Efficacy of adjuvant chemotherapy after complete resection of pulmonary metastasis from colorectal cancer

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Abstract. The most effective treatment for pulmonary metastasis from colorectal cancer (CRC) is complete resection. However, as the recurrence rate after resection of the pulmonary metastases from CRC is high, postoperative adjuvant chemotherapy is often performed in clinical practice. The purpose of the present study was to evaluate the efficacy and safety of single-agent adjuvant chemotherapy after resection of pulmonary metastasis from CRC. The medical records of 16 patients who underwent the first complete resection of pulmonary metastasis from CRC were retrospectively reviewed. A total of eight patients were treated with single-agent adjuvant chemotherapy after resection of pulmonary metastasis, and oral fluoropyrimidines were selected in all regimens. As a result, the relapse-free survival rate after resection of pulmonary metastasis in the group that received postoperative adjuvant chemotherapy was significantly improved in comparison with the group treated with surgery alone. In the subgroup analysis, patients who benefited from postoperative adjuvant chemotherapy in some high-risk groups were selected, including patients with a high tumor stage or poor immunological status. In conclusion, single-agent adjuvant chemotherapy after resection of pulmonary metastasis from CRC was effective for reducing the risk of recurrence and was safe to administer. In addition, certain risk factors may identify patients who would receive more benefit from postoperative adjuvant chemotherapy after resection of pulmonary metastasis from CRC.

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Introduction

Pulmonary metastasis of colorectal cancer (CRC) is the second-most frequent type of metastasis after liver metastasis and has been reported to occur in 10-29% patients of CRC (1-7). Thus, the establishment of a treatment strategy for pulmonary metastasis from CRC is important. The resection of metastasis, radiofrequency ablation, systemic drug therapy and radiation treatments have been applied in the treatment of pulmonary metastasis from CRC. However, unlike other cancers, in CRC, there is a great deal of evidence to support that complete resection of metastasis leads to an improved prognosis in comparison to other treatments, including chemotherapy (7-10); thus, resection of pulmonary metastasis is considered the most effective treatment for metastasis from CRC and has been generally accepted as the only potentially curative treatment (9-14). However, it is difficult to say that surgery alone is a sufficient treatment, because the 5-year survival rate after complete resection of pulmonary metastasis from CRC is only 30-60% (15,16).

In clinical practice, adjuvant chemotherapy is often performed after resection of pulmonary metastasis from CRC and its effectiveness has been reported a number of times (17,18). However, the efficacy and safety of adjuvant chemotherapy after resection of pulmonary metastasis remain controversial, because its effectiveness has not been reported in any large clinical trials and the optimal regimen has not been described. The purpose of this study was to evaluate the efficacy or safety of single-agent adjuvant chemotherapy after complete resection of pulmonary metastasis from CRC.

Materials and methods

Patients and therapy. We retrospectively reviewed the medical records of 16 patients who underwent complete macroscopic and microscopic (R0) resection of pulmonary metastasis from CRC at Osaka City University Hospital between April 1998 and October 2019. All patients enrolled in this study had undergone resection of pulmonary metastasis for the first time. In all patients, the primary tumors were resected before surgical treatment for pulmonary metastasis. After the operation for primary tumor, contrast-enhanced computed tomography (CT) was performed routinely every six months. The details of

pulmonary metastases and the presence or absence of other distant metastases were evaluated by contrast-enhanced CT. Patients who had extrapulmonary metastasis were excluded from this study. It was defined that the pulmonary metastasis found at the resection of primary tumor as synchronous metastasis and the pulmonary metastasis found after the resection of primary tumor as metachronous metastasis.

Eight patients were treated with single-agent adjuvant chemotherapy after resection of pulmonary metastasis and oral fluoropyrimidines was selected in all regimens. The other 8 patients were treated with the resection of pulmonary metastasis alone. The administration period of postoperative single-agent adjuvant chemotherapy was 6 months. The decision as to whether or not postoperative adjuvant chemotherapy should be administered, and the selection of the regimen was at the discretion of the treating physician. We evaluated the correlation between relapse-free survival (RFS) rate after the first complete resection of pulmonary metastasis from CRC and postoperative adjuvant chemotherapy.

The feasibility of postoperative adjuvant chemotherapy was evaluated to calculate completion rate and relative dose intensity (RDI) and to investigate adverse events. Adverse events were graded using the Common Terminology Criteria for Adverse Events version 5.0 (19).

Classification of patients according to risk factors. In addition, a subgroup analysis of patients who were divided according to each clinicopathological factor was performed. We divided the patients into 2 groups according to sex, age and the risk (high or low) of some clinicopathological factors that were reported to be associated with the prognosis after resection of pulmonary metastasis of CRC. The clinicopathological factors included the primary T/N classification, as defined by the Union for International Cancer Control 8th edition (20,21), the timing of metastasis (metachronous or synchronous) (20,22), number of metastases (13,23), diameter of the metastatic tumors (23) and the carcinoembryonic antigen (CEA) level before the resection of pulmonary metastases (13,14,24,25). We also included the immunological prognostic factors for CRC that we have reported (26). These factors were the neutrophil-to-lymphocyte ratio (NLR), as a systemic inflammatory marker (27-29), and the density of tumor-infiltrating lymphocytes (TILs), which reflects the immunological status in the tumor microenvironment (26,30,31).

According to previous reports, patients with a CEA level of <5.0 mg/dl were classified into the CEA Low-group and those with a CEA level of ≥5.0 mg/dl were classified into the CEA High-group (14,23-25).

The NLR was calculated from a blood sample obtained within 2 weeks before pulmonary surgery by dividing the absolute neutrophil count by the absolute lymphocyte count. Based on the median value, patients were classified into the NLR-High or NLR-Low groups.

We set cluster of differentiation (CD)3 as the pan-T cell marker and CD8 as the cytotoxic T cell marker.

Regarding the immunohistochemistry protocol of CD3/CD8, all of the resected specimens of the pulmonary metastases from CRC were fixed in 10% buffered formalin and embedded in paraffin. Immunohistochemical staining was performed on 4-μm-thick sections. All of the sections were deparaffinized in xylene and dehydrated in decreasing concentrations of ethanol. The sections were then subjected to endogenous peroxidase blocking in 1% H_2O_2 solution in methanol for 15 min. Antigen retrieval was performed by autoclaving the sections at 105°C for 15 min in Dako Target Retrieval Solution (Dako; Agilent Technologies, Inc.). The serum blocking was performed with 10% normal rabbit serum for 10 min. All of the sections were incubated at 4 C overnight with the primary mouse monoclonal antibody CD3/CD8 (clone F7.2.38; Dako; dilution 1:400;/colon C8/144B, Dako; dilution 1:200). The secondary antibody was a biotin-labeled rabbit anti-mouse IgG, IgA, IgM for 10 min. All of the sections were labeled with the peroxidase-labeled streptavidin for 5 min. The 10% normal rabbit serum, biotin-labeled rabbit anti-mouse antibody and peroxidase-labeled streptavidin were included in the Histofine SAB-PO(M) kit (Nichirei Biosciences, Inc.) and used according to the protocol of the manufacturer. Detection was performed with the 3,3'-diaminobenzidine tetrahydrochloride kit (Histofine Simple Stain kit; Nichirei Biosciences, Inc.). All of the sections were counterstained with hematoxylin, dehydrated, cleared and mounted on glass coverslips.

Based on the approach in a previous report, the number of CD3$^+$TILs/CD8$^+$TILs at the invasive margin of the pulmonary metastases was counted in 5 randomly selected fields at a magnification of x400. The mean of the 5 values obtained was then used for the analysis (26).

To determine the appropriate cut-off value, we performed a receiver operating characteristic curve analysis. Based on the cut-off values, patients were classified into the TIL-high or TIL-low groups.

The association between RFS rate after resection of pulmonary metastasis and postoperative adjuvant chemotherapy was evaluated according to each risk factor.

Statistical analysis. Fisher's exact test and Mann-Whitney U test were used to analyze the significance of the association among the background factors between surgery alone and adjuvant chemotherapy. RFS was defined as the interval between the date of resection of pulmonary metastasis and the date of the diagnosis of the first recurrence, death from any cause or last follow-up. Survival curves were made using the Kaplan-Meier method. Differences in survival curves were assessed using the log-rank test. A multivariate Cox proportional hazards model was used to evaluate the prognostic factors associated with the RFS. The factors with P-values of <0.10 on the univariate analysis were included in the multivariate analysis.

All statistical analyses were performed using JMP 14.2.0 (SAS Institute). P-values of <0.05 were considered to indicate statistical significance.

Ethical considerations. This retrospective study was approved by the Ethics Committee of Osaka City University (approval no. 2020-026) and conducted in accordance with the Declaration of Helsinki. All patients provided their written informed consent.

Results

Patient characteristics. The patient characteristics are summarized in Table I. The study cohort included

10 males and 6 females, with a median age of 69.5 years (range=57-84 years). The primary tumor site was located on the right in 2 patients (from the cecum to transverse colon) on the left in 14 patients (from descending colon to rectum). The T factor of the primary tumor was T1-T3 in 11 patients and T4 in 5 patients. The N factor of the primary tumor was N0 in 7 patients and N1-N3 in 9 patients. The histological type of 16 patients was well or moderately differentiated adenocarcinoma. Six patients had synchronous pulmonary metastasis and 10 patients had metachronous pulmonary metastasis. Regarding distant metastases other than pulmonary metastases, six patients had a history of liver metastases, all of whom had undergone curative resection of liver metastases before resection of pulmonary metastases. Three patients had received preoperative chemotherapy for pulmonary metastases, and two of them had undergone hepatectomy followed by pulmonary resection after chemotherapy for simultaneous liver and pulmonary metastases. Three patients had K-RAS wild-type, two patients had K-RAS mutant-type, and the other patients had no data. BRAF mutations were not evaluated in any patients. One patient had undergone chemotherapy with the addition of a molecular-targeted drug before resection of pulmonary metastasis. Fifteen patients had pulmonary metastasis in one lung field and one patient had pulmonary metastasis in both lung fields. Ten patients had only one lesion of pulmonary metastasis and 6 patients had 2 or more lesions. The maximum diameter of pulmonary metastasis was <20 mm in 11 patients and ≥20 mm in 5 patients. The CEA level within 2 weeks before the resection of pulmonary metastasis was ≤5 ng/ml in 11 patients and >5 ng/ml in 5 patients. The median NLR was 1.89, and the value was ≤18.9 in 8 patients and >18.9 in 8 patients.

Eight patients were treated with surgery alone and 8 were treated with surgery and postoperative single-agent adjuvant chemotherapy. The regimens were oral agents with fluoropyrimidines as follows: tegafur-uracil and leucovorin (n=4); capecitabine (n=2); and S-1 (n=2). As no particular complications were observed after lung resection, no patients had delayed initiation of adjuvant chemotherapy due to complications. Three patients had undergone chemotherapy with the addition of a molecular-targeted drug after recurrence that occurred after resection of pulmonary metastases.

There was a significant male and low-NLR predominance among patients who received postoperative adjuvant chemotherapy (P=0.039, P=0.046, respectively). The other patient characteristics of the surgery alone and postoperative adjuvant chemotherapy groups did not differ to a statistically significant extent (Table I).

Eleven patients (68.8%) had recurrence, and the 5-year RFS rate after complete resection of pulmonary metastasis from CRC was 22.6%. In the 11 patients, the types of recurrence after resection of pulmonary metastasis were as follows: pulmonary metastasis (n=6); peritoneal metastasis (n=2); lymph node metastasis (n=2); and hepatic metastasis (n=1).

The correlation between RFS rate and postoperative adjuvant chemotherapy. In the group that received postoperative adjuvant chemotherapy RFS rate was significantly improved in comparison to the surgery alone group (P=0.024) (Fig. 1).
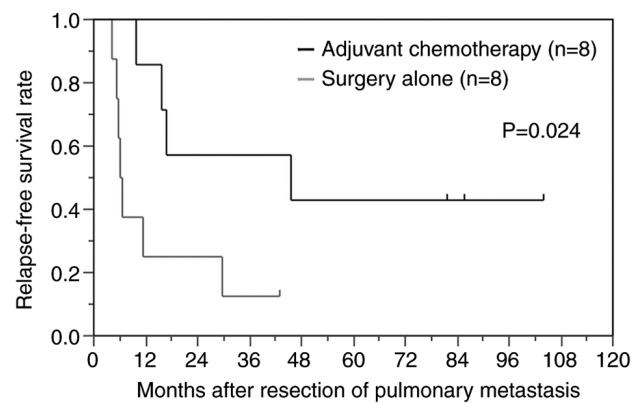

Figure 1. Kaplan-Meier survival curve for relapse-free survival. Curves calculated after complete resection of pulmonary metastasis of colorectal cancer, according to the single-agent adjuvant chemotherapy regimen of 16 patients.

Cut-off value for the number of positive TILs. The number of positive TILs, which was a continuous variable, was used as the test variable and the occurrence of recurrence after the complete resection of pulmonary metastases was used as the state variable. When the cut-off value for the number of positive TILs was investigated using the ROC curve, the appropriate cut-off value for the CD3$^+$TILs was 13.6 (sensitivity of 63.6%; specificity of 100.0%) (Fig. 2A). Using the ROC curve in the same manner, the cut-off value for the CD8$^+$TILs was set at 21.0 (sensitivity of 100.0%; specificity of 40.0%) (Fig. 2B). With each of these values set as the cut-off value, the patients were classified into respective high and low groups.

Evaluation of prognostic factors for RFS. The correlation was evaluated between RFS and the prognostic factors, such as sex, the timing of the detection of metastasis, the number of pulmonary metastases, the location of pulmonary metastasis, the size of pulmonary metastasis, the CEA value before resection of pulmonary metastasis, whether or not postoperative adjuvant chemotherapy had been performed, the NLR and the CD3/CD8$^+$ TIL density. According to a univariate analysis, the RFS after resection of pulmonary metastasis in the male group, the ≥2 pulmonary metastases group, the surgery alone group and the low-CD3$^+$TIL group was significantly shorter than in the female group, the single pulmonary metastasis group, the adjuvant chemotherapy group and the high-CD3$^+$TIL group (P=0.044, P=0.007, P=0.028, P=0.019, respectively). The multivariate analysis indicated that the number of pulmonary metastases, and the postoperative adjuvant chemotherapy and the density of CD3$^+$ TILs were independent prognostic factors for RFS (P=0.001, P=0.002, P=0.010, respectively) (Table II).

Feasibility and adverse events in patients who received postoperative adjuvant chemotherapy. The completion rate of the 8 patients who received adjuvant chemotherapy was 100.0% and the median RDI of adjuvant chemotherapy in these 8 patients was 100.0%. Some adverse events were occurred, including fatigue (n=2), hand and foot syndrome (n=1) and oral mucositis (n=1). However, no patients experienced grade 3-5 adverse events (Table III).

Table I. Association of backgrounds between surgery alone and adjuvant chemotherapy.

Preoperative patient characteristics (n=16)	Surgery alone (n=8) (%)	Adjuvant chemotherapy (n=8) (%)	P-value
Sex, n (%)			
Male	3 (37.5)	7 (87.5)	0.039
Female	5 (62.5)	1 (12.5)	
Median age, years (range)	74 (61-84)	66.5 (57-77)	0.247
Location of primary tumor, n (%)			
Right colon	0 (0)	2 (25.0)	0.131
Left colon and rectum	8 (100)	6 (75.0)	
Primary T status, n (%)			
≤T3	5 (62.5)	6 (75.0)	0.59
T4	3 (37.5)	2 (25.0)	
Lymph node metastasis of primary tumor, n (%)			
N0	3 (37.5)	4 (50.0)	0.614
≥N1	5 (62.5)	4 (50.0)	
Histological type of primary tumor, n (%)			
Well/Moderately differentiated adenocarcinoma	8 (100)	8 (100)	>0.999
Poorly differentiated/mucinous adenocarcinoma	0 (0)	0 (0)	
Detection of pulmonary metastases, n (%)			
Metachronous	5 (62.5)	5 (62.5)	>0.999
Synchronous	3 (37.5)	3 (37.5)	
History of resection of liver metastases before the resection pulmonary metastases, n (%)			
No	4 (50.0)	6 (75.0)	0.302
Yes	4 (50.0)	2 (25.0)	
History of chemotherapy for the pulmonary metastases before the resection pulmonary metastases, n (%)			
No	7 (87.5)	6 (75.0)	0.521
Yes	1 (12.5)	2 (25.0)	
Location of pulmonary metastases, n (%)			
One lung field	7 (87.5)	8 (100)	0.302
Both lung fields	1 (12.5)	0 (0)	
Number of pulmonary metastases, n (%)			
1	4 (50.0)	6 (75.0)	0.302
≥2	4 (50.0)	2 (25.0)	
Maximum diameter of pulmonary metastases, n (%)			
<20 mm	4 (50.0)	7 (87.5)	0.106
≥20 mm	4 (50.0)	1 (12.5)	
Method of resection of pulmonary metastases, n (%)			
Segmentectomy	7 (87.5)	8 (100)	0.302
Lobectomy	1 (12.5)	0 (0)	
CEA level before resection of pulmonary metastases, n (%)			
≤5 ng/ml	5 (62.5)	6 (75.0)	0.59
>5 ng/ml	3 (37.5)	2 (25.0)	
Neutrophil-to-lymphocyte ratio before the resection of pulmonary metastases, n (%)			
≤1.89	2 (25.0)	6 (75.0)	0.046
>1.89	6 (75.0)	2 (25.0)	

CEA, carcinoembryonic antigen.

Table II. Correlations between relapse-free survival and clinicopathological factors.

Clinicopathological factors	Univariate analysis			Multivariate analysis		
	HR	95% CI	P-value	HR	95% CI	P-value
Sex (Male vs. Female)	0.268	0.067-0.964	0.044	1.477	0.271-10.88	0.655
Detection of pulmonary metastases Synchronous vs. Metachronous	0.490	0.107-1.703	0.272			
Location of pulmonary metastases One lung field vs. both lung fields	6.984	0.325-72.95	0.172			
Number of pulmonary metastases 1 vs. ≥2	6.559	1.690-31.63	0.007	30.93	3.193-1205.6	0.001
Maximum diameter of pulmonary metastases <20.0 mm vs. ≥20.0 mm	1.328	0.347-4.418	0.656			
CEA level before resection of pulmonary metastases ≤5.0 ng/ml vs. >5.0 ng/ml	1.434	0.373-4.796	0.575			
Treatment performed to pulmonary metastases Surgery alone vs. single-agent adjuvant chemotherapy after resection	0.234	0.050-0.855	0.028	0.026	0.001-0.285	0.002
NLR before resection of pulmonary metastases ≤18.9 vs. >18.9	1.448	0.434-5.043	0.542			
Density of CD3$^+$ TILs of pulmonary metastasis >13.6 vs. ≤13.6	4.402	1.282-17.32	0.019	16.08	1.830-415.9	0.010
Density of CD8$^+$ TILs of pulmonary metastasis >21.0 vs. ≤21.0	3.509	0.667-64.54	0.158			

HR, hazard ratio; CI, confidence interval; CEA, carcinoembryonic antigen; NLR, neutrophil-to-lymphocyte ratio; TILs, tumor-infiltrating lymphocytes.

The effectiveness of postoperative adjuvant chemotherapy for suppressing recurrence according to each risk factor. In the subgroups of patients who were positive for lymph node metastasis of the primary tumor, patients with 2 or more pulmonary metastases and patients with a low density of CD3$^+$TILs or a low density of CD8$^+$TILs at the site of pulmonary metastasis, postoperative adjuvant chemotherapy significantly reduced the risk of recurrence in comparison to surgery alone (P=0.017; 0.049; 0.025; 0.008, respectively). In the subgroups of patients with a high NLR(>1.89), postoperative adjuvant chemotherapy tended to reduce the risk of recurrence in comparison to surgery alone (P=0.092) (Fig. 3).

Discussion

In cases of distant metastasis from CRC, unlike other cancers, the complete resection of distant metastasis is reported to improve the prognosis in comparison to chemotherapy. Thus, the resection of metastasis from CRC has been performed positively (7-10). However, the recurrence rate after complete resection of distant metastasis from CRC was comparatively high, thus, postoperative adjuvant chemotherapy has been often performed in clinical practice.

Regarding adjuvant chemotherapy after complete resection of pulmonary metastasis from CRC, some studies reported that it was effective for suppressing recurrence and prolonging

Table III. Feasibility and adverse event of postoperative single-agent adjuvant chemotherapy in eight patients.

Parameter	Patients
Feasibility	
Completion rate, %	100%
Median relative dose intensity, % (range)	100% (75.0-100.0%)
Adverse event, grade 1-2, n (%)	
Fatigue	2 (25.0%)
Oral mucositis	1 (12.5%)
Hand and foot syndrome	1 (12.5%)

the prognosis (17,18). On the other hand, other studies reported that it was not effective (32,33). The reason why the results can be different between cohorts for the adjuvant chemotherapy after resection of pulmonary metastases of colorectal cancer was considered to be the difference of regimen. In the existing reports, the single-agent adjuvant chemotherapy regimen and the combination adjuvant chemotherapy regimen were evaluated simultaneously, and the percentage of these regimen were different in each cohort. In addition, there have
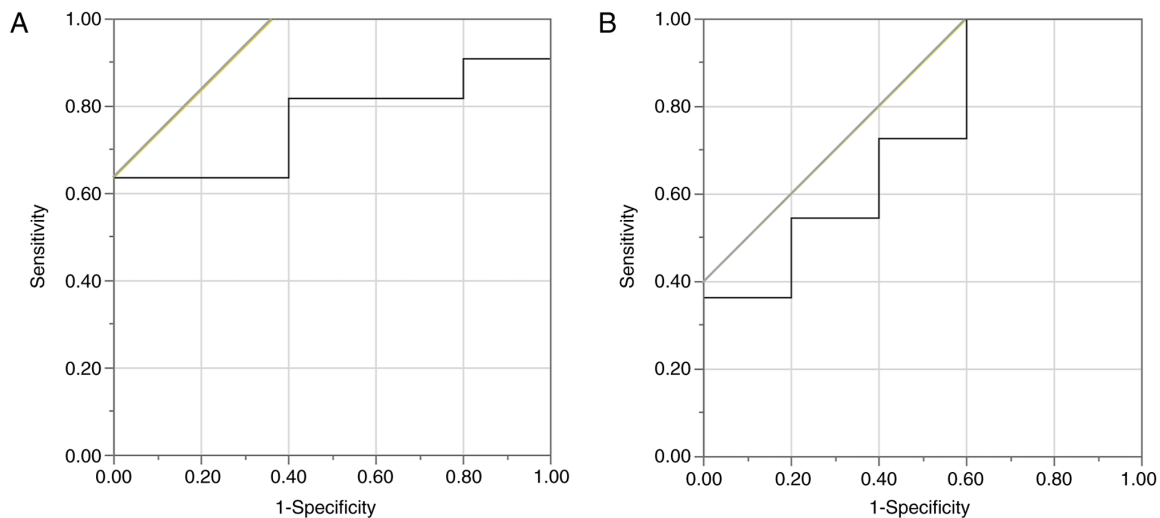
Figure 2. Receiver operating characteristic curves of the number of tumor-infiltrating lymphocytes and relapse-free survival status after resection of pulmonary metastases. (A) Receiver operating characteristic curve of the number of CD3^{+} tumor-infiltrating lymphocytes and relapse-free survival status after resection of pulmonary metastases. Area under the curve=0.764; 95% confidence interval=0.459-0.925; P=0.194. (B) Receiver operating characteristic curve of the number of CD8^{+}tumor-infiltrating lymphocytes and relapse-free survival status after resection of pulmonary metastases. Area under the curve=0.727; 95% confidence interval=0.383-0.920; P=0.117.

been no reports based on the results of large clinical trials; thus, the efficacy of adjuvant chemotherapy after resection of pulmonary metastasis from CRC has remained controversial. Therefore, in clinical practice, the indication and regimen of adjuvant chemotherapy largely depends on the judgment of the individual physician.

In this study, RFS rate was significantly improved in the group that received single-agent fluoropyrimidine adjuvant chemotherapy after resection of pulmonary metastasis. With the exception of sex and the NLR, the patient characteristics of the adjuvant chemotherapy and surgery alone groups did not differ to a statistically significant extent; thus, the postoperative adjuvant chemotherapy was correlated with the extension of the prognosis. In addition, the rate of incidences of adverse events was not high and no Grade 3-5 adverse events were occurred. Thus, the tolerability of single-agent adjuvant chemotherapy after resection of pulmonary metastasis from CRC was considered acceptable.

It has been reported that single-agent adjuvant chemotherapy was effective for suppressing recurrence not only after complete resection of primary CRC (34) but also after complete resection of hepatic metastasis from CRC (35). Similarly, in this study, in patients with pulmonary metastasis of CRC, the RFS rate of patients who received single-agent adjuvant chemotherapy with fluoropyrimidines was significantly improved. Thus, it was suggested that even single-agent adjuvant chemotherapy reduced the risk of recurrence. Additionally, single-agent adjuvant chemotherapy was associated with few adverse events and was safe to administer to patients with decreased physical strength after resection of pulmonary metastasis. Therefore, it was suggested that single-agent adjuvant chemotherapy was one of the treatment options after complete resection of pulmonary metastasis from CRC.

Okumura *et al* reported that the efficacy of adjuvant chemotherapy after resection of pulmonary metastasis tended to be recognized by the risk classification and limitation of the patients who are likely to benefit from

postoperative adjuvant chemotherapy (36). We hypothesize that the fact that postoperative adjuvant chemotherapy was performed without considering the risk classifications and limitations of patients is one of the reasons why the prognosis was not effectively prolonged by postoperative adjuvant chemotherapy in the previous reports. Even in our small study population, we found that some subgroups of patients with risk factors of recurrence based on patient clinicopathological or immunological factors may receive more benefit from adjuvant chemotherapy after resection of pulmonary metastasis. As systemic inflammation or a poor local immune status provide a favorable environment for the development of micrometastases (37-40), the risk of recurrence after the resection of pulmonary metastases increases in high NLR patients or in low density TILs patients (26). Therefore, the risk classification according to the status of immunological biomarkers as well as the risk factors of recurrence, which have been described in previous reports, may help in the patient selection process to identify those who will most benefit from postoperative adjuvant chemotherapy.

The present study was associated with some limitations. First, this was a retrospective study with a relatively small population of patients who were treated at a single institution. A prospective study in multiple institutions with an increased number of patients is considered necessary. Second, the prognosis was only evaluated by RFS rate. This was because the chemotherapies used to treat recurrence after complete resection of pulmonary metastasis have changed over the past 20 years with the development of oxaliplatin, irinotecan and molecular targeted drugs; thus, overall survival rate was difficult to evaluate. Third, the treatment methods were not unified because the decision of whether to perform postoperative adjuvant chemotherapy was made by the attending physician. Fourth, in this study, no patients received combination adjuvant chemotherapy and the difference in the effectiveness or safety between
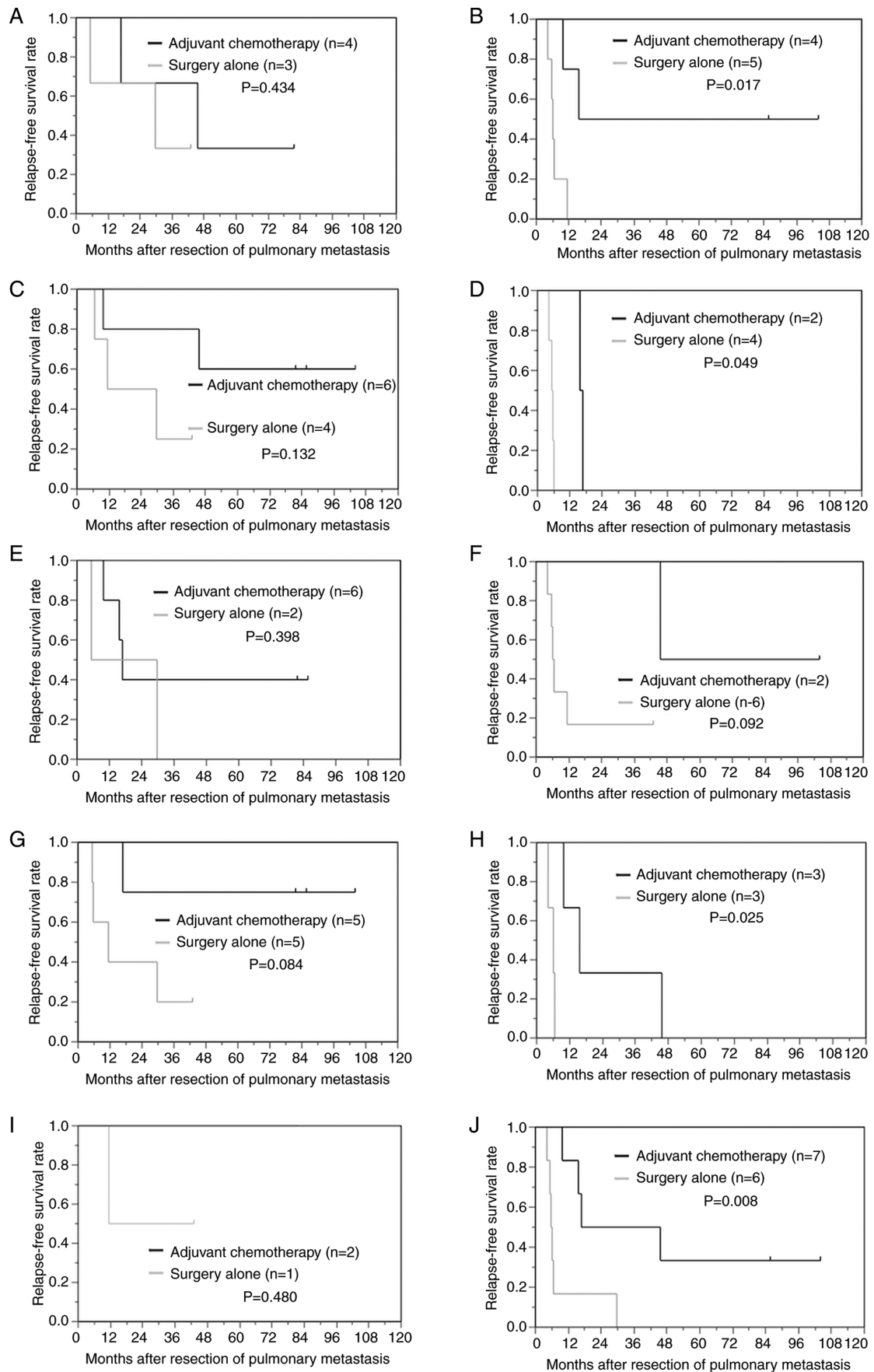
Figure 3. Kaplan-Meier survival curves for relapse-free survival after complete resection of pulmonary metastasis of colorectal cancer according to the single-agent postoperative adjuvant chemotherapy regimen in subgroups divided according to each clinicopathological factor. (A) Primary N status, N0. (B) Primary N status, N1-3. (C) Number of pulmonary metastases=1. (D) Number of pulmonary metastases=≥2. (E) Neutrophil-to-lymphocyte ratio ≤ median. (F) Neutrophil-to-lymphocyte ratio > median. (G) High density of CD3^{+} tumor-infiltrating lymphocytes group. (H) Low density of CD3^{+} tumor-infiltrating lymphocytes. (I) High density of CD8^{+} tumor-infiltrating lymphocytes. (J) Low density of CD8^{+} tumor-infiltrating lymphocytes.

single-agent adjuvant chemotherapy and combination adjuvant chemotherapy was not compared.

A large prospective study is necessary to identify patients who will be benefit from postoperative adjuvant chemotherapy and to determine the most effective regimen.

In conclusion, single-agent adjuvant chemotherapy after the resection of pulmonary metastasis from CRC was effective for reducing the risk of recurrence and was safe to administer. In addition, certain risk classifications based on clinicopathological factors, including immunological markers, may be useful for identifying patients who would receive more benefit from adjuvant chemotherapy after resection of pulmonary metastasis from CRC.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

YO designed the study, performed the statistical analysis and drafted the manuscript. MS designed the study and assisted in writing the manuscript. EW, HN, TF and YI collected the clinical data and revised the manuscript critically. YO, MS and EW confirm the authenticity of all the raw data. KM, KH and MO assisted with designing the study and critically reviewed the manuscript. All the authors have read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Osaka City University (approval no. 2020-026) and all patients provided their written informed consent. All procedures performed in studies involving human participants were in accordance with the Declaration of Helsinki.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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