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Original Research

Efficacy of adjuvant chemotherapy after resection of pulmonary metastasis from colorectal cancer: a propensity score–matched analysis

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KEYWORDS
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Abstract ***Background:*** Pulmonary metastases from colorectal cancer are resected due to the favourable 5-year overall survival rates of 30–60% reported in many studies. However, the efficacy of subsequent adjuvant chemotherapy remains unclear.

Patient and methods: We retrospectively collected clinical data of 1237 patients who underwent surgical resection of pulmonary metastasis from colorectal cancer at 46 Japanese institutions between 2004 and 2008. Patients with non-curative resection, pre-operative chemotherapy, extra-thoracic metastasis, complications after surgery, and inadequate data were excluded. Then, a 1:1 propensity score nearest-neighbour matching between patients with and without adjuvant chemotherapy was performed, considering relevant co-variables, and survival of patients between groups was compared.

Results: Data of 524 patients (surgery alone, 269 patients; surgery with adjuvant chemotherapy, 255 patients) were used for matching. From each group, 192 patients with similar background characteristics between groups were selected. Adjuvant chemotherapies included

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fluoropyrimidine alone (71%), an oxaliplatin-containing regimen (23%), or an irinotecan-containing regimen (6%). In the surgery alone and adjuvant chemotherapy groups, 5-year overall survival rates were 68% and 69%, and 5-year disease-free survival rates were 40% and 34%, respectively. There were no significant differences between the two groups in terms of overall survival (hazard ratio [HR]: 1.00, 95% confidence interval [CI]: 0.69–1.45, P = 1.00) and disease-free survival (HR: 1.07, 95% CI: 0.82–1.39, P = 0.62).

Conclusions: Adjuvant chemotherapy after curative resection of lung-limited metastasis from colorectal cancer did not show a survival benefit in the propensity score–matched analysis and should not be recommended without further clinical trials.

1. Introduction

Pulmonary metastasis (PM), the second most common organ metastasis from colorectal cancer (CRC) after liver metastasis, accounts for 10–29% of metastatic CRC cases [1–4]. The incidence of synchronous PM in CRC patients was reported at approximately 2–3% [5,6], while PM from rectal cancer is 1.5-fold higher than that of colon cancer [7].

The 5-year survival rates after curative resection of PM from CRC have been reported at approximately 30–60% in several retrospective studies [3,8,9] and reached over 70% in those with good prognostic factors [9,10]. From systematic reviews and meta-analyses, the good prognostic factors related to the resection of PM include long disease-free interval (DFI) between primary tumour resection and appearance of PM, normal serum carcinoembryonic antigen (CEA) level, absence of thoracic node involvement and other organ metastases and solitary pulmonary lesion [9]. Metastasectomy is recommended as a practical treatment option for resectable PM from CRC especially with good prognostic factors, although there are no prospective or randomised controlled studies to corroborate these findings. Moreover, the efficacy of adjuvant chemotherapy after curative resection of PM from CRC is still unclear, although adjuvant chemotherapy is often used with an expectation of similar significant survival benefit following the use of adjuvant chemotherapy for stage III colon cancer [11–13] as well as the marginal efficacy of adjuvant or perioperative chemotherapy after the resection of liver metastases [14,15].

Our previous retrospective study suggested no survival benefit of adjuvant chemotherapy in 785 patients who underwent curative resection of PM from CRC [10]; however, that study included possible biases such as differences in the patients' background characteristics between the surgery alone group and the surgery followed by adjuvant chemotherapy group. To minimise those biases in this study, we selected patients with lung-limited metastases from the previous study cohort and adjusted for patients' background characteristics between the two groups using a propensity score matching method. Then we investigated the significance of adjuvant chemotherapy after curative resection of PM-CRC in the matched cohort.

2. Methods

2.1. Patients

Initially, we retrospectively collected clinical data of 1237 patients who underwent surgical metastasectomy for PM from CRC at 46 Japanese institutions from January 2004 to December 2008. We set this study period because the use of infusional 5-fluorouracil (5-FU) with leucovorin plus irinotecan or oxaliplatin was approved for treatment of metastatic CRC in 2004 in Japan.

The main inclusion criteria for the original cohort [10] were as follows: (1) first resection of PM from CRC, (2) clinically and pathologically assessed curative resection (R0), (3) pathological confirmation of PM from CRC, (4) no pre-operative chemotherapy and (5) curative treatment of extrathoracic lesions including the primary tumour. The exclusion criterion was history of malignancies other than CRC. Additionally, for this study, we excluded from the original cohort: (1) patients in poor general condition (the Eastern Cooperative Oncology Group performance status of $\geq$2), (2) patients with extrathoracic metastatic lesions except for the primary site and regional lymph node metastasis and (3) patients with major surgical complications in order to estimate the efficacy of adjuvant chemotherapy accurately. To minimise bias in this study, we selected patients with lung-limited metastases from our previous study cohort and adjusted for the patients' background characteristics between the two groups using a propensity score matching method.

This study was approved by the ethical committees of all participating institutions and was conducted according to the Ethical Guidelines for Epidemiological Research in Japan. The requirement of informed consent was waived owing to the retrospective nature of the study.

2.2. Data collection

The detailed process of data collection has been described in our previous study [10]. Briefly, clinical data from the pre-specified case report forms for all patients fulfilling the criteria were sent to the data office of the Tsukuba Cancer Clinical Trial Group. The collected data were as follows: gender, age, Eastern Cooperative Oncology Group performance status, serum CEA level, primary tumour site, stage, date of primary surgery, type of surgery, pre-operative/perioperative/post-operative chemotherapy, extrathoracic lesions and their curability, date of PM detection, number of PM, laterality and maximum diameter of the tumour, date and surgical procedure of pulmonary metastasectomy, extent of lymph node dissection, regional lymph node metastasis from PM originating from CRC, post-operative complications, completeness of pulmonary resection and other treatments, date of recurrence or last confirmation of disease-free status, sites of recurrence after resection of PM from CRC and date of death or last confirmed survival.

2.3. Statistical analysis

Overall survival (OS) was defined as the time between the date of pulmonary metastasectomy and that of death from any cause, and surviving patients were censored at the date of the last follow-up. Disease-free survival (DFS) was defined as the time between the date of pulmonary metastasectomy and that of recurrence or death, and surviving patients without recurrence were censored at the date of the last follow-up. DFI was defined as the time between the date of the primary tumour resection and that of the first detection of PM by imaging. If the primary cancer was simultaneously detected with PM or after pulmonary metastasectomy, the DFI was considered to be '0'.

The propensity score was calculated using a multivariable logistic regression model including 13 variables (number of PM, DFI, synchronicity of PM with the primary tumour [synchronous metastasis was defined as metastasis resected within 3 months of primary tumour resection], serum CEA level, laterality of PM and maximum tumour size of PM, as prognostic factors of OS, which were previously reported in CRC patients who underwent pulmonary metastasectomy [9,16–18], as well as the location of primary tumour and surgical procedure for resection, as prognostic factors of DFS after metastasectomy of CRC [9,19]. In addition, age, gender, performance status, regional lymph node metastasis of the primary tumour and adjuvant chemotherapy after resection of the primary tumour, as common prognostic factors of stage IV CRC). A 1:1 propensity score matching was performed using the nearest-neighbour matching method. For the univariable comparisons of background factors, Mann–Whitney U test was used for continuous variables including age, DFI and tumour size. A chi-square test was used for other variables. Survival was compared using the log-rank test. Multivariable Cox proportional regression analysis was performed to identify independent prognostic factors of DFS and OS.

Statistical significance was set at $P < 0.05$ for all tests. Data analyses were conducted using SAS, version 9.4 (SAS Institute Inc., Cary, MC, USA) and SPSS, version 24.0 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Patients' characteristics

Among 1237 patients who underwent metastasectomy for PM from CRC, we excluded patients who had pre-operative chemotherapy (n = 232), extrathoracic lesions or unknown (n = 187), non-curative PM resection (n = 116), surgical complications (n = 64), inadequate follow-up (n = 47), ineligible time of resection (n = 34) and other reasons for exclusion (n = 35; Fig. 1). As a result, 524 patients were included in this study. After a 1:1 propensity score matching, 384 patients were selected: 192 patients with surgery alone (S group) and

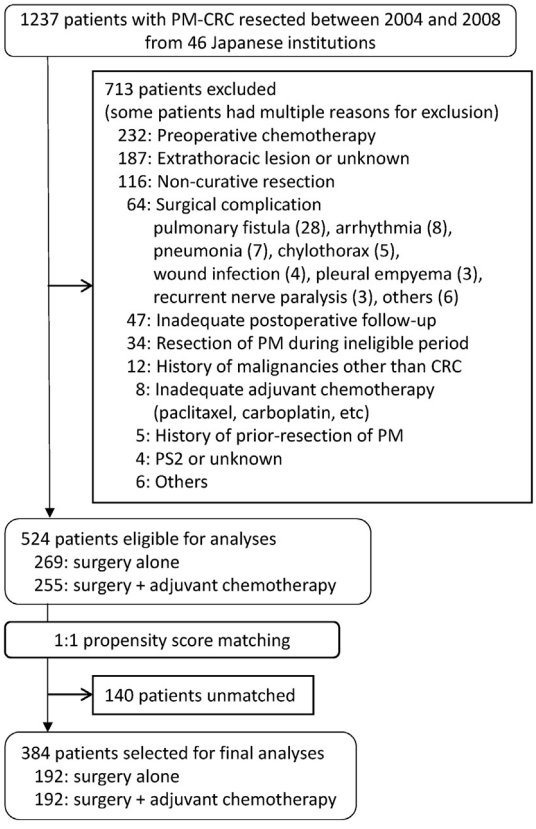

Fig. 1. Flowchart of patients' selection for analysis. PM-CRC, pulmonary metastases from colorectal cancer; PS, performance status.

192 patients with surgery followed by adjuvant chemotherapy (A group; Fig. 1). Patients' background characteristics were well balanced without significant differences between the two matched groups (Table 1 and Supplemental Fig. 1). In the A group, 136 patients (71%) received adjuvant chemotherapy with fluoropyrimidine monotherapy such as bolus 5-FU plus leucovorin (n = 20), continuous 5-FU (n = 4), tegafur-uracil plus leucovorin (n = 48), tegafur-uracil (n = 20), S-1 (n = 32), capecitabine (n = 6) and doxifluridine (n = 6) after resection of PM. The remaining 56 patients (29%) received adjuvant chemotherapy with fluoropyrimidine combined with oxaliplatin (n = 44) or irinotecan (n = 12).

3.2. OS and DFS

The median duration of follow-up in the matched 384 patients was 4.5 years (range, 0.02–9.0 years). A total of 56 patients in the S group and 58 patients in the A group died during the study. The median OS was not reached in the S group and that was 8.0 years in the A group. There was no difference in the OS between the two groups (hazard ratio [HR]: 1.00; 95% confidence interval [CI]: 0.69–1.45; P = 1.00; Fig. 2A). Disease recurrence or death occurred in 108 patients of the S group and in 119 patients of the A group. The median DFS was 2.2 years in the S group and 2.1 years in the A group. There was no difference in DFS between the two groups (HR: 1.07; 95% CI: 0.82–1.39; P = 0.62; Fig. 2B). The 5-year

Table 1
Patients' characteristics.

Characteristic	Before matching (n = 524)			After matching (n = 384)		
	Surgery alone n = 269	Surgery plus adjuvant chemotherapy n = 255	P[a]	Surgery alone n = 192	Surgery plus adjuvant chemotherapy n = 192	P[a]
	n (%)	*n* (%)		*n* (%)	*n* (%)	
Age, y						
Median, range	68, 32–87	64, 29–85	0.002	67, 32–87	65, 29–85	0.45
Sex						
Male/female	157 (58)/112 (42)	132 (52)/123 (48)	0.13	104 (54)/88 (46)	108 (56)/84 (44)	0.68
ECOG PS						
0/1	250 (93)/19 (7)	244 (96)/11 (4)	0.18	184 (96)/8 (4)	182 (95)/10 (5)	0.63
Location of primary tumour						
Colon/rectum	119 (44)/150 (56)	106 (42)/149 (58)	0.54	79 (41)/113 (59)	79 (41)/113 (59)	1.00
Regional LN metastasis of primary tumour						
Absent/present/unknown	97 (36)/154 (57)/18 (7)	97 (38)/148 (58)/10 (4)	0.36	76 (40)/116 (60)/0 (0)	68 (35)/124 (65)/0 (0)	0.40
Adjuvant chemotherapy after resection of primary tumour			0.003			0.84
None	163 (61)	127 (50)		106 (55)	104 (54)	
Adjuvant for primary resection	95 (35)	126 (49)		86 (45)	88 (46)	
Fluoropyrimidine	87	117		79	83	
Oxaliplatin-based	0	3		0	2	
Irinotecan-based	5	2		4	0	
Others	3	4		3	3	
Unknown	11 (4)	2 (1)		0 (0)	0 (0)	
Disease-free interval (d)						
Median, range	554, 0–5815	540, 0–3333	0.15	517, 0–5815	559, 0–3333	0.75
<2 y/≥2 y	170 (63)/99 (37)	156 (61)/99 (39)	0.77	129 (67)/63 (33)	116 (60)/76 (40)	0.17
Tumour status						
Synchronous/metachronous	23 (9)/246 (92)	39 (15)/216 (85)	0.02	21 (11)/171 (89)	24 (13)/168 (87)	0.63
Serum CEA level						
<5 ng/ml/≥5 ng/ml/unknown	177 (66)/89 (33)/3 (1)	161 (63)/91 (35)/3 (2)	0.53	127 (66)/65 (34)/0 (0)	121 (63)/71 (37)/0 (0)	0.52
Site of pulmonary metastasis						
Unilateral/bilateral	244 (91)/25 (9)	229 (90)/26 (10)	0.73	173 (90)/19 (10)	174 (91)/18 (9)	0.86
Radiological number of pulmonary lesions						
Range	1–7	1–6		1–7	1–6	
Solitary/multiple	202 (75)/67 (25)	197 (77)/58 (23)	0.56	149 (78)/43 (22)	152 (79)/40 (21)	0.71
Mode of pulmonary resection						
Wedge resection/segmentectomy/lobectomy or larger	166 (62)/34 (13)/69 (25)	152 (60)/31 (12)/72 (28)	0.80	117 (61)/24 (12)/51 (27)	119 (62)/22 (11)/51 (27)	0.95
Pathologic maximum tumour size (mm)						
Median, range	18, 5–72	17, 5–58	0.17	18, 5–72	16.5, 5–58	0.11

ECOG PS = the Eastern Cooperative Oncology Group performance status; LN = lymph node; CEA = carcinoembryonic antigen.
[a] P values for categorical and continuous characteristics were calculated by Chi-square and Mann–Whitney U tests, respectively.

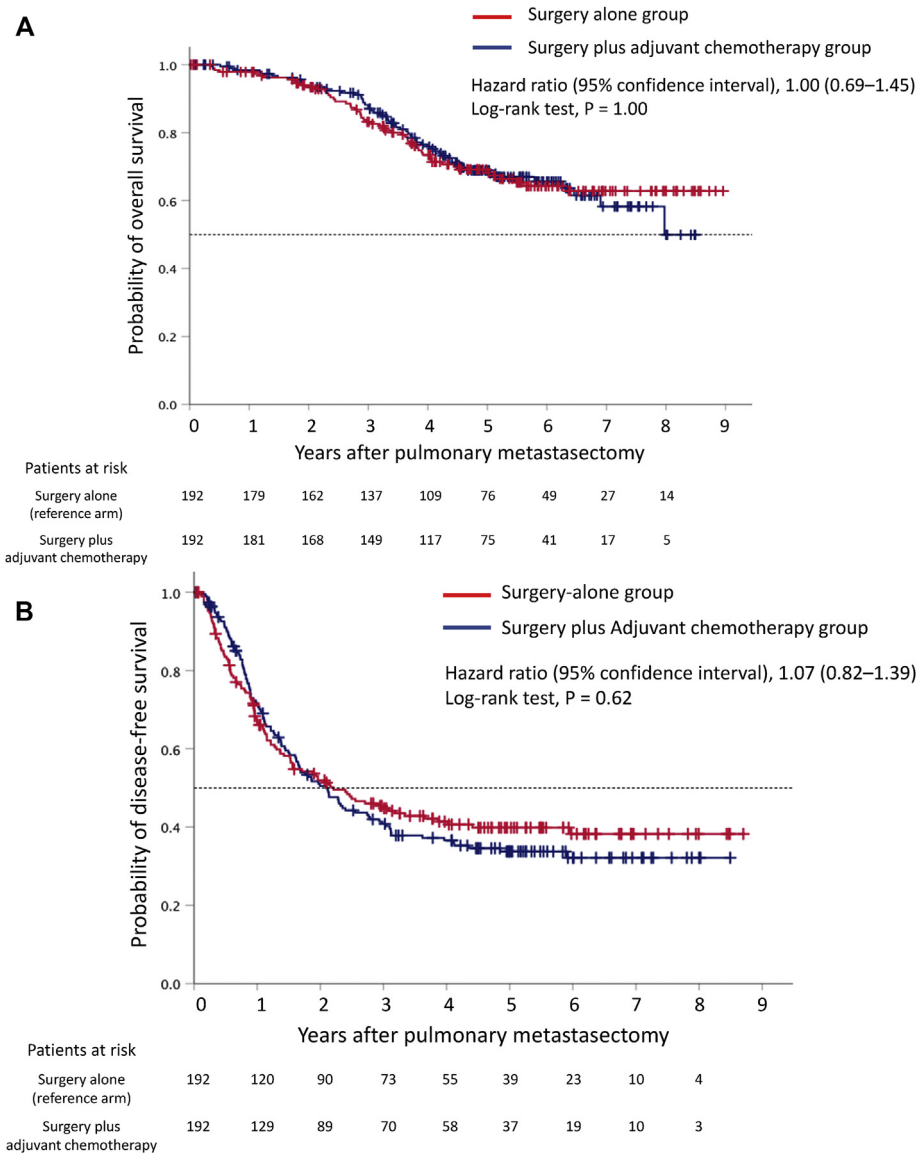

Fig. 2. Kaplan–Meier curve of overall survival (A) and disease-free survival (B) after resection of pulmonary metastases from colorectal cancer. Red line indicates the surgery-alone group, while the blue line indicates the surgery plus adjuvant chemotherapy group.

OS rates were 68% and 69%, while the 5-year DFS rates were 40% and 34% in the S and A groups, respectively.

In the subgroup analyses for OS (Fig. 3A) and DFS (Fig. 3B), there were no significant interactions between the patients' background characteristics and treatment groups.

3.3. Multivariable analysis for prognostic factors

Multivariable analyses were performed to explore the prognostic factors for OS and DFS in this propensity score–matched cohort. Age (<70 versus. ≥70 years; HR: 1.54; 95% CI: 1.06–2.24; P = 0.023), regional lymph node metastasis of the primary tumour (absent versus. present; HR: 1.53; 95% CI: 1.02–2.29; P = 0.041), DFI (≥2 versus. <2 years; HR: 1.78; 95% CI: 1.17–2.73; P = 0.008), number of PM (1 versus. ≥2; HR: 1.52; 95% CI: 1.00–2.30; P = 0.049) and serum CEA level (<5 versus. ≥5 ng/ml; HR: 2.24; 95% CI: 1.54–3.25; P < 0.001) were identified to be independent prognostic factors of OS (Fig. 4A). The serum CEA level (<5 versus. ≥5 ng/ml; HR: 1.47; 95% CI: 1.12–1.92; P = 0.005) and synchronicity with the primary tumour (metachronous versus. synchronous, HR: 2.32; 95% CI: 1.63–3.30; P < 0.001) were independent prognostic factors of DFS (Fig. 4B).

4. Discussion

To our knowledge, no prospective study has been conducted to investigate the efficacy of adjuvant chemotherapy after metastasectomy of PM from CRC thus

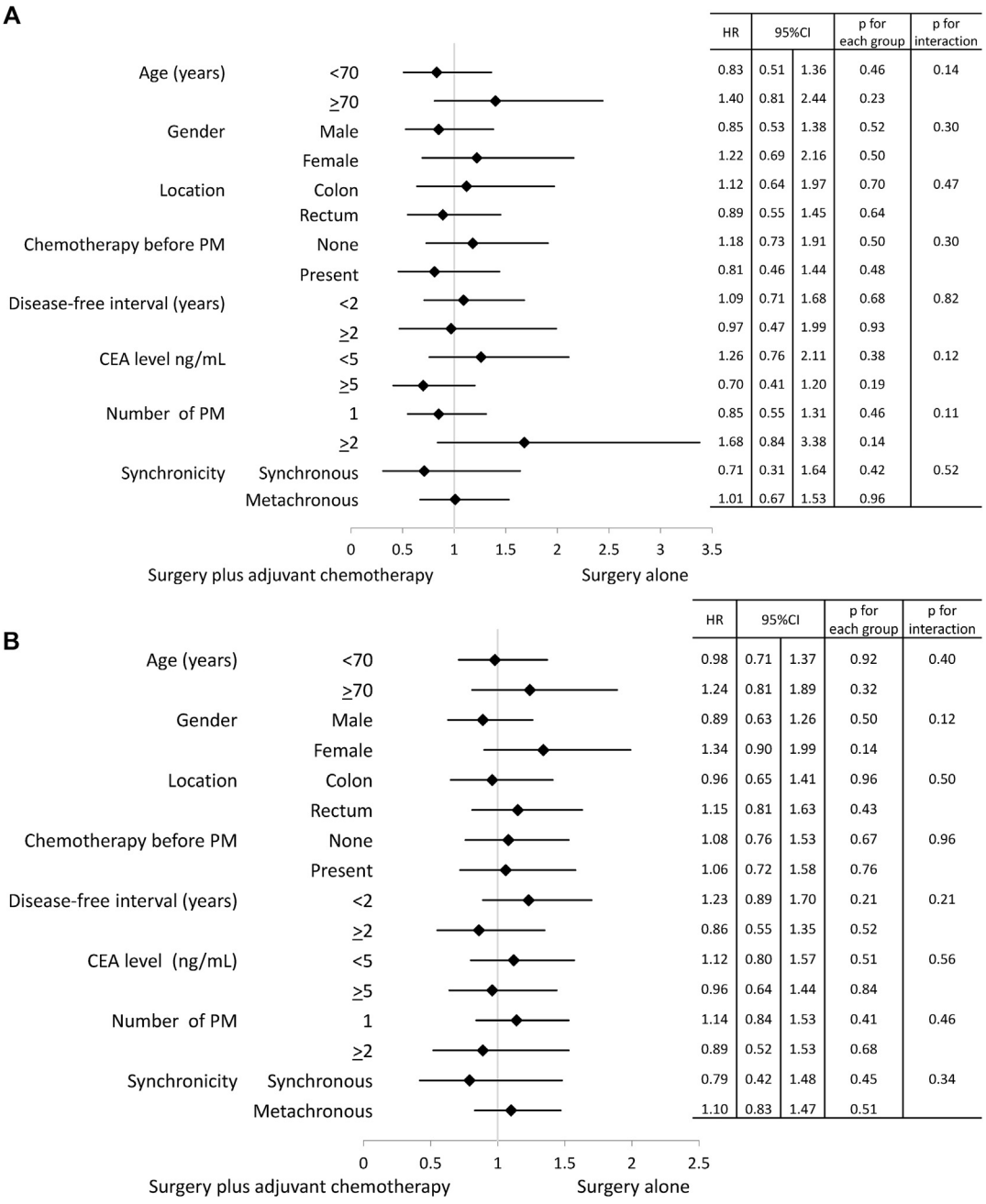

Fig. 3. Forest plots of interaction of patient background factors and treatments for overall survival (A) and disease-free survival (B). P values for each group and for the interaction were calculated by log-rank and interaction tests, respectively. PM, pulmonary metastases; CEA, carcinoembryonic antigen; HR, hazard ratio; CI, confidence interval.

far. In only one multicentre randomised phase III trial, adjuvant chemotherapy after curative metastasectomy was evaluated in patients with PM and/or liver metastases [20]. The number of patients with PM included in this study was very few (n = 13). This study was terminated early because of poor accrual, and it showed no improvement in trend for DFS and OS in the adjuvant group. The survival benefit of adjuvant chemotherapy after metastasectomy was reported for DFS or relapse-free survival but not for OS, in a few retrospective studies [21,22]. However, sample sizes of most studies were small, and the subjects in some studies included patients with liver metastases rather than PM. Recently, our large multicentre retrospective cohort study reported no survival benefit of adjuvant chemotherapy after resection of PM [10]. It is considered that these inconsistent results may be caused by heterogeneity of the study population and imbalance in patients' background characteristics. In the present study, we targeted patients with lung-limited metastasis from CRC and investigated the efficacy of adjuvant chemotherapy using propensity score–matched analysis to minimise

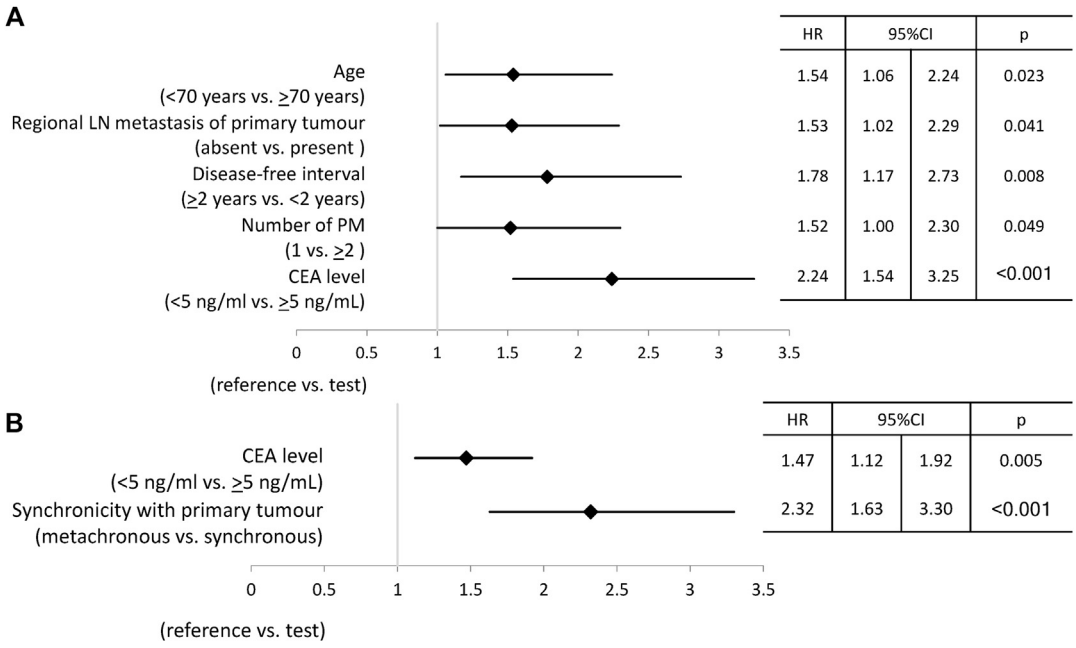

Fig. 4. Forest plots of multivariable analysis for prognostic factors in overall survival (A) and disease-free survival (B). LN, lymph node; PM, pulmonary metastases; CEA, carcinoembryonic antigen; HR, hazard ratio; CI, confidence interval.

bias due to confounding factors. However, our current study did not show any survival benefits of adjuvant chemotherapy.

We have outlined the possible reasons for our negative results as follows. First, the OS in our current study was better than that reported previously [3,8,17,23,24]; the 5-year OS rates were approximately 70% in both groups. This could be due to the process of patient selection, which was to avoid confounding factors as much as possible, by excluding patients with poor general conditions, metastases other than those of the lung and complications after pulmonary metastasectomy. In addition, the patients' background characteristics such as low CEA levels (<5 ng/ml in 65% of patients) and small number of lung metastases (solitary in 78% of patients) in this study were initially good. The good condition of the patients possibly led to the favourable outcomes seen in the surgery alone group, making it difficult to demonstrate the efficacy of adjuvant chemotherapy. Second, most patients (71%) in the A group received adjuvant chemotherapy with fluoropyrimidine alone. A pooled analysis of two randomised controlled trials of adjuvant chemotherapy with bolus 5-FU plus leucovorin after resection of CRC metastases (majorly liver metastases) did not demonstrate survival benefit after metastasectomy compared to surgery alone [14]. Moreover, perioperative adjuvant chemotherapy could not prolong OS in a phase III study for liver-limited CRC metastases even with the use of a combination therapy of 5-FU/leucovorin plus oxaliplatin (FOLFOX) [15]. These reports may support our results. However, the current standard regimen for adjuvant chemotherapy in stage III colon cancer is a combination therapy of FOLFOX or capecitabine plus oxaliplatin, both of which are definitively superior to fluoropyrimidine alone [25,26]. Moreover, in a randomised controlled trial of CRC patients with resectable liver-limited metastasis, perioperative chemotherapy with FOLFOX showed a benefit in progression-free survival in eligible and resected patient cohorts [15]. Considering these factors, fluoropyrimidine monotherapy used for the majority of the patients in our study might be too weak to eliminate micro-PM. Still, it is not clear whether more intensive adjuvant chemotherapy like FOLFOX might be beneficial in such patients. Another group conducted a single-arm phase II trial of adjuvant-modified FOLFOX6 after curative resection of PM from CRC (WJOG5810G study). Presently, the patient-recruitment phase has been completed, and the final results will be published in 2019 (UMIN ID: UMIN000005693).

In the multivariable analysis in the current study, several poor prognostic factors were identified: high CEA level (≥5 ng/ml) for both DFS and OS and synchronous PM for DFS and old age (≥70 years), short DFI (<2 years), existence of regional lymph node metastasis from the primary tumour and two or more number of PM for OS. These were compatible with previously reported prognostic factors except for regional lymph node metastasis from the primary tumour [9,27]. There are few reports on the prognostic significance of regional lymph node metastasis from primary CRC in patients after resection of PM because its presence has not been studied as a variable for analyses. These results should be verified in other patient cohorts, and our findings would be helpful in planning

future comparative studies in a population similar to ours. On the other hand, thoracic lymph node metastases were reported as a poor prognostic factor in a recent meta-analysis [9]. However, systemic lymph node dissection is not routinely performed in the resection of PM from CRC. In our study, the proportion of patients who had pathological lymph node metastases, at 4%, was very small (data not shown). Thoracic lymph node metastasis is difficult to diagnose pre-operatively, and resection of PM is not performed in patients with radiologically positive lymph node metastasis. Therefore, we did not use this as a variable for analyses because of the small number of patients and the possible bias.

This study has several methodological limitations due to its retrospective nature. Although we conducted a propensity-matched analysis to reduce the selection bias, such an analysis cannot completely avoid a bias in physician's and patient's decisions toward adjuvant chemotherapy. The indications of metastasectomy, surgical procedures, indication of adjuvant chemotherapy and regimens of chemotherapy differed among the participating institutions, and the compliance of adjuvant chemotherapy was not known. These may have influenced our results and underestimated the efficacy.

5. Conclusions

The propensity score–matched analysis on adjuvant chemotherapy after resection of lung-limited metastasis from CRC found no survival benefit of adjuvant chemotherapy. A large, prospective, well-designed observational study or a randomised clinical trial with oxaliplatin-based combination chemotherapy is needed.

Conflict of interest statement

Dr. Gosho has received honoraria from company Daiichi-Sankyo, Ferring, Taiho and Kowa. Dr. Boku has received honoraria from company Taiho, Chugai, Merck Serono, Takeda, Ono and Shionogi. Dr. Hyodo has received honoraria from company Taiho, Chugai, Daiichi-Sankyo and Yakult-Honsha. Dr. Moriwaki received honoraria from company Taiho, Chugai, Merck Serono, Takeda, Lilly, Sanofi and Yakult-Honsha. The remaining authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2018.10.003.

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