were administered oral chemotherapy with drugs such as oral 5-fluorouracil, 5′-doxifluridine, carmofur, or uracil-tegafur with leucovorin, as the most commonly used drugs, for approximately 6 to 12 months.[1,10,11]

We conducted a review of the hospital records to obtain clinicopathological information about the patients, including the sex and age (median, 58 years), lesion location, macroscopic configuration of the tumor, maximum tumor size (median size, 5 cm), greatest depth of invasion of the tumor (pT1 + pT2 vs pT3 + pT4), histological type of the tumor, presence/absence of lymphatic invasion and venous invasion, and the number of metastasis-positive lymph nodes. Adenocarcinomas of the rectum are graded predominantly on the basis of their glandular appearance and are classified as well or moderately differentiated or others, according to the World Health Organization histopathological classification of tumors of the colon and rectum, and the Japanese Classification of Colorectal Carcinoma.

Rectal cancer is defined as a tumor whose lowest border is located between the anal verge and the sacral promontory. Lesions are classified as upper or lower rectal cancers depending on their location with respect to the peritoneal reflection. The tumors are classified into 2 types on the basis of their macroscopic appearance: mass type or diffuse type. The mass type includes the superficial, polypoid, and ulcerated types of tumors with a clear margin, and the diffuse type includes the ulcerated type with infiltration, diffuse infiltrating, and unclassified types. The number of positive lymph nodes was categorized as less than 3 or more than 4.

All data are expressed as the mean ± SD. The Fisher exact probability text, univariate logistic regression, and multivariate stepwise logistic regression analysis were subsequently performed to identify factors that might influence ECI-positive lymph node metastasis. The log-rank test was used to evaluate the differences in the overall survival rate and the disease-free survival rate between groups. Statistical significance was set at $p < 0.05$.

RESULTS

Table 1 shows the relationship between the ECI status and clinicopathological findings. No significant differences were observed in relation to the sex, age, tumor location, tumor macroscopic configuration, tumor size, greatest depth of tumor invasion, tumor histological type, presence/absence of lymphatic or venous invasion, or the number of positive lymph nodes in pN3 rectal cancer.

Table 2 shows the results of the univariate analysis performed to identify factors that might be correlated with the disease-free survival rate. Although no significant differences in the disease-free survival rate were observed in relation to the age, tumor location, tumor macroscopic configuration, tumor size, greatest depth of tumor invasion, tumor histological type, presence/absence of lymphatic or venous invasion, or the number of positive lymph nodes in pN3 rectal cancer, the rate differed significantly depending on the sex and pN3-ECI status. Male patients, in comparison with female patients, and pN3-ECI-positive patients, in comparison with the pN3-ECI-negative patients, showed significantly poorer prognoses in terms of the disease-free survival rates ($p = 0.024$ and $p = 0.003$).

TABLE 1. The relationship between the ECI status and clinicopathological findings

	pN3-ECI positive (n = 19)	*pN3-ECI negative (n = 33)*	*p*
Sex			
Male	11(57.9)	18(54.5)	0.523
Female	8(42.1)	15(45.5)	
Age			
<58	9(47.4)	16(48.5)	0.584
≥58	10(52.6)	17(51.5)	
Location			
Upper rectum	2(10.5)	6(18.2)	0.378
Lower rectum	17(89.5)	27(81.8)	
Macroscopic configuration			
Massive	14(73.7)	29(87.9)	0.178
Diffuse	5(26.3)	4(12.1)	
Tumor size			
<5 cm	12(63.2)	18(54.5)	0.379
≥5 cm	7(36.8)	15(45.5)	
Greatest depth invasion			
pT1+pT2	4(21.1)	6(18.2)	0.536
pT3+pT4	15(78.9)	27(81.8)	
Histological type			
W/M	15(78.9)	27(81.8)	0.536
Others	4(21.1)	6(18.2)	
Lymphatic invasion			
Present	14(73.7)	25(75.8)	0.560
Absent	5(26.3)	8(24.2)	
Venous invasion			
Present	11(57.9)	21(63.6)	0.452
Absent	8(42.1)	12(36.4)	
No. of positive LNs			
<3	6(31.6)	14(42.4)	0.318
≥4	13(68.4)	19(57.6)	

Values shown are n (%).
W/M = well and moderately differentiated adenocarcinoma; LNs = lymph nodes; ECI = extracapsular invasion.

Table 3 shows the results of univariate analysis performed to identify factors that might be correlated with the overall survival rate. Although no significant differences in the overall survival rate were observed in relation to the age, tumor location, tumor macroscopic configuration, greatest depth of tumor invasion, tumor histological type, presence/absence of lymphatic or venous invasion, or the number of positive lymph nodes, the rate differed significantly depending on the sex, tumor size, and pN3-ECI status. Male patients, patients with a tumor diameter of greater than 5 cm, and pN3-ECI-positive patients showed

TABLE 2. Univariate analysis of the disease-free survival rates in pN3 cases

	n (%)	p
Sex		
Male	29(55.8)	0.024
Female	23(44.2)	
Age		
<58	25(47.4)	0.686
≧58	27(52.6)	
Location		
Upper rectum	8(15.4)	0.139
Lower rectum	44(84.6)	
Macroscopic configuration		
Massive	43(82.7)	0.574
Diffuse	9(17.3)	
Tumor size		
<5 cm	30(80.8)	0.253
≧5 cm	22(19.2)	
Greatest depth invasion		
pT1+pT2	10(19.2)	0.309
pT3+pT4	42(80.8)	
Histological type		
W/M	42(80.8)	0.219
Others	10(19.2)	
Lymphatic invasion		
Present	39(75.0)	0.180
Absent	13(25.0)	
Venous invasion		
Present	32(61.5)	0.378
Absent	20(38.5)	
No. of positive LNs		
<3	20(38.5)	0.072
≧4	32(61.5)	
pN3-ECI		
Positive	19(36.5)	0.003
Negative	33(63.5)	

W/M = well and moderately differentiated adenocarcinoma; LNs = lymph nodes; ECI = extracapsular invasion.

TABLE 3. Univariate analysis of the overall survival rates in pN3 cases

	n (%)	p
Sex		
Male	29(55.8)	0.021
Female	23(44.2)	
Age		
< 58	25(47.4)	0.185
≧ 58	27(52.6)	
Location		
Upper rectum	8(15.4)	0.265
Lower rectum	44(84.6)	
Macroscopic configuration		
Massive	43(82.7)	0.934
Diffuse	9(17.3)	
Tumor size		
<5 cm	30(80.8)	0.047
≥5 cm	22(19.2)	
Greatest depth invasion		
pT1+pT2	10(19.2)	0.243
pT3+pT4	42(80.8)	
Histological type		
W/M	42(80.8)	0.272
Others	10(19.2)	
Lymphatic invasion		
Present	39(75.0)	0.589
Absent	13(25.0)	
Venous invasion		
Present	32(61.5)	0.765
Absent	20(38.5)	
No. of positive LNs		
<3	20(38.5)	0.129
≥4	32(61.5)	
pN3-ECI		
Positive	19(36.5)	0.008
Negative	33(63.5)	

W/M = well and moderately differentiated adenocarcinoma; LNs = lymph nodes; ECI = extracapsular invasion.

significantly poorer prognoses in terms of the overall survival rate in comparison with the female patients, patients with a tumor diameter of less than 5 cm, and pN3-ECI-negative patients ($p = 0.024$, $p = 0.047$, and $p = 0.008$).

Table 4 shows the results of multivariate analysis performed to identify variables that might be independently correlated with the overall and disease-free survival rates. pN3-ECI was identified as the only variable found to show a statistically significant correlation with the disease-free survival rate ($p = 0.011$), whereas none of the examined factors were statistically significantly correlated with the overall survival rate.

Figure 2 shows the disease-free survival rates in the patients enrolled in the study. No significant differences in the disease-free survival rate were observed among the pN2a, pN2b, and pN3 cases overall (left side). However, when the pN3 patients were stratified further according to the presence/absence of ECI in the main/lateral groups of lymph nodes, ie, pN3-ECI-positive/pN3-ECI-negative, the disease-free survival rate was statistically significantly lower in the pN3-ECI-positive cases in comparison with that in the pN2b cases ($p = 0.034$). The disease-free survival rate also differed significantly between the pN3-ECI-positive and pN3-ECI-negative cases ($p = 0.003$).

Figure 3 shows the overall survival rates in the patients enrolled in this study. No significant differences in the overall survival rate were observed among the pN2a, pN2b, and pN3 cases overall (left side). However, when the

TABLE 4. Multivariate analysis of the overall survival rates and disease-free survival rates

	HR	95% CI	p
Disease-free survival rates			
Sex	0.509	0.244–1.0063	0.072
pN3-ECI	0.411	0.206–0.816	0.011
Overall survival rates			
Sex	0.481	0.229–1.009	0.053
Tumor size	0.756	0.518–1.103	0.147
pN3-ECI	0.503	0.244–1.037	0.603

ECI = extracapsular invasion.

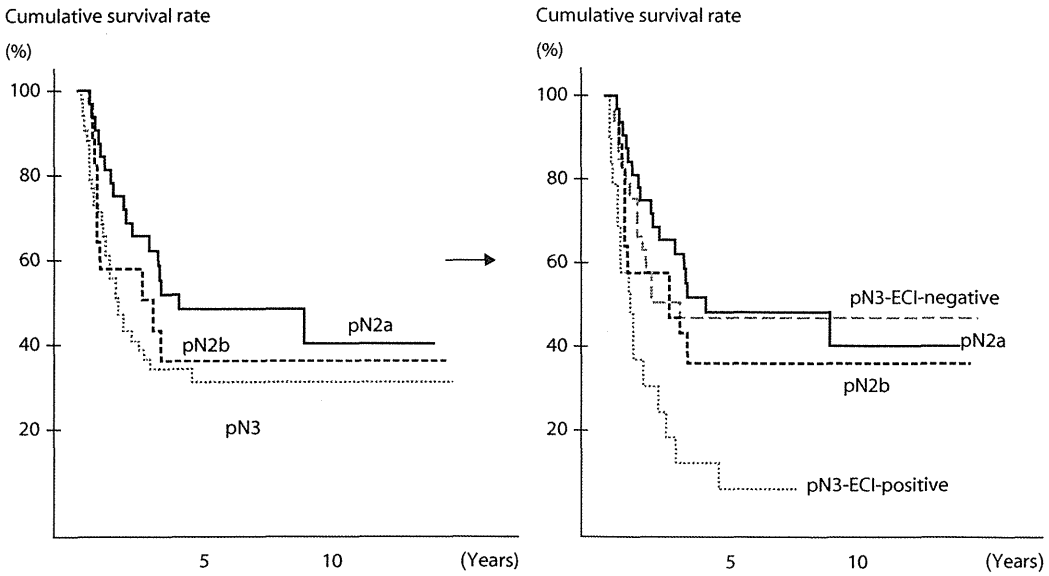

FIGURE 2. Disease-free survival rates in the enrolled patients. Left, pN2a, pN2b, and pN3 cases. Right, pN2a, pN2b, pN3-ECI-positive, and pN3-ECI-negative cases. ECI = extracapsular invasion.

pN3 patients were stratified further according to the presence/absence of ECI in the main/lateral groups of lymph nodes, ie, pN3-ECI-positive/pN3-ECI-negative, the overall survival rate was lower in the pN3-ECI-positive cases in comparison with that in the pN2b cases ($p = 0.077$). The overall survival rate also differed significantly between the pN3-ECI-positive and pN3-ECI-negative cases ($p = 0.008$).

DISCUSSION

Patients with TNM stage III colorectal cancer constitute a heterogeneous population with respect to the prognosis, with some showing a better prognosis than others. The patients have been divided into pN1, pN2, and pN3 cases according to the Japanese Classification of Colorectal Carcinoma, Second English Edition; pN1 cases have a more favorable prognosis than the pN2 or pN3 cases. In the present study, we demonstrated the absence of any significant differences in the overall or disease-free survival rates between the pN2 and pN3 cases.

Several previous studies have reported the presence of ECI in the metastatic lymph nodes as a poor prognostic factor in a variety of cancers.[4–7] It is significant that Fujii et al[12] reported that the presence of ECI in the metastatic lymph nodes may be a useful marker to identify patients with colorectal cancer who are at a high risk for disease recurrence in the short term. Furthermore, they reported that the presence of ECI in the N1 metastatic lymph nodes may be a marker of metastasis in more distant regional lymph node groups (N2) in patients with colorectal cancer, because it possibly represents the ability of the colorectal tumor cells to disseminate to distant lymph nodes,[13] but no relationship was noted with the presence/absence of metastasis in the N3 lymph nodes. However, there have been no studies on the significance of the presence/absence of ECI in relation to the lymph node group involved. This study is the first to determine the prognostic significance of the presence/absence of ECI in the main/lateral lymph nodes in pN3 patients. We demonstrated that pN3-ECI positivity was the only factor that was statistically significantly associated with the disease-free survival rate. Yano et al[6] also reported that the presence of ECI in the metastatic lymph nodes was the only factor that was statistically significantly associated with the disease-free survival; however, their report did not refer to the location of the metastatic lymph nodes showing ECI. Heide et al[7] reported that the presence of ECI in the metastatic lymph nodes had a strong negative impact on the local control rate, independent of other prognostic factors, and that it was also associated with a high frequency of distant metastasis.

Two critically important implications of this study need to be emphasized here. First, stratification of pN3 cases based on the ECI status is useful. Patients without ECI in the main metastatic lymph nodes, ie, pN3-ECI-negative cases were analogous, in terms of the prognosis, to pN2 cases, whereas the prognosis was significantly poorer in the pN3-ECI-positive cases. Second, while determining the lymph node metastasis status for staging, de-

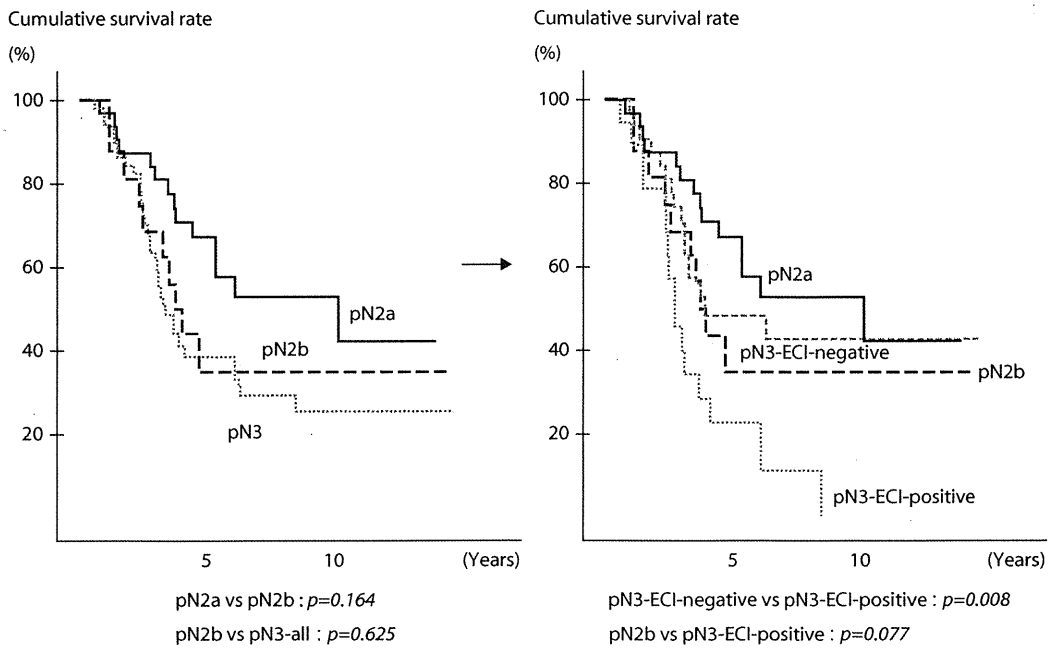

FIGURE 3. Overall survival rates in the enrolled patients. Left, pN2a, pN2b, and pN3 cases. Right, pN2a, pN2b, pN3-ECI-positive, and pN3-ECI-negative cases. ECI = extracapsular invasion.

termination of not only the number of metastatic lymph nodes, but also that of the lymph node groups involved has a crucial role in predicting the prognosis. Kanemitsu et al[14] reported that high ligation of the inferior mesenteric artery allows curative resection and long-term survival in patients with sigmoid colon or rectal cancer and emphasized that complete resection of the main lymph nodes was important. Especially, although pN3-ECI-positive was dominated in the systemic recurrence, the presence of ECI in the metastatic lymph nodes was a predictor of potential systemic involvement.

Assessment of the ECI status in the metastatic lymph nodes can be easily performed by routine staining, ie, H & E staining of tissue sections, without any need for the use of immunostaining techniques. Yano et al[6] also reported that the presence of ECI in the metastatic lymph nodes determined by routine H & E staining is a potent prognostic factor in patients with stage III colorectal cancer. In this study, ECI was defined as invasion of the perinodal fat or extranodal location of the tumor cells continuously, hence, not discontinuously. In Japan, most surgeons commonly separate the lymph nodes from the resected specimens before presenting them to the pathologists. Consequently, it is difficult to retrieve discontinuous tumor cells. If the resected specimens were submitted intact to the pathologists, discontinuous tumor cells could also be examined, as in the case of the extranodal cancer deposits reported by Ueno et al.[9] However, this is not easy and not very common in practical clinical use.

CONCLUSION

Detailed stratification of pN3 cases based on the presence/absence of ECI has the potential to contribute significantly to more available prediction of the prognosis of patients with stage III colorectal cancer.

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Tumor Necrosis in Patients with TNM Stage IV Colorectal Cancer without Residual Disease (R0 Status) Is Associated with a Poor Prognosis

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Abstract. *Aim: To examine the usefulness of the histopathological finding of tumor necrosis for stratifying TNM stage IV colorectal cancer in R0 status. Patients and Methods: We enrolled 98 patients with stage IV colorectal cancer, without residual disease after resection. The extent of necrosis was assessed using published thresholds, the extent was graded as "absent", "moderate" (<30% of tumor area), or "severe" (≥30%) in each section. Results: In multivariate analysis, the only significant difference in the disease-free survival rate was related to tumor necrosis (p=0.01) and the significant differences in the overall survival rates were related to the maximum tumor size and the degree of tumor necrosis (p=0.02 and p=0.001, respectively). Conclusion: Tumor necrosis is associated with a poor prognosis in colorectal cancer and may allow the stratification of TNM stage IV patients without residual disease after surgery.*

The use of specific histopathological findings, for example "tumor budding", in resected specimens to predict poor prognosis in colorectal cancer has been assessed in a number of studies (1, 2). In recent years, tumor necrosis has become recognized as a potential prognostic marker for a variety of solid tumor types, including those of the breast (3), lung (4), pancreas (5), kidney (6), and upper urinary tract (7, 8), as well as for soft tissue sarcomas (9). Non-clinical studies have shown that tumor necrosis is correlated with local and systemic inflammation especially the one caused by IL-6, apoptosis, and microsatellite instability (10, 11). More recently, there have been a number of clinical studies on tumor necrosis in colorectal cancer (12, 13). However, previous reports have included only patients with TNM stage II or III colorectal cancer (12, 13). Here, we report the findings of the first study, to our knowledge, on tumor necrosis in TNM stage IV colorectal cancer.

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Key Words: Tumor necrosis, stage IV colorectal cancer, without residual disease (R0 status), inflammatory response.

Patients and Methods

We enrolled 98 patients who underwent resection for stage IV colorectal cancer without any residual cancer being detected at the end of surgery. This study took place at the Department of Gastroenterological Surgery, Aichi Cancer Center Hospital, Nagoya, Japan, between January 1980 and December 2006. None of the patients had received chemotherapy or radiation therapy prior to surgery. Complete dissection of all the regional lymph nodes was performed in all cases.

In cases where liver and/or lung metastases were present, the metastatic lesion was removed non-concurrently, usually between two and three months after the primary tumor had been removed. In cases of metachronous liver metastasis, it is generally accepted at our Institution, that delaying resection allows for a more accurate assessment of the number and location of hepatic metastases, which in turn is of benefit in determining which patients should undergo surgery, and in selecting the most appropriate surgical procedure (14, 15). In cases of resectable peritoneal and distant lymph node metastases, the primary tumor was removed synchronously with the metastatic lesion.

The resected specimens were fixed with 10% formalin for several days, and the tumor-containing tissue samples were sliced into 4-μm sections in the region with the deepest tumor invasion. Histopathological diagnoses were established on the basis of hematoxylin and eosin staining at low magnification (×40) using standard procedures without specific immunostaining.

The extent of necrosis was assessed semi-quantitatively and, by using published thresholds, this extent was graded as "absent" (none), "moderate" (<30% of tumor area), or "severe" (>30% of tumor area) in each section before an assessment was made of the overall extent of necrosis (Figures 1 and 2).

We reviewed the hospital records to obtain clinicopathological information regarding the patients, including their gender and age (median, 61 years), lesion location, maximum tumor size (median, 5

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cm), greatest depth of invasion of the tumor (pT1+pT2+pT3 vs. pT4), histological type of tumor, presence/absence of lymphatic and venous invasion, the number of metastasis-positive lymph nodes, and use of adjuvant chemotherapy, with regimens including oral 5-fluorouracil, 5'-doxifluridine, carmofur or uracil-tegafur with leucovorin, as the most commonly used drugs, for about 6 to 12 months (16-18). Adenocarcinoma of the rectum was graded predominantly on the basis of glandular appearance, and classified as well/moderately differentiated or "other", according to the WHO histopathological classification of tumors of the colon and rectum (19) and the Japanese Classification of Colorectal Carcinoma (20). Lesions were classified according to whether they were located in the colon or rectum, with the latter defined as a tumor whose lowest border was located between the anal verge and the sacral promontory.

All data are expressed as the mean±SD. Statistical analysis was performed using the Chi-square independence test. Multivariate stepwise logistic regression analysis was subsequently performed to identify factors that might have influenced the outcome. The log-rank test was used to evaluate differences in the overall survival rates and disease-free survival rates. Statistical significance was set at $p<0.05$ and confidence intervals (CIs) were determined at the 95% level.

Results

The data presented in Table I show that no significant difference in the extent of necrosis was observed with respect to gender, average patient age, histological type, maximum tumor size, and lymphatic or venous invasion. There was a significant difference with respect to tumor location, with tumors in the moderate group mainly being located in the rectum, and absent group tumors mainly being located in the colon ($p=0.009$). In an analysis of the greatest invasion depth, moderate group tumors were mainly scored pT1+pT2+pT3, whereas severe group tumors were mainly scored pT4 ($p=0.041$).

There were no significant differences with respect to the presence of synchronous hepatic metastasis, synchronous peritoneal metastasis, metastasis in distant lymph nodes, or adjuvant chemotherapy between the groups (Table II). There were, however, significant differences between absent and moderate groups with respect to metastasis to regional lymph nodes ($p=0.012$), being more frequent in the latter, and between moderate and severe groups for synchronous pulmonary metastasis ($p=0.025$), again being more frequent in the latter.

Table III shows the results of univariate and multivariate analysis performed to identify factors that might be correlated with the disease-free survival rate. In univariate analysis, no significant differences in the disease-free survival rate were observed in relation to gender, age, cancer location, greatest depth of tumor invasion, presence/absence of lymphatic or venous invasion, synchronous hepatic metastasis, synchronous pulmonary metastasis, synchronous peritoneal metastasis, metastasis to distant lymph nodes, or adjuvant chemotherapy. However, the rates differed significantly in relation to the histological type, maximum tumor size, metastasis to regional lymph nodes, and tumor necrosis status ($p=0.039$, $p=0.047$, $p=0.031$, and $p=0.016$, respectively). In multivariate analysis, the only significant difference in the disease-free survival rate were observed with respect to tumor necrosis status ($p=0.011$).

Table IV shows the results of univariate and multivariate analyses performed to identify factors that might be correlated with the overall survival rates. In univariate analysis, no significant differences in the overall survival rates were observed in relation to gender, age, cancer location, greatest depth of tumor invasion, presence/absence of lymphatic or venous invasion, metastasis in distant lymph nodes, or adjuvant chemotherapy. However, the rates differed significantly in relation to the histological type, maximum tumor size, metastasis in regional lymph nodes, synchronous hepatic metastasis, synchronous pulmonary metastasis, synchronous peritoneal metastasis, adjuvant chemotherapy, and tumor necrosis status ($p=0.017$, $=0.033$, <0.0001, $=0.009$, $=0.028$, $=0.040$, and <0.0001, respectively). In multivariate analysis, significant differences in the overall survival rates were observed in the maximum tumor size and tumor necrosis status ($p=0.019$ and $=0.001$).

Figure 3 shows the disease-free and overall survival rates after surgery, of patients who were found not to have residual cancer. Significant differences in the disease-free survival rates were observed between the moderate group and the severe group ($p=0.023$), and in the overall survival rates between the absent group and the moderate group ($p=0.005$), as well as the moderate group and the severe group ($p=0.023$) with survival being poorer in the latter.

Discussion

The present study confirmed that the presence of tumor necrosis, as part of the pathological findings of resected tumor specimens, is a potential stage-independent prognostic factor in TNM stage IV colorectal cancer without residual cancer after resection and might help in determining whether a follow-up with high-potency adjuvant therapy is warranted.

However, this study had two potential problems that need to be considered. One is that tumor necrosis was measured using a semi-quantitative technique; however, it is very difficult to estimate necrosis quantitatively, and all previous reports have used the same semi-quantitative estimation with the same classifications (absent, focal, moderate, or extensive) (12, 13). The second potential difficulty is the lack of subjective cases, and this, we hope, will be addressed by future prospective trials where the significance of tumor necrosis status is assessed in more patients with prognostic information.

In recent years, histopathologically-identified tumor necrosis has been recognized as a potential prognostic marker for a variety of solid tumors including those of the

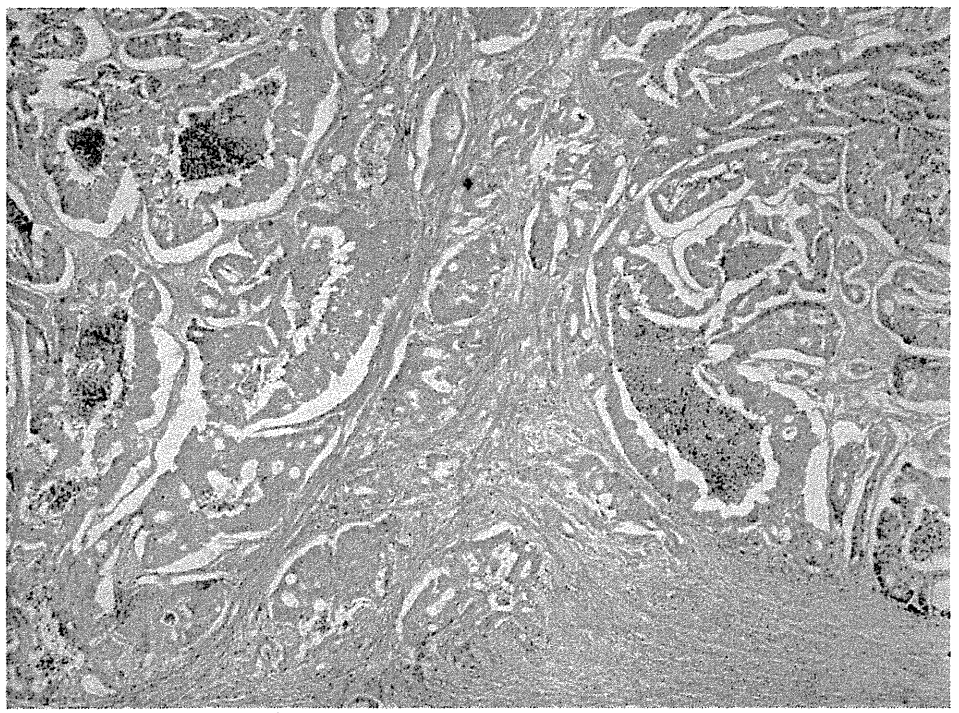

Figure 1. *Moderate necrosis: Nuclear fragmentation is present without any structures consistent with ductal carcinoma. The area of necrotic cells is <30% of the total tumor area. Original magnification, ×200.*

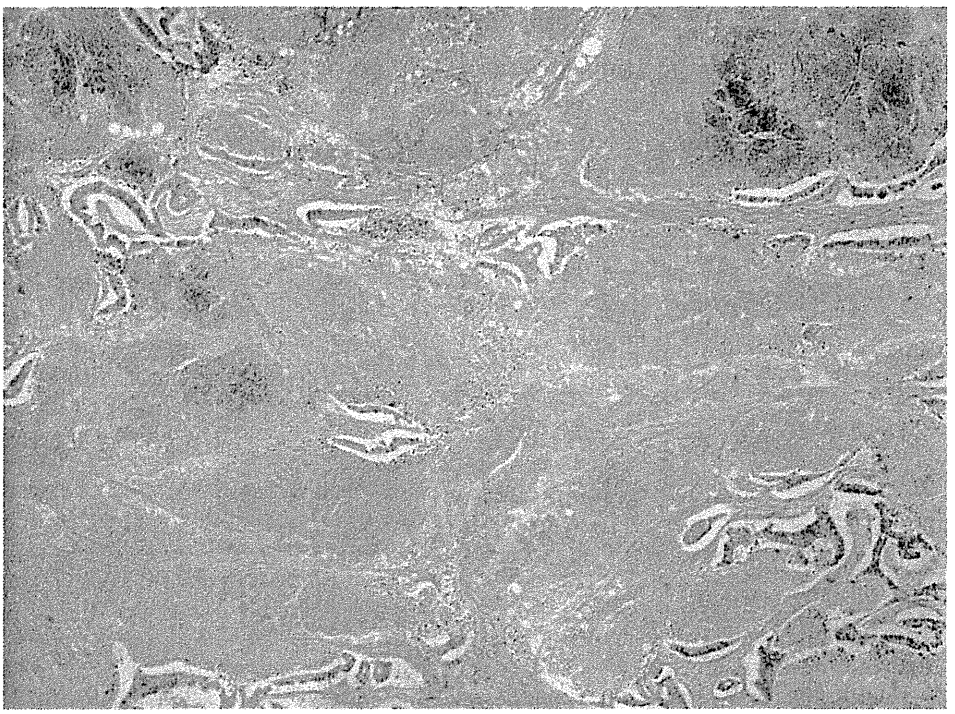

Figure 2. *Nuclear fragmentation is present without any structures consistent with ductal carcinoma. The area of necrotic cells is >30% of the total tumor area. Original magnification, ×200.*

Table I. *Clinicopathological fingings.*

	None (n=15)	Moderate (n=69)	Severe (n=14)	*p*-Value	
				None *vs.* Moderate	Moderate *vs.* Severe
Gender					
Male	5 (33.3%)	39 (56.5%)	10 (71.4%)	0.089	0.223
Female	10 (66.7%)	30 (43.5%)	4 (28.6%)		
Age, years					
≥61	6 (40.0%)	37 (53.6%)	9 (64.3%)	0.215	0.334
<60	9 (60.0%)	32 (46.4%)	5 (35.7%)		
Cancer location					
Colon	14 (93.3%)	41 (59.4%)	10 (71.4%)	0.009	0.229
Rectum	1 (6.7%)	28 (40.6%)	4 (28.6%)		
Histological type					
W/M	13 (86.7%)	60 (87.0%)	10 (71.4%)	0.627	0.146
others	2 (13.3%)	9 (13.0%)	4 (28.6%)		
Greatest invasion depth					
pT1+pT2+pT3	7 (46.7%)	45 (65.2%)	5 (35.7%)	0.148	0.041
pT4	8 (53.3%)	24 (42.0%)	9 (64.3%)		
Maximum tumor size, cm					
<5	5 (33.3%)	29 (58.0%)	3 (21.4%)	0.375	0.125
≥5	10 (66.7%)	40 (42.9%)	11 (78.6%)		
Lymphatic invasion					
Present	11 (73.3%)	55 (79.7%)	11 (78.6%)	0.405	0.586
Absent	4 (26.7%)	14 (20.3%)	3 (21.4%)		
Vascular invasion					
Present	10 (66.7%)	47 (68.1%)	11 (78.6%)	0.568	0.333
Absent	5 (33.3%)	22 (31.9%)	3 (21.4%)		

W/M: Well- and moderately-differentiated adenocarcinoma.

Table II. *Clinicopathological fingings.*

	None (n=15)	Moderate (n=69)	Severe (n=14)	*p*-Value	
				None *vs.* Moderate	Moderate *vs.* Severe
Metastasis in regional lymph nodes					
None	1 (6.7%)	13 (18.8%)	2 (14.3%)		
≤3	11 (73.3%)	22 (31.9%)	6 (42.9%)	0.012	0.723
≥4	3 (20.0%)	24 (49.3%)	6 (42.9%)		
Synchronous hepatic metastasis					
Present	9 (53.3%)	32 (57.1%)	4 (41.7%)	0.251	0.177
Absent	6 (46.7%)	37 (42.9%)	10 (58.3%)		
Synchronous pulmonary metastasis					
Present	2 (13.3%)	4 (5.8%)	4 (41.7%)	0.290	0.025
Absent	13 (86.7%)	65 (94.2%)	10 (58.3%)		
Synchronous peritoneal metastasis					
Present	4 (26.7%)	17 (24.6%)	3 (21.4%)	0.551	0.550
Absent	11 (73.3%)	52 (75.4%)	11 (78.6%)		
Metastasis in distant lymph nodes					
Present	3 (20.0%)	22 (31.9%)	5 (35.7%)	0.281	0.503
Absent	12 (80.0%)	47 (68.1%)	9 (64.3%)		
Adjuvant chemotherapy					
Present	7 (46.7%)	24 (34.8%)	5 (35.7%)	0.281	0.587
Absent	8 (53.3%)	45 (65.2%)	9 (64.3%)		

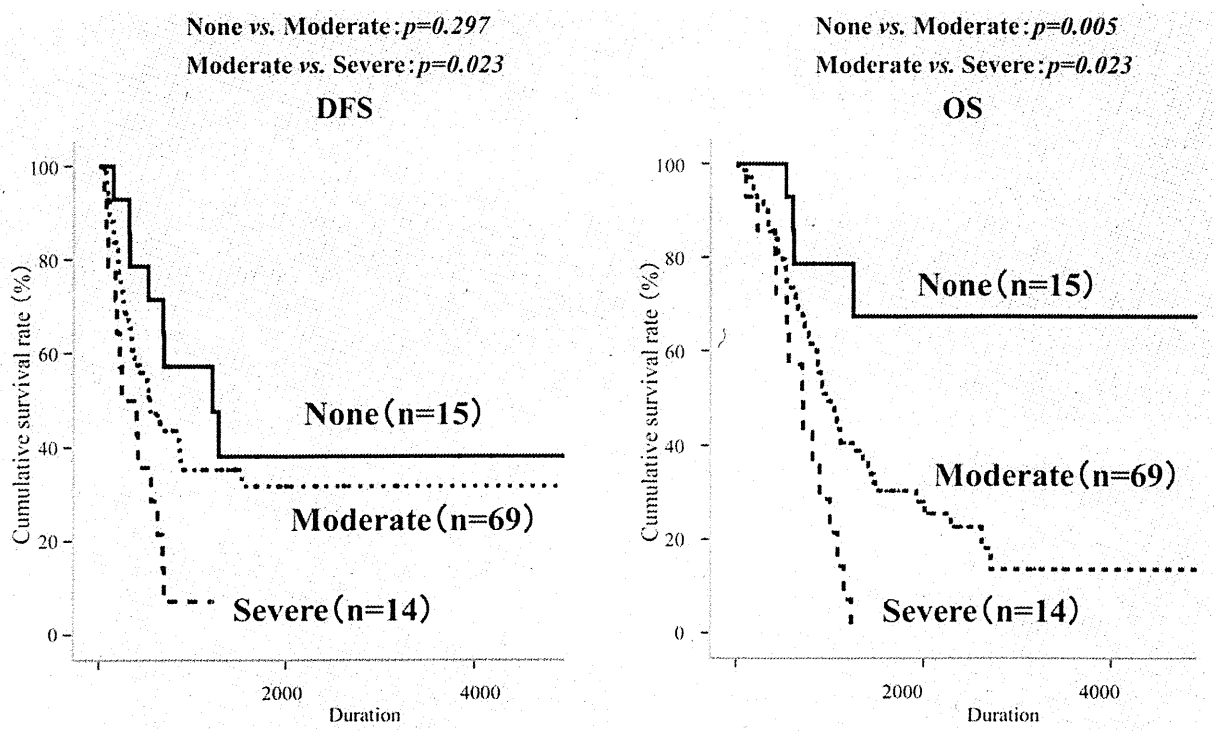

Figure 3. *Disease-free survival (left) and the overall survival (right) rates for the "absent", "moderate", and "severe" categories of tumor necrosis.*

Table III. *Factors associated with disease-free survival rates.*

	p-Value	
	Univariate	Multivariate
Gender	0.743	–
Age	0.675	–
Cancer location	0.063	–
Histological type	0.039	0.102
Greatest invasion depth	0.725	–
Maximum tumor size	0.047	0.055
Lymphatic invasion	0.269	–
Vascular invasion	0.566	–
Metastasis to regional lymph nodes	0.031	0.256
Synchronous hepatic metastasis	0.754	–
Synchronous pulmonary metastasis	0.118	–
Synchronous peritoneal metastasis	0.647	–
Metastasis to distant lymph nodes	0.131	–
Tumor necrosis	0.016	0.011
Adjuvant chemotherapy	0.801	–

Table IV. *Factors associated with overall survival rates.*

	p-Value	
	Univariate	Multivariate
Gender	0.213	–
Age	0.782	–
Cancer location	0.244	–
Histological type	0.017	0.250
Greatest invasion depth	0.645	–
Maximum tumor size	0.033	0.019
Lymphatic invasion	0.715	–
Vascular invasion	0.273	–
Metastasis to regional lymph nodes	<0.0001	0.127
Synchronous hepatic metastasis	0.009	0.357
Synchronous pulmonary metastasis	0.088	–
Synchronous peritoneal metastasis	0.028	0.552
Metastasis to distant lymph nodes	0.058	–
Tumor necrosis	<0.0001	0.001
Adjuvant chemotherapy	0.040	0.128

breast (3), lung (4), pancreas (5), kidney (6), and upper urinary tract (7, 8), as well as for soft tissue sarcomas (9). Studies on tumor necrosis in colorectal cancer are few in number, but this area has been the focus of much attention recently. It has been established that tumor necrosis is the result of two distinct pathways, one of which is the conventional route involving apoptosis, whereas the other results from the stimulation of the inflammatory pathway

due to rapid tumor growth, resulting in vascular insufficiency and tissue hypoxia (12). The results of our study show that the maximum tumor size and tumor necrosis status were statistically significant factors for predicting a poor prognosis with regard to overall survival, indicating the possible importance of the latter pathway. We also showed that tumor necrosis is a stage-independent prognostic factor in colorectal cancer, the inference being that if tumors have outgrown their blood supply, histological tumor necrosis is consequently a marker of tumor aggressiveness and poor prognosis.

Another study has made reference to inflammation with tumor necrosis, in which the presence of tumor necrosis, itself associated with a weak local inflammatory cell infiltrate, may represent a trigger for the host to initiate a systemic inflammatory response and an attenuation of the local inflammatory cell infiltrate (12). It has also been reported that tumor necrosis status is closely associated with expression of the urokinase-type plasminogen activator (21). There is also a reported association between inflammatory infiltration and microsatellite instability (10).

High concentrations of IL-6 in the tumor have also been shown to be directly associated with increased necrosis, proliferation, differentiation, and vascular invasion, whereas circulating concentrations of IL-6 are directly associated with T-stage, C-reactive protein concentrations, and poor survival. Thus, IL-6 has emerged as a key mediator in the relationship between tumor necrosis, local and systemic inflammatory responses, and outcome in patients with colorectal cancer (11, 22).

There have been a number of previous reports on the significance of tumor necrosis in colorectal cancer, but these have only involved patients with TNM stage II or III disease (12, 13, 23). To our knowledge, our study gives the first detailed description of TNM stage IV colorectal cancer in patients with no apparent residual cancer after surgery, and who, as a result, generally have a good prognosis (24). We excluded patients who did have residual disease after surgery as in these cases, the prognosis is far less certain (25). It is also noteworthy that the use of hematoxylin and eosin staining for the assessment of tumor necrosis status is straightforward and highly reproducible in terms of histopathological diagnosis. A poor prognosis predicted on the basis of the presence of tumor necrosis after surgery indicates the need for intensive follow-up with high-potency adjuvant therapy.

The results of our study imply that the extent of tumor necrosis should be considered during clinical review as a potential indicator of disease prognosis and, hence, the future treatment of the patient. Further, large-scale prospective studies are warranted to confirm these findings and also to further evaluate whether they can be extended to other disease grades and possibly other types of cancer.

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Outcomes After Hepatic and Pulmonary Metastasectomies Compared With Pulmonary Metastasectomy Alone in Patients With Colorectal Cancer Metastasis to Liver and Lungs

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Abstract
Background Surgical resection is the most effective treatment for colorectal cancer that has metastasized to the liver. Similarly, surgical resection improves survival for selected patients with pulmonary colorectal metastases. However, the indication for pulmonary metastasectomy is not clear in patients with both hepatic and pulmonary colorectal metastases. Therefore, we evaluated outcomes after pulmonary resection of colorectal metastases in patients with or without a history of curative hepatic metastasectomy.
Methods We retrospectively analyzed 96 patients who underwent pulmonary metastasectomy from March 1999 to November 2009. Patients were grouped according to treatment: resection of pulmonary metastases alone (lung metastasectomy group) or resection of both hepatic and pulmonary metastases (liver and lung metastasectomy group). Overall survival (OS) and disease-free survival (DFS) were evaluated by Kaplan–Meier analysis. Survival curves were compared using the log-rank test.
Results The 5-year OS for all patients was 61.3 %, and the 5-year DFS was 26.7 %. Group comparisons showed that the 5-year OS of the lung metastasectomy group was significantly better than that of the liver and lung metastasectomy group (69 vs. 43 %; $p = 0.030$). However, the 5-year DFS rates of the lung metastasectomy group (25.8 %) and liver and lung metastasectomy group (28.0 %) did not differ significantly. Recurrence was higher after resection of both hepatic and pulmonary metastases than after pulmonary metastases alone (79 vs. 45 %; $p = 0.025$).
Conclusions Resection of pulmonary colorectal metastases may increase survival. However, the combination of liver and lung metastasectomies had a worse prognosis than pulmonary metastasectomy alone. In selected patients, combined liver and lung metastasectomy can be beneficial and result in acceptable DFS.

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Introduction

The most frequent sites of distant metastases from colorectal cancer are the liver and lung [1]. After curative resection for colorectal cancer, hepatic metastases are detected in 8–30 % of patients [2, 3] and pulmonary metastases in 10–20 % [4, 5].

Surgical resection is the most effective treatment for colorectal cancer that has metastasized to the liver. This treatment is widely accepted and has produced 5-year survival rates of 25–58 % [6–10]. Lung metastases were previously thought to be incurable and were treated primarily with systemic chemotherapy. However, recent studies have shown that resection of pulmonary metastases from colorectal cancer is beneficial for selected patients, reporting 5-year survival rates of 30–48 % [11–17]. Also, some reports have suggested that resection of both hepatic and pulmonary colorectal metastases can increase survival after colorectal cancer has metastasized to both liver and lungs [18, 19]. In these patients, the outcome of pulmonary metastasectomy after previous hepatic resection is unclear. For example, Ike et al. [20] reported that survival rates did not differ between patients who underwent sequential hepatic and pulmonary resections compared with those who underwent pulmonary

resection alone. In the present study, we evaluated outcomes after pulmonary resection of colorectal metastases in patients with or without a history of curative hepatic metastasectomy.

Materials and methods

Between March 1999 and November 2009, a total of 96 patients underwent pulmonary resection for metastatic colorectal cancer at the Aichi Cancer Center. These patients were divided into two groups based on treatment: resection of pulmonary metastases alone (lung metastasectomy group) or resection of both hepatic and pulmonary metastases (liver and lung metastasectomy group). Demographic, perioperative, and survival data were evaluated by retrospective review.

The selection criteria for resection of hepatic metastases were (1) control of the primary colorectal cancer; (2) no extrahepatic metastases except resectable pulmonary metastases; (3) completely resectable liver lesions diagnosed by preoperative imaging; (4) liver function that was sufficient for resection of all liver lesions. Liver resection procedures (partial resection, segmentectomy, lobectomy) were selected with curative intent regardless of tumor size, number, or location. The selection criteria for resection of pulmonary metastases were (1) control of the primary colorectal cancer; (2) no extrathoracic metastases; (3) completely resectable lung lesions diagnosed by preoperative imaging; (4) respiratory function that was adequate for resection of all lung lesions. Lung resection procedures included partial resection for lesions in the peripheral lung or tumors $\leq$3.0 cm in diameter and lobectomy performed for multiple tumors in the same lobe or tumors >3.0 cm in diameter. In all, 207 patients did not fulfill the selection criteria for resection: recurrence at the primary site ($n = 11$), extrahepatic or extrathoracic metastases ($n = 85$), unresectable liver lesions ($n = 81$), unresectable lung lesions ($n = 30$) . When metastasis to the liver and/or lung was detected at the time of diagnosis of colorectal cancer, we resected the primary tumor first and, in the absence of disease progression, performed the metastasectomy 3 months later [21]. When patients presented with simultaneous liver and lung metastases, we resected the hepatic lesion(s) first to rule out extrahepatic abdominal lesions. Pulmonary resection was performed about 4 weeks later.

Patient characteristics are shown in Table 1. The primary tumor originated in the rectum in 39 patients (58 %) of the lung metastasectomy group and in 16 patients (55 %) of the liver and lung metastasectomy group. Regional lymph node metastases from the primary tumor were identified in 43 patients (64 %) of the lung metastasectomy group and 19 patients (66 %) of the liver and lung metastasectomy group. The disease-free interval (DFI) was calculated as the interval between the day of primary tumor resection and the day of pulmonary metastasectomy. The median DFI was 20 months in the lung metastasectomy group and 17 months in the liver and lung metastasectomy group. Most cases of lung metastasis exhibited solitary, unilateral tumors <3 cm and a prethoracotomy carcinoembryonic antigen (CEA) value <5 ng/ml; these results did not differ significantly between the two patient groups.

Table 1 Patient characteristics

Characteristic	Lung metastasectomy ($n = 69$)	Liver and lung metastasectomy ($n = 29$)	p
Median age at pulmonary resection (years)	63 (36–84)	60 (46–75)	
Sex (M:F)	27:40	17:12	0.12
Location of primary tumor			
Colon	28	13	0.82
Rectum	39	16	
Lymph node metastasis of primary tumor			
Present	43	19	0.97
Absent	20	9	
Disease-free interval (months)	20	17	0.35
No. of pulmonary metastases			
Solitary	37	20	0.26
Multiple	30	9	
Location of pulmonary metastasis			
Unilateral	52	26	0.25
Bilateral	15	3	
Maximum size of pulmonary metastasis (cm)			
>3	13	8	0.19
$\leq$3	54	21	
Prethoracotomy CEA level (ng/ml)			
$\geq$5	21	8	0.81
<5	44	20	

CEA carcinoembryonic antigen

The primary endpoint for this study was overall survival (OS), defined as the interval from the date of pulmonary resection to the date of last follow-up or death. The secondary endpoint was disease-free survival (DFS), defined as the interval from the date of pulmonary resection to the date of disease recurrence. OS and DFS were evaluated by Kaplan–Meier analysis, and survival curves were compared using the log-rank test. Multivariate analysis was performed using the Cox proportional hazard regression model to identify independent survival factors. Statistical significance was set at $p < 0.05$.

Results

Surgical resection procedures and complications

The pulmonary resection procedure was partial resection for 45 patients (67 %) of the lung metastasectomy group and 18 patients (62 %) of the liver and lung metastasectomy group. Regarding liver resection procedures, 9 patients (31 %) underwent partial resection and 13 (45 %) underwent lobectomy (Table 2).

Five patients experienced minor postoperative complications. One patient in each group had a pulmonary infection. The complications after liver resection were abdominal abscess ($n = 2$) and bile leakage ($n = 2$). No patients required laparotomy for complications, and no deaths occurred during surgery or during the postoperative period (Table 2).

Adjuvant chemotherapy after pulmonary resection

In all, 21 patients (31 %) of the lung metastasectomy group and 8 patients (28 %) of the liver and lung metastasectomy group received postoperative chemotherapy following the pulmonary resection. Among the patients who received adjuvant chemotherapy, 15 in the lung metastasectomy group (15/21, 71 %) received oral chemotherapy such as UFT and TS-1. Four patients of the liver and lung metastasectomy (4/8, 50 %) group received oxaliplatin-based chemotherapy.

Overall survival and disease-free survival

The median follow-up after pulmonary resection was 50.8 months. For all patients, the 5-year survival rate was 61.3 %. Group comparison revealed a significantly better 5-year survival rate in the lung metastasectomy group than in the liver and lung metastasectomy group (69 vs. 43 %; $p = 0.030$) (Fig. 1). The 5-year DFS rate was 26.7 % for all patients and did not differ significantly between groups (lung metastasectomy 25.8 %; liver and lung metastasectomy 28.0 %; $p = 0.616$) (Fig. 2).

Table 2 Types of surgical resection and complications

Parameter	Lung metastasectomy ($n = 67$)	Liver and lung metastasectomy ($n = 29$)
Pulmonary resection		
Partial resection	45	18
Segmentectomy	8	2
Lobectomy	14	9
Hepatic resection		
Partial resection		9
Segmentectomy		7
Lobectomy		13
Complications		
Pulmonary infection	1	1
Abdominal abscess		2
Bile leakage		2

Recurrence after pulmonary metastasectomy

Recurrence after pulmonary metastasectomy is shown in Table 3. In all, 43 patients (64.2 %) in the lung metastasectomy group experienced tumor recurrence: liver only ($n = 2$), lung only ($n = 22$), liver + lung ($n = 1$), liver + lymph node ($n = 2$), lung + lymph node ($n = 10$), lung + brain or bone ($n = 3$), other organs ($n = 3$). Altogether, 19 patients (65.5 %) in the liver and lung metastasectomy group experienced tumor recurrence: liver only ($n = 3$), lung only ($n = 1$), liver plus lung ($n = 2$), lung plus lymph node ($n = 4$), liver plus brain or bone ($n = 3$), lung plus brain or bone ($n = 3$), other organs ($n = 3$). Most patients in the lung metastasectomy group who experienced recurrence (24/43, 55 %) had only one metastatic organ (e.g., remnant lung). In contrast, most patients in the liver and lung metastasectomy group who experienced recurrence (15/19, 79 %) had two or more metastatic organs (e.g., remnant lung, liver, brain, bone, lymph node) ($p = 0.025$).

Repeat pulmonary resection

Among patients with remnant lung recurrence, 18 (50 %) in the lung metastasectomy group and 2 (20 %) in the liver and lung metastasectomy group underwent repeat resection. Postoperative morbidity occurred in 10 %. The complications were wound infection ($n = 1$) and

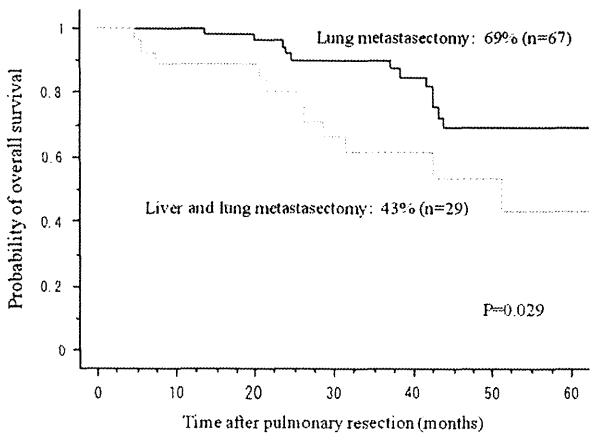

Fig. 1 Overall survival for the two patient groups

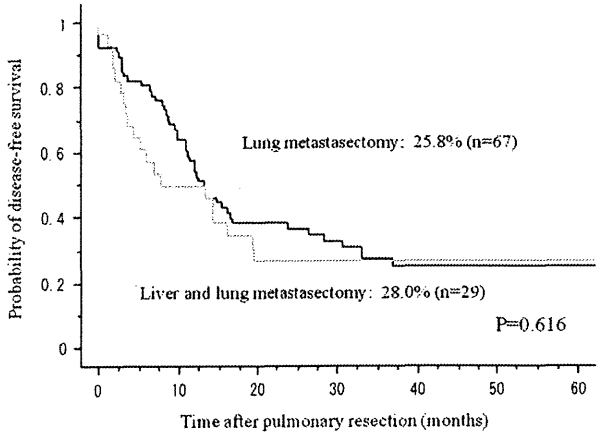

Fig. 2 Disease-free survival for the two patient groups

Table 3 Outcome of recurrence after pulmonary metastasectomy

Recurrence parameters	Lung metastasectomy ($n = 67$)	Liver and lung metastasectomy ($n = 29$)	p
Recurrence rate	43 (64.2 %)	19 (65.5 %)	
Recurrence pattern			
Liver only	2	3	
Lung only	22	1	
Liver + lung	1	2	
Liver + lymph node	2	–	
Lung + lymph node	10	4	
Liver + brain or bone	–	3	
Lung + brain or bone	3	3	
Other	3	3	
Metastatic sites			0.025
One organ	24	4	
Two or more organs	19	15	

pulmonary infection ($n = 1$). No postoperative mortality was observed. Of the 20 patients who underwent repeat pulmonary resection, overall and disease-free 5-year survivals were 69.0 and 35.5 %, respectively, after the second metastasectomy.

Prognostic factors

Table 4 shows the results of univariate analysis of prognostic factors and survival after pulmonary resection. Factors associated with prognosis were regional lymph node metastases from the primary tumor ($p = 0.015$), previous liver resection ($p = 0.035$), DFI ($p = 0.030$), and prethoracotomy serum CEA level ($p = 0.018$). Multivariate analysis revealed that regional lymph node metastases from the primary tumor ($p = 0.016$), previous liver resection ($p = 0.008$), and DFI ($p = 0.017$) were independent predictors of survival (Table 5).

Discussion

The liver and lung are common sites of colorectal cancer metastasis. Although chemotherapy has significantly improved overall survival [22], chemotherapy alone cannot cure metastatic colorectal cancer. Surgical resection of metastatic colorectal cancer is the only curative treatment [23]. Surgical resection of hepatic colorectal metastases has been shown to be safe, with reported mortality rates of 0–5 % and morbidity rates of 11–42 % [24–26]. Resection of pulmonary colorectal metastases provides similar outcomes, with mortality rates of 0–4 % and a morbidity rate of 12.2 % [11, 27, 28]. In the present study, the perioperative mortality rate was 0 %, and morbidity rates after liver and lung resection were 14 and 2 %, respectively. These results were acceptable. All four complications were minor, and none required reoperation.

Reported rates of overall survival after liver and lung metastasectomy are shown in Table 6. The 5-year survival rates after both liver and lung metastasectomy have previously been reported as ranging from 11 to 50 % [12, 15, 20, 28–35]. Comparisons of patient outcomes after lung metastasectomy alone with outcomes after both liver and lung metastasectomies showed that 5-year survival rates did not differ significantly [12, 15, 20, 29–32]. In the present study, the 5-year survival of all patients after pulmonary resection was 61.3 %, which was higher than that reported by many previous studies [11–17]. We found that the 5-year survival rate in the lung metastasectomy group was significantly better than that of the liver and lung metastasectomy group (69 vs. 43 %; $p = 0.030$). Multivariate analysis identified three independent prognostic factors for survival after lung metastasectomy: regional lymph node metastases from the primary tumor, DFI, previous liver metastasectomy. Previous studies reported the following independent prognostic factors after lung metastasectomy: number of pulmonary metastases [11, 13], hilar or mediastinal lymph node metastasis [12, 13, 28], time when pulmonary metastases were detected [29], prethoracotomy CEA level [36, 37], distribution of pulmonary metastases [12], liver metastasectomy before thoracotomy [28]. The better prognosis in our study may be because many of the lung tumors were solitary, unilateral, and <3 cm. We also excluded patients for whom hilar or mediastinal lymph node enlargement was detected by computed tomography. Patients with liver and lung metastases are thought to have two metastasizing lymphatic drainage routes: one through the portal venous system to the liver and the other through the systemic venous system to the lung. Thus, malignant cells can

Table 4 Univariate analysis of prognostic factors for overall survival after pulmonary metastasectomy

Prognostic factors	No.	5-Year survival (%)	*p*
Median age at pulmonary resection			
≥60	57	45.2	0.096
<60	39	71.1	
Sex (M/F)	44/52	48.8/74.6	0.191
Location of primary tumor			
Colon	41	69.5	0.279
Rectum	55	56.4	
Lymph node metastasis of primary tumor			
Present	62	50.0	0.015
Absent	29	87.7	
Previous liver resection			
Yes	29	43.0	0.035
No	67	69.0	
Disease-free survival			
≥6 months	79	67.1	0.030
<6 months	17	35.6	
No. of pulmonary metastases			
Solitary	57	65.4	0.364
Multiple	39	50.9	
Location of pulmonary metastasis			
Unilateral	78	64.8	0.051
Bilateral	18	44.6	
Maximum size of pulmonary metastasis (cm)			
≥3	21	64.9	0.761
<3	74	60.0	
Prethoracotomy CEA level			
≥5.0	30	41.4	0.018
<5.0	66	73.5	
Adjuvant chemotherapy after pulmonary resection			
Yes	29	73.2	0.312
No	67	59.8	

Table 5 Multivariate analysis of prognostic factors after pulmonary metastasectomy

Variable	Relative risk	95 % CI	*p*
Lymph node metastasis of primary tumor			
Present	1		
Absent	0.155	0.034–0.708	0.016
Previous liver resection			
Present	1		
Absent	0.307	0.129–0.732	0.008
Disease-free interval (months)			
<6	1		
≥6	0.344	0.143–0.829	0.017
Prethoracotomy CEA level (ng/ml)			
<5.0	1		
≥5.0	1.864	0.804–4.322	N.S.

CI confidence interval

Table 6 Survival after pulmonary metastasectomy for colorectal cancer: lung metastasectomy alone versus liver and lung metastasectomy

Study	Year	Lung metastasectomy alone 5-year survival (%)	Liver and lung metastasectomy 5-year survival (%)	*p*
Okumura et al. [28]	1996	45	33	0.009
Regnard et al. [30]	1998	27	11	NS
Kobayashi et al. [31]	1999	40	31	0.23
Nagakura et al. [32]	2001	46	27	0.29
Ike et al. [20]	2002	73	50	0.57
Saito et al. [12]	2002	41	34	0.38
Iizasa et al. [15]	2006	44	32	0.39
Koga et al. [29]	2006	24	41	0.26
Brouquet et al. [33]	2011	–	50	–
Gonzalez et al. [34]	2012	–	39	–
Sakamoto et al. [35]	2012	–	48	–
Present case	2012	69	43	0.029

spread through both routes in these patients, resulting in a worse prognosis. Surgical resection of both liver and lung metastases from colorectal cancer is thought to prolong survival in highly selected patients. Therefore, prospective data analysis is needed to establish operative indications.

In this study, the 5-year DFS rate of all patients after pulmonary metastasectomy was 26.7 %. Group comparison showed 5-year DFS rates of 25.8 % in the lung metastasectomy group and 28.0 % in the liver and lung metastasectomy group. Recurrence after pulmonary metastasectomy was ~60 %. The most common site of recurrence in both groups was the remnant lung, although the recurrence pattern differed between groups. In patients who underwent both liver and lung metastasectomy, tumors were later detected in bone, brain, and adrenal gland. There were significantly more metastatic organs in the liver and lung metastasectomy group than in the lung metastasectomy group. After recurrence in the remnant lung, 18 patients (50 %) of the lung metastasectomy group and 2 patients (20 %) of the liver and lung metastasectomy group underwent repeat lung resection. In previous studies, the 5-year survival rate after repeat lung resection for

recurrence of colorectal cancer has been reported at 30–40 % [11, 15, 29]. The 5-year survival rate for the 20 patients who underwent a second metastasectomy was 69.0 %. This result was favorable when compared with that of the initial metastasectomies performed in our institution and was a lot better when compared with previous reports. We did not perform a second metastasectomy in cases of bilateral lesions. This is one reason that can explain the better prognosis. Repeated pulmonary resection may provide good outcomes in patients who can undergo resection.

Conclusions

Surgical resection for lung metastases alone or for both liver and lung metastases produced good outcomes. However, the survival rate after both liver and lung metastasectomies was worse than the survival rate after lung metastasectomy alone. The number of metastatic organs was significantly higher after resection of hepatic and pulmonary metastases than after lung metastasectomy alone. Thus, the different survival rates may be due to differential patterns of recurrence after pulmonary resection. Tumor recurrence after pulmonary metastasectomy is high. Therefore, multimodality therapy with systemic chemotherapy may provide a survival benefit.

Conflict of interest None

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特集　直腸癌側方リンパ節転移のすべて

6. 直腸癌側方郭清手技
—— 開腹*

金光幸秀　志田　大　塚本俊輔**

〔要旨〕自律神経温存の側方郭清術は日本において発展した術式であり，予防的郭清だけでなく，側方リンパ節転移が存在した場合も5年生存率は30～50％と報告されており，一定の治療効果が期待できる手術手技である．術野を十分に展開し，解剖学的剝離層を視認して操作をすすめることが肝要であり，的確に郭清するためには，リンパ流理解のうえに立った正しい実践が求められる．膀胱側間隙を開き腹膜外からの操作を加える腹膜外ルートから，下膀胱動静脈を払った内陰部動静脈を尾骨筋に入るまで郭清する方法が有用である．

はじめに

直腸癌に対する手術療法の原則は，癌の主病巣と癌の転移が生じやすい所属リンパ節，すなわち中枢方向，腸管軸方向のリンパ節を一括して切除することにあり，下部進行直腸癌ではこれに側方向のリンパ節切除が加わる．下部進行直腸癌は従来その局所再発が高率であることより，ほかの大腸癌と比べて予後不良とされ，治療成績を向上させるために種々の治療法が行われてきた．本邦では，中直腸動脈から内腸骨動脈周囲につながるリンパ節への転移が局所再発の一つの原因として考えられ，内腸骨血管支配領域の側方郭清による局所制御を推奨し，その結果手術療法を重視した独自の道を発展させてきた．寛骨で囲まれた狭い骨盤腔内という空間的な制約下と，リンパ節郭清と神経温存の両立性を図るという二律背反性の制約下のもと，筋膜の系統的解剖学を導入し洗練がなされた外科手技は，癌手術の「究極型」といえる．

本稿では，先達の努力の成果である自律神経温存側方リンパ節郭清について，実際の手技上のポイントを紹介する．

Ⅰ．側方郭清の適応

1. Rb，cMP以深を適応としている

Rb，pMPでは，『大腸癌治療ガイドライン』(2010年版)で9％，筆者の前任施設である愛知県がんセンター中央病院で7.5％[1]，現施設の国立がん研究センター中央病院でも9.6％の転移を認めている．術前の深達度診断がSM癌以外は確実でないため(表1)，Rbではc MPから側方リンパ節郭清の適応としている．cMPでも実際にはpAである症例が混じるため，cMPの側方転移率は9.6％で，これを無視できない頻度と考えるか

キーワード：直腸癌，側方郭清，開腹手術，腹膜外アプローチ

* Techniques of lateral lymph node dissection for rectal cancer；open surgery

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