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ORIGINAL ARTICLE

Prognostic predictions based on pathological findings of peritoneal dissemination in patients with stage IV colorectal cancer without residual disease (R0 status)

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Abstract

Purpose This study aimed to clarify the prognosis of patients after resection of stage IV colorectal cancer and synchronous peritoneal metastasis (no residual disease: R0 status) based on histopathologic findings.

Methods The subjects of this study were 26 patients who underwent radical resection of synchronous peritoneal metastases of stage IV colorectal cancer. Only patients with one synchronous peritoneal metastasis were included in this study. The peritoneal lesions were initially classified into two categories based on the presence or absence of adenocarcinoma on their surface: RM-negative or RM-positive. The lesions were subsequently classified as being of massive or diffuse type and of small (< 6 mm) or large (≥ 6 mm) type according to the maximum metastatic tumor dimension.

Results Multivariate analysis revealed that massive type metastatic tumors were associated with a better disease-free survival (DFS; $p = 0.047$) and overall survival (OS; $p = 0.033$), than diffuse type tumors.

Conclusion A detailed stratification of pathological findings could contribute remarkably to prognostic predictions for patients with synchronous peritoneal metastases.

Keywords peritoneal metastasis · Stage IV · R0 status

Introduction

The 2018 guidelines of the Japanese Society for Cancer of the Colon and Rectum (JSCCR) [1] state that the efficacy of resection of peritoneal dissemination has not been proven. However, previous reports describe the long-term survival of some patients after the resection of localized dissemination alongside the primary tumor. This suggests that if the resection is not extensive, then the peritoneal dissemination should be resected simultaneously. Similarly, if both the distant metastases (such as hepatic metastases) and the primary tumor are resectable, the primary tumor should be resected curatively and resection of the metastasis should be considered. Although there have been many reports on the histopathologic investigation of hepatic metastases of colorectal adenocarcinomas, in line with therapeutic advances in chemotherapy [2], few have addressed peritoneal metastasis in connection with histopathologic findings. Moreover, while several articles have discussed the prognosis of patients with peritoneal metastases of colorectal cancers [3–6], very few have described histopathologic investigation of peritoneal metastases of colorectal adenocarcinoma. Accordingly, we investigated the prognosis of patients with peritoneal metastases based on histopathologic findings.

Patients and methods

The subjects of this retrospective study were 26 patients who underwent radical resection of synchronous peritoneal metastases (R0 status) of stage IV colorectal cancer at the

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Department of Gastroenterological Surgery, Aichi Cancer Center Hospital, Nagoya, Japan between January 1980 and December 2016. The patients were limited to those with only one synchronous peritoneal metastasis. Comprehensive informed consent was obtained from all patients prior to surgery. None of the patients had received preoperative neoadjuvant radiochemotherapy. All patients underwent complete dissection of all regional lymph nodes and total mesorectal excision of rectal cancer with postoperative adjuvant chemotherapy. The median follow-up duration was 20 months.

The resected specimens were fixed in 10% formalin for several days, after which 4-mm sections were obtained by slicing the entire tumor across its largest dimension. Histopathological diagnoses were made by examining sections stained routinely with hematoxylin and eosin, without specific immunostaining, under a simple light microscope.

We assessed, retrospectively, the relationship between the prognosis following radical resection of synchronous peritoneal metastases of stage IV colorectal cancers and the pathological findings of resected metastatic lesions. The tumors were broadly classified as either metastatic or primary. First, tumors were classified as RM-negative or RM-positive, based on the presence or absence of adenocarcinoma on the surface of the resected peritoneal metastases. Specifically, RM-negative peritoneal metastatic lesions were enclosed in non-cancerous tissue such as a capsule or adipose tissue, whereas RM-positive lesions had ductal carcinoma exposed on their surface (Fig. 1). Second, metastatic lesions were classified into massive type and diffuse type. Ductal adenocarcinomas that developed continuously were classified as the massive type, whereas those that developed discontinuously were classified as diffuse type (Fig. 2). The

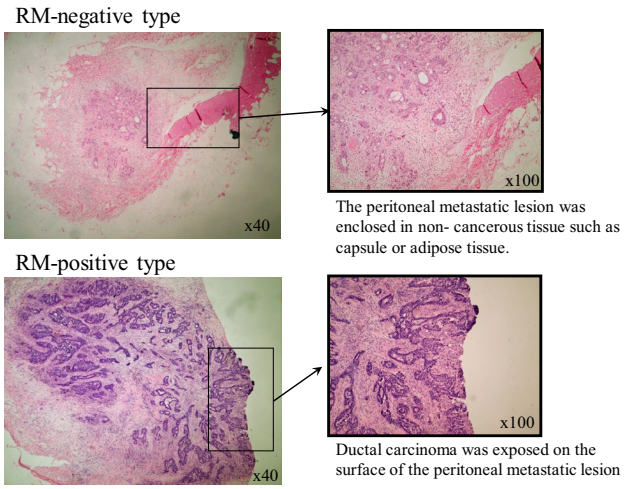

Fig. 1 "RM-negative type" and "RM-positive type" peritoneal metastatic tumors. "RM-negative type" tumors were enclosed in non-cancerous tissue such as a capsule or adipose tissue. "RM positive type" tumors had ductal carcinoma exposed on the surface

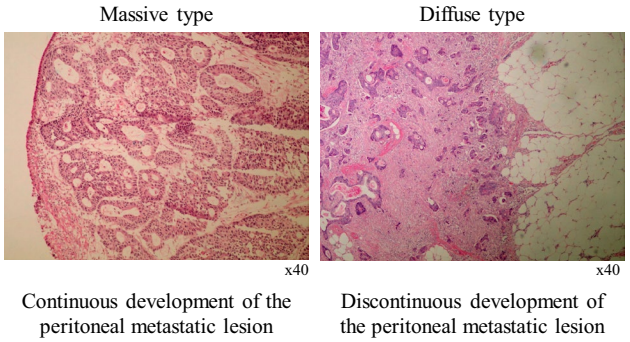

Fig. 2 "Massive type" and "diffuse type" peritoneal metastatic tumors. Ductal adenocarcinomas developed continuously in "massive type" lesions and discontinuously in "diffuse type" lesions

classification of intermingled massive and diffuse type was based on the predominant type. Finally, peritoneal metastasis was also classified into two categories based on the maximal tumor size: small or large. The small type was defined as <6 mm and the large type was defined as ≥ 6 mm (median: 6 mm).

The following factors related to the primary lesions were investigated: sex (male vs. female), age (<62 vs. ≥ 63 years, median: 62 years), maximum size of the primary lesion (<6 vs. ≥ 6 cm, median: 6 cm), cancer location (colon vs. rectum), histological type of the primary lesion (tub1 + tub2 vs. Others), greatest depth (pT3 vs. pT4), and the presence or absence of lymph node metastasis, lymphatic invasion, and venous invasion. Regarding the histological type of primary lesion, adenocarcinomas were mainly graded according to their glandular appearance and classified as well, moderately, or poorly differentiated according to the World Health Organization histopathological classification of colon and rectal tumors [7] and the Japanese Classification of Colorectal Carcinomas [8].

Differences in histopathological findings between the primary and peritoneal metastatic lesions were evaluated. Patients whose primary lesions were classified as tub1 + tub2 and peritoneal metastases were classified as diffuse were included in the Down Group. Conversely, those whose primary lesions were classified as tub1 + tub2 and peritoneal metastases were classified as massive, and those whose primary lesions were classified as anything other than tub1 + tub2 and peritoneal metastases were classified as diffuse, were included in the Equal Group. Two patients whose primary lesions were classified as a type other than tub1 + tub2 with peritoneal metastases classified as massive were excluded from the analysis.

Statistical analysis

Univariate and multivariate stepwise logistic regression analyses were performed to identify the factors influencing the overall (OS) and relapse-free survival rates. The log-rank test was used to evaluate differences in disease-free survival (DFS) and OS rates between the groups. Statistical significance was set at a p value of < 0.05.

Results

The first relapses were as follows. There were 22 systemic recurrences excluding peritoneal recurrences, 1 systemic recurrence including peritoneal recurrence, and 3 peritoneal recurrences only. Univariate analysis revealed no significant differences between patients with RM-negative and those with RM-positive type peritoneal tumors in terms of either DFS or OS (Fig. 3). However, RM-negative tumors were associated with a better OS prognosis than RM-positive tumors. There were no significant differences in DFS and OS between the patients with massive type and those with diffuse type peritoneal tumors (Fig. 4). However, the massive type was associated with a better DFS and OS prognosis than the diffuse type. There were no significant differences in DFS and OS between patients with small and those with large peritoneal tumors (Fig. 5). However, large tumors were associated with a better OS prognosis than small tumors.

Multivariate analysis revealed significant differences in both DFS ($p = 0.047$) and OS ($p = 0.033$) between the massive type and diffuse type peritoneal tumors (Table 1). Similarly, a significant difference in OS was observed between patients with small and those with large peritoneal tumors ($p = 0.047$). There were no significant differences in the clinicopathologic factors of the primary lesion in the univariate analysis (Table 2).

There were no significant differences in DFS between the Down Group and Equal Group ($p = 0.344$; Fig. 6); however, the Down Group had a worse DFS prognosis than the Equal Group. Similarly, no significant differences in OS were observed between the Down Group and the Equal Group ($p = 0.275$), but again, the Down Group had worse OS than the Equal Group.

Discussion

Several previous articles have described the prognosis of patients with peritoneal metastasis of colorectal cancer [3–6]. Similarly, several articles have reported the prognosis associated with hepatic metastasis of colorectal cancer, and in recent years, some reports have described risk factors for hepatic lesions in terms of histopathologic diagnosis [2, 9]. However, little is known about the pathological findings of synchronous peritoneal metastases of colorectal cancers. To our knowledge, this is the first study to investigate the

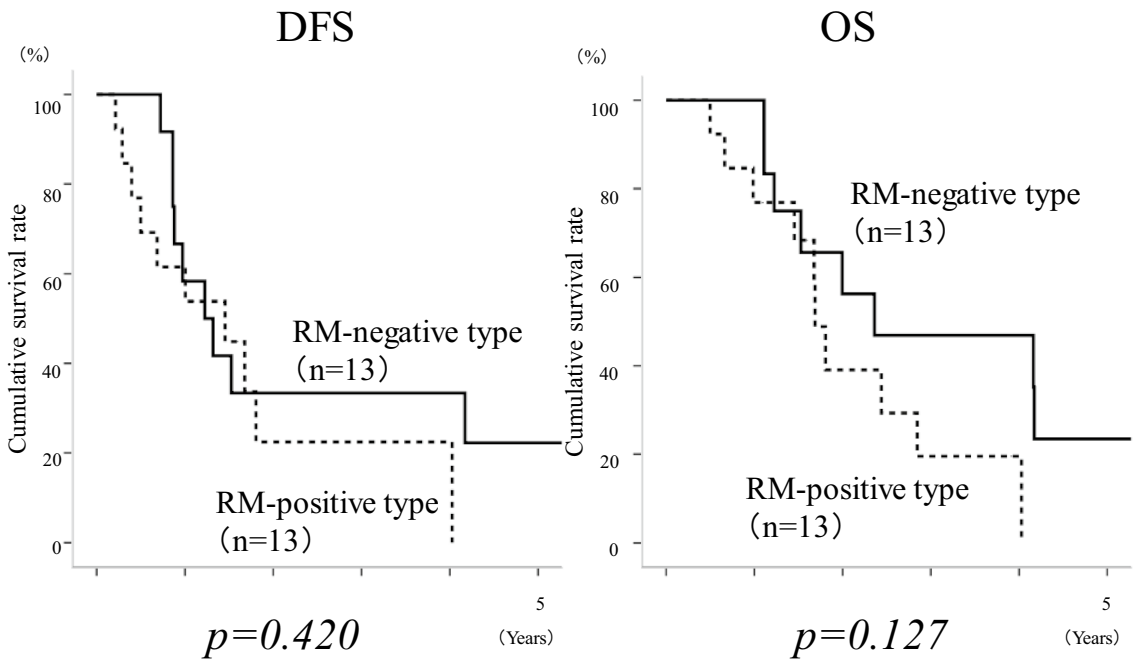

Fig. 3 Univariate analysis revealed that patients with "RM-negative type" lesions tended to have a better prognosis than those with "RM-positive type" lesions in relation to overall survival (OS)

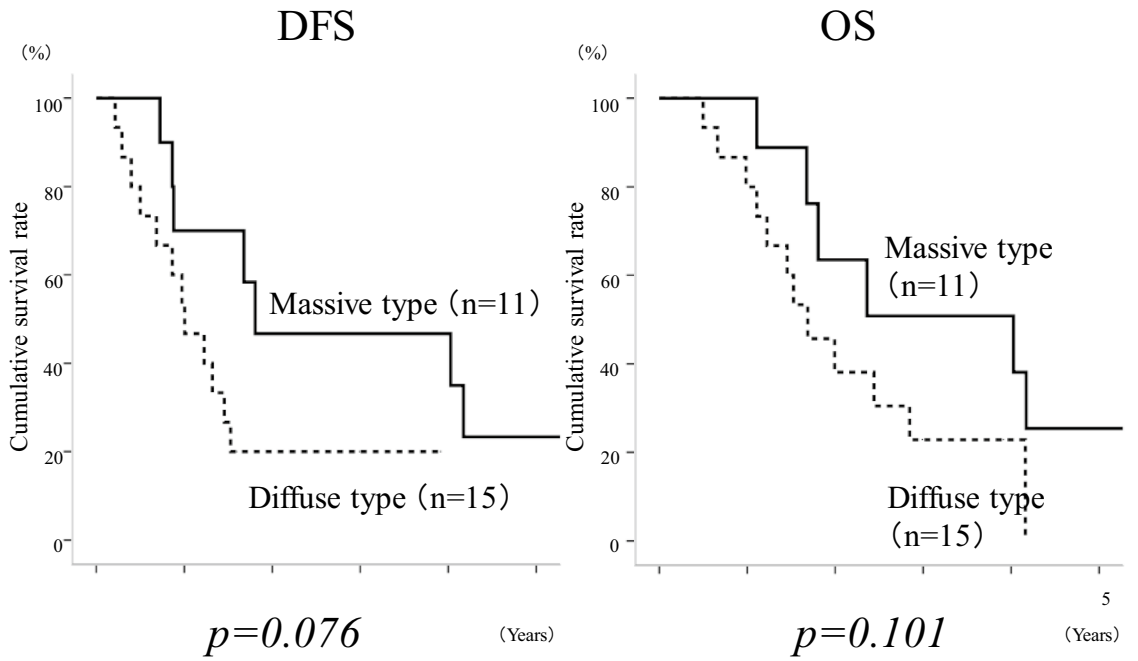

Fig. 4 Univariate analysis revealed that patients with "massive type" lesions tended to have a better prognosis than those with "diffuse type" lesions in relation to both disease-free survival (DFS) and overall survival (OS)

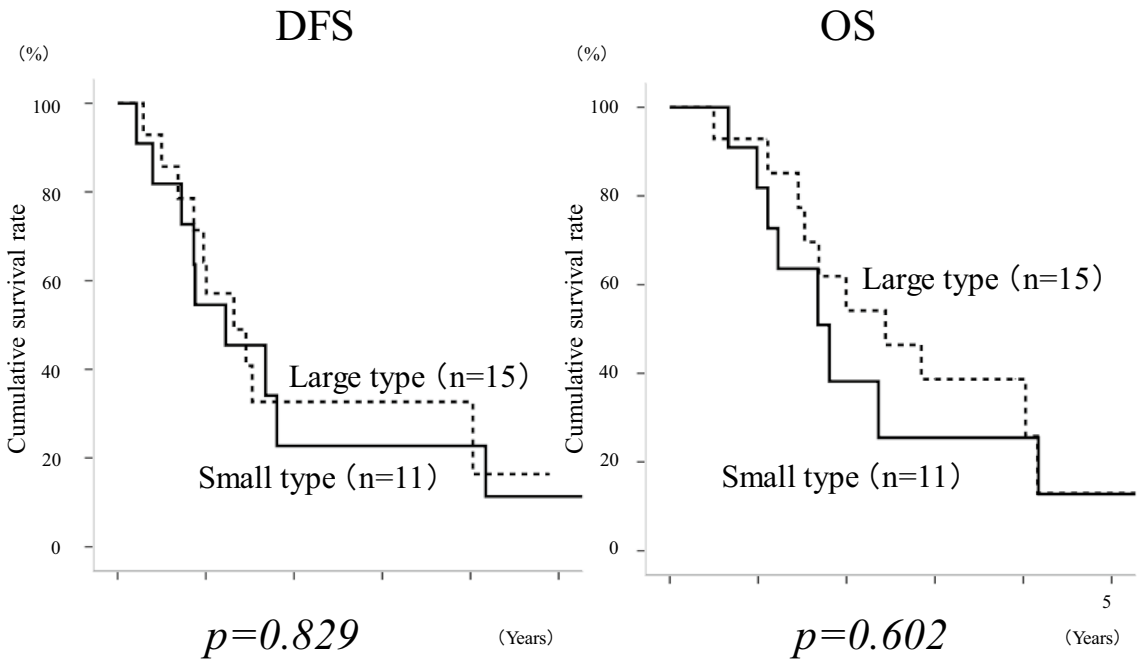

Fig. 5 Univariate analysis revealed that the prognosis of patients with "large type" lesions was better than that of patients with "small type" lesions in relation to overall survival (OS)

prognostic nature of the pathological findings of stage IV colorectal cancer with resection of synchronous peritoneal metastases (no residual disease: R0 status).

Regarding the histopathological findings of metastatic lesions, and particularly the resection margin, researchers have long known that the inability to achieve resection

Table 1 Multivariate analysis

	n	DFS		OS	
		p	Odds ratio(95% CI)	*p*	Odds ratio(95% CI)
Radial margin (RM)					
RM negative type	13 (50.0%)	0.458	1.432 (0.554–3.699)	0.195	2.061 (0.691–6.145)
RM positive type	13 (50.0%)				
Histological type					
Massive type	13 (50.0%)	0.047	3.276 (1.017–10.558)	0.033	4.536 (1.130–18.209)
Diffuse type	13 (50.0%)				
Maximal size					
Small type: < 6 mm	11 (42.3%)	0.259	1.779 (0.655–4.829)	0.047	3.567 (1.014–12.547)
Large type: ≧6 mm	15 (57.7%)				

Table 2 Univariate analysis of clinicopathologic features of the primary lesion

	n	*p*	
		DFS	OS
Gender			
Male	12 (46.2%)	0.181	0.340
Female	14 (53.8%)		
Age			
< 60	12 (46.2%)	0.966	0.416
≥ 60	14 (53.8%)		
Maximal tumor size (cm)			
< 6	13 (50.0%)	0.243	0.319
≥ 6	13 (50.0%)		
Cancer location			
Colon	17 (65.4%)	0.578	0.631
Rectum	9 (34.6%)		
Histological type			
tub1 + tub2	19 (73.1%)	0.423	0.618
Others	7 (26.9%)		
Greatest depth			
pT3	10 (38.5%)	0.187	0.312
pT4	16 (61.5%)		
Lymph node metastasis			
Present	4 (15.4%)	0.253	0.140
Absent	22 (84.6%)		
Lymphatic invasion			
Present	21 (80.8%)	0.970	0.715
Absent	5 (19.2%)		
Venous invasion			
Present	17 (65.4%)	0.330	0.257
Absent	9 (34.6%)		

margin clearance; that is, the distance from the tumor surface to the cut surface of the liver, of > 10 cm, is associated with a significantly higher risk of disease recurrence and consequently, poor survival [10]. Broadly speaking, our results were not consistent with this rule. Subsequently, we predicted that RM-negative tumors would be associated with a significantly better prognosis than RM-positive tumors; however, we confirmed only a tendency toward this outcome and failed to demonstrate a significant difference. We attribute our findings to the following limitations: first, our study sample size was too small; second, the study design was retrospective; third, subject bias was present as a consequence of defects in pathology specimens; and fourth, the evaluations of pathology specimens was incomplete because only one area, rather than multiple slices, was subject to pathological examination. A larger number of cases may have revealed a significant difference in this regard. In any case, our study was the first to demonstrate pathologically that the surgical margin of a peritoneal metastasis affected prognosis.

Few aspects of the histopathology of metastatic lesions have been described. Kuo et al. [11] reported that hepatic metastatic lesions could be classified into three types, histopathologically: well differentiated, moderately differentiated, and poorly differentiated. They found significant differences in both the DFS and OS between patients with well differentiated and those with poorly differentiated lesions. Similarly, significant differences in DFS and OS were observed between patients with moderately differentiated and those with poorly differentiated lesions. These results were consistent with our finding of significant differences between these types of lesions. Moreover, no previous reports have described changes in histopathological findings from the primary lesion to the metastatic lesion. Therefore, our description of these changes is valuable.

Recent reports have investigated the size of peritoneal metastases of stage IV colorectal cancer. In a multi-institutional retrospective analysis of the sizes of peritoneal metastases during a 17-year period, Ozawa et al. used qualitative assessments to allocate numerical values to these lesions; namely, the classifications of miliary and thumb-sized were converted to < 5 mm and 5–20 mm, respectively [12]. Similarly, Sato et al. recorded the sizes of a few disseminated lesions, miliary/rice-sized lesions, and azuki bean-sized/

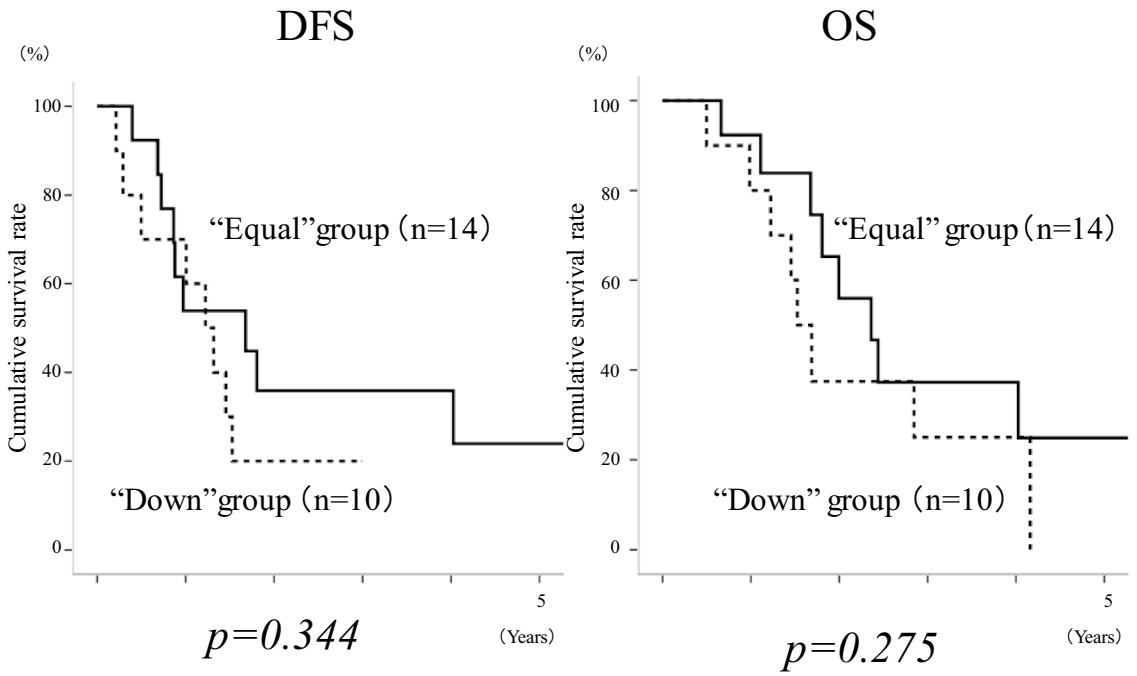

Fig. 6 Univariate analysis revealed that the "Down group" had a worse prognosis than the "Equal group" in relation to disease-free survival (DFS) and overall survival (OS)

thumb-sized lesions as ≤ 3, ≤ 5, and 5–20 mm, respectively, and compared the lesions classified according to sizes of ≤ 5 and > 6 mm 4. We used the same analytical method in our study. Kobayashi et al. reported broadly that the size of peritoneal metastasis (≤ 5, 6–20, and 21 mm) was a significant prognostic risk factor for all patients and those with R0 resection, according to multivariate analyses [5]. Therefore, our study was the first to conduct a quantitative assessment, which highlights its importance.

All of these reported findings warrant a prospective study of this topic in the future. Realistically, cases of stage IV colorectal cancer with resection of synchronous peritoneal metastases (no residual disease: R0 status) are rare. Ozawa et al. [12] reported that 43 of 72 cases (59.7%) of resection of synchronous peritoneal metastases (no residual disease: R0 status) involved a single metastatic lesion in a multi-institutional retrospective analysis conducted over a 17-year period. Consequently, it would be difficult to accumulate additional subjects. From a practical viewpoint, a prospective study may not be possible, again highlighting that our study is invaluable.

Our findings raise some questions. For example, a single lymph nodal metastasis may be mistaken for a single synchronous peritoneal metastasis; however, if the lymph node architecture is retained, it is possible to distinguish these types of metastatic lesions. Still, it may be difficult to differentiate a single synchronous peritoneal metastasis from a lymph node metastasis.

The results of this study were obtained postoperatively and, therefore, were useful in the context of postoperative adjuvant therapy. However, it is doubtful whether adjuvant chemotherapy is effective for stage IV colorectal cancer with resection of synchronous peritoneal metastases (no residual disease: R0 status) [13]. Our findings suggest that adjuvant chemotherapy must be adapted for patients in the Down Group, given their unfavorable prognosis.

Conclusion

A detailed stratification of pathological findings may enhance the prognostic predictions for patients with stage IV colorectal cancer after the resection of synchronous peritoneal metastases (no residual disease: R0 status). These results could facilitate the administration of postoperative adjuvant chemotherapy to these patients.

Compliance with ethical standards

Ethical standards This research project was approved by the Ethics Committee of our institution (2018-1-137) and conformed to the provisions of the Declaration of Helsinki.

Conflict of interest We have no conflicts of interest to declare in relation to this study.

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