present study, intraoperative lavage cytology was performed in 68.3% of cases. Surprisingly, over half of the cases that underwent cytology showed negative findings for cancer cells despite PM. However, despite the lack of significance, the median RFS and median OS of cases with negative cytological findings were 15.7 and 116.7 months, respectively. These findings suggested that intraoperative lavage cytology may become a powerful prognostic tool in the future.

High levels of CA19-9 were extracted as an independent prognostic factor in a multivariate analysis, and patients with high levels of CA19-9 had a significantly shorter RFS than those with lower levels according to the univariate analysis in this study. Ihemelandu listed CA19-9 as a significant prognosticator along with the platelet-lymphocyte ratio and Onodera's nutritional index, in patients with PM of colonic cancer (16). Park *et al.* reported that an elevated CA19-9 level was more closely associated with PM than hepatic metastases and that patients with high levels of CA19-9 tended to develop relapse in the peritoneum (17). Our own results were consistent with these, suggesting that patients with high levels of CA19-9 with colorectal PM should be carefully considered for surgery.

In the present study, lack of POAC was extracted as an independent factor for early relapse in a multivariate analysis. Four out of the five patients who achieved a cure in the present study received POAC, and the remaining patient without POAC had received systemic chemotherapy in the past. These results suggest the importance of systemic chemotherapy in the surgical treatment of colorectal PM. In an effort to achieve a better outcome, we have introduced NAC for extremely advanced colorectal cancer (18). Nine patients in the present study underwent NAC, but no significant difference was observed in the RFS or OS between the NAC cases and other cases probably due to the small number of cases. Further studies will be needed to clarify the efficacy of NAC.

Several limitations associated with the present study warrant mention. Firstly, this was a retrospective study of cases in which it was possible to resect peritoneal metastases macroscopically. Cases with severe PM that could not be resected without CRS were excluded. Secondly, this study was performed at a single institution with a small number of cases.

In conclusion, even when targeting mild cases of PM from colorectal cancer, relatively good results were obtained with

Table IV. Details of five cases survived without relapse for more than 5 years, which were regarded as 'cured'.

Age, years/ gender	Timing of PM	Primary site	Time from primary resection (months)	Pathological type	CEA (ng/ml)	CA 19-9 (U/ml)	PCI	Distant metastases other than PM	Lavage cytology	Surgical procedure	Chemotherapy
75/F	Metachronous	Rectum	14.4	Well	1.4	1.8	1	None	Negative	TE	Pre/post
60/F	Metachronous	Ascending colon	48.1	Moderately	39	<0.1	4	None	Positive	PPE	Pre/post
81/M	Metachronous	Cecum	6.3	Well	1.8	14.8	4	Abdominal wall	Negative	TE	Post
35/F	Metachronous	Transverse colon	24.1	Well	10.4	14.4	2	None	Negative	TE	None
65/F	Synchronous	Rectum	–	Well	36.7	NA	1	None	Negative	LAR+TE	Post

F: Female; M: male; PM: peritoneal metastases; PCI: peritoneal carcinoma index; CEA: carcinoembryonic antigen; CA19-9: carbohydrate antigen 19-9; TE: tumor extirpation; PPE: posterior pelvic exenteration; LAR: low anterior resection.

a 5-year OS rate of 38.4%, which was comparable to that for hepatic or lung metastasis. Furthermore, we showed that it was possible to cure more than a few colorectal PM cases without resorting to the highly invasive treatment of CRS and POIC.

Conflicts of Interest

The Authors declare no conflicts of interest for this article.

Authors' Contributions

Gaku Ohira designed the study and wrote the initial draft of the article. All other Authors have contributed to data collection and interpretation, and critically reviewed the article. All Authors approved the final version of the article and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

- 1 Franko J, Shi Q, Goldman CD, Pockaj BA, Nelson GD, Goldberg RM, Pitot HC, Grothey A, Alberts SR and Sargent DJ: Treatment of colorectal peritoneal carcinomatosis with systemic chemotherapy: A pooled analysis of north central cancer treatment group phase III trial N9741 and N9841. *J Clin Oncol* 30(3): 263-267, 2012. PMID: 22162570. DOI: 10.1200/JCO.2011.37.1039
- 2 Sugarbaker PH and Ryan DP: Cytoreductive surgery plus hyperthermic perioperative chemotherapy to treat peritoneal metastases from colorectal cancer: Standard of care or an experimental approach? *Lancet Oncol* 13(8): e362-369, 2012. PMID: 22846841. DOI: 10.1016/S1470-2045(12)70210-3
- 3 Bushati M, Rovers KP, Sommariva A, Sugarbaker PH, Morris DL, Yonemura Y, Quadros CA, Somashekhar SP, Ceelen W, Dube P, Li Y, Verwaal VJ, Glehen O, Piso P, Spiliotis J, Teo MCC, Gonzales-Moreno S, Cashin PH, Lehmann K, Deraco M, Moran B and se Hingh IHJT: The current practice of cytoreductive surgery and HIPEC for colorectal peritoneal metastases: Results of a worldwide web-bases survey of the peritoneal surface oncology group international (PSOGI). *Eur J Surg Oncol* 44(12): 1942-1948, 2018. PMID: 30075978. DOI: 10.1016/j.ejso.2018.07.003
- 4 Levine EA, Stewart JH, Shen P, Russell GB, Loggie BL and Votanopoulos KI: Intraperitoneal chemotherapy for peritoneal surface malignancy: experience with 1000 patients. *J Am Coll Surg* 218(4): 573-585, 2014. PMID: 24491244. DOI: 10.1016/j.jamcollsurg.2013.12.013
- 5 Konstantinidis IT, Chouliaras K, Levine EA, Lee B and Votanopoulos KI: Frailty correlates with postoperative mortality and major morbidity after cytoreductive surgery with hyperthermic intraperitoneal chemotherapy. *Ann Surg Oncol* 24(13): 3825-3830, 2017. PMID: 29019118. DOI: 10.1245/s10434-017-6111-0
- 6 Kobayashi H, Kotake K, Funabashi K, Hase K, Hirata K, Iiai T, Kameoka S, Kanemitsu Y, Maeda K, Murata A, Ohue M, Shirouzu K, Takahashi K, Watanabe T, Yano H, Yatsuoka T, Hashiguchi Y and Sugihara K: Clinical benefit of surgery for stage IV colorectal cancer with synchronous peritoneal metastasis. *J Gastroenterol* 49(4): 646-654, 2014. PMID: 23793379. DOI: 10.1007/s00535-013-0820-3
- 7 Ozawa H, Kotake K, Kobayashi H and Sugihara K: Prognostic factors for peritoneal carcinomatosis originating from colorectal cancer: An analysis of 921 patients from a multi-institutional database. *Sur Today* 44(9): 1643-1650, 2014. PMID: 24077999. DOI: 10.1007/s00595-013-0735-x
- 8 Nagata H, Ishihara S, Hata K, Murono K, Kaneko M, Yasuda K, Otani K, Nishikawa T, Tanaka T, Kiyomatsu T, Kawai K, Nozawa H and Watanabe T: Survival and prognostic factors for metachronous peritoneal metastasis in patients with colon cancer. *Ann Surg Oncol* 24(5): 1269-1280, 2017. PMID: 27995451. DOI: 10.1245/s10434-016-5732-z
- 9 Brierley JD, Gospodarowicz MK and Wittekind C: TNM Classification of Malignant Tumours. UICC International Union Against Cancer, Eighth Edition. New York: Wiley; 2016.
- 10 Goere D, Malka D, Tzanis D, Gava V, Boige V, Eveno C, Maggiori L, Dumont F, Ducreux M and Elias D: Is there a

- possibility of a cure in patients with colorectal peritoneal carcinomatosis amenable to complete cytoreductive surgery and intraperitoneal chemotherapy? *Ann Surg* 257(6): 1065-1071, 2013. PMID: 23299520. DOI: 10.1097/SLA.0b013e31827e9289
- 11 Tsai MS, Su YH, Ho MC, Liang JT, Chen TP, Lai HS and Lee PH: Clinicopathological features and prognosis in resectable synchronous and metachronous colorectal liver metastasis. *Ann Surg Oncol* 14: 786-794, 2007. PMID: 17103254. DOI: 10.1245/s10434-006-9215-5
 - 12 Kumar R, Price TJ, Beeke C, Jain K, Patel G, Padbury R, Young GP, Order D, Townsend A, Bishnoi S and Karapetis CS: Colorectal cancer survival: An analysis of patients with metastatic disease synchronous and metachronous with the primary tumor. *Clin Colorectal Cancer* 13(2): 87-93, 2014. PMID: 24373733. DOI: 10.1016/j.clcc.2013.11.008
 - 13 Pelz JO, Chua TC, Esquivel J, Stojadinovic A, Doerfer J, Morris DL, Maeder U, Germer CT and Kerscher AG: Evaluation of best supportive care and systemic chemotherapy as treatment stratified according to the retrospective Peritoneal Surface Disease Severity Score (PSDSS) for peritoneal carcinomatosis of colorectal origin. *BMC Cancer* 10: 689, 2010. PMID: 21176206. DOI: 10.1186/1471-2407-10-689
 - 14 Bloemendaal AL, Verwaal VJ, van Ruth S, Boot H and Zoetmulder FA: Conventional surgery and systemic chemotherapy for peritoneal carcinomatosis of colorectal origin: A prospective study. *Eur J Surg Oncol* 31(10): 1145-1151, 2005. PMID: 16084051. DOI: 10.1016/j.ejso.2005.06.002
 - 15 Klaver YL, Leenders BJ, Creemers GJ, Rutten HJ, Verwaal VJ, Lemmens VE and de Hingh IH: Addition of biological therapies to palliative chemotherapy prolongs survival in patients with peritoneal carcinomatosis of colorectal origin. *Am J Clin Oncol* 36(2): 157-161, 2013. PMID: 22314003. DOI: 10.1097/COC.0b013e3182438c55
 - 16 Ihemelandu C: Inflammation-based prognostic scores: utility in prognostication and patient selection for cytoreduction and perioperative intraperitoneal chemotherapy in patients with peritoneal metastasis of colonic origin. *Ann Surg Oncol* 24(4): 884-889, 2017. PMID: 27896506. DOI: 10.1245/s10434-016-5693-2
 - 17 Park JJ, Choi GS and Jun SH: Prognostic value of serum tumor antigen CA19-9 after curative resection of colorectal cancer. *Anticancer Res* 29(10): 4303-4308, 2009. PMID: 19846991
 - 18 Ohira G, Miyauchi H, Suzuki K, Nishimori T, Tohma T, Narushima K and Matsubara H: Neoadjuvant chemotherapy for advanced colorectal cancer. *Jpn J Chemother* 40(12): 1626-1628, 2013. PMID: 24393870.

Received March 3, 2020

Revised March 30, 2020

Accepted April 1, 2020