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Pulmonary Oligometastases Treated by Stereotactic Body Radiation Therapy: A Nationwide Survey of 1,378 Patients

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Abstract. *Aim: This study was performed to confirm the superior overall survival (OS) after pulmonary oligo-recurrence compared to pulmonary sync-oligometastases in a large nationwide study. Patients and Methods: Patients that met the following criteria were included: 1 to 5 lung-only metastases at the beginning of stereotactic body radiation therapy (SBRT) was performed between January 2004 and June 2015, and the biological effective dose (BED) of SBRT was 75 Gy or more. The parameters included in the analyses were age, gender, ECOG PS, primary lesion, pathology, oligoetastatic state, SBRT date, chemotherapy before SBRT, chemotherapy concurrent SBRT, chemotherapy after SBRT, maximum tumor diameter, number of metastases, field coplanarity, dose prescription, BED_{10}, OTT of SBRT. Results: In total, 1,378 patients with 1,547 tumors were enrolled. Oligo-recurrence occurred in 1,016 patients, sync-oligometastases in 118, and unclassified oligometastases in 121. The three-year OS was 64.0% for oligo-recurrence and 47.5% for sync-oligometastasis ($p<0.001$). In the multivariate analysis, the hazard ratio (HR) for sync-oligometastases versus oligo-recurrence was 1.601 ($p=0.014$). Adverse events of Grade 5 were occurred in 3 patients. Conclusion: This is the first nationwide to indicate that the OS*

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of patients with pulmonary oligo-recurrence is better than that of patients with sync-oligometastases.

Distant metastasis or distant recurrence at any site or in any organ was considered to indicate the terminal stage of cancer before the 2010s. However, this above status is not always indicative of the terminal stage in cancer patients. In particular, between 1995 and the early 2010s, the status of five or less metastases or recurrences was introduced and classified as oligometastases, oligo-recurrence, or sync-oligometastases (1-3). The investigation of oligometastases has since progressed, and currently, the term is used to denote 1 to 5 metastases or recurrences in patients with cancer, regardless of whether the primary lesions are controlled. These metastases or recurrences are treated by local therapy including surgery, radiotherapy, or radiofrequency ablation and other local therapies (2-4).

Nowadays, oligometastases is classified into two statuses: The first is oligo-recurrence, which refers to cancer patients with 1 to 5 recurrences that are treated by local therapy, with controlled primary lesions (2-4). The other status is called sync-oligometastases and refers to cancer patients with 1 to 5 recurrences and active primary lesions, all treated by local therapy (3, 4). In 2016, Niibe *et al.* first reported that when limited to lung and/or brain non-small cell lung cancer (NSCLC), oligo-recurrence achieved a better overall survival (OS) than sync-oligometastases, although only 61 patients were included in that study because of rare occurrence (4). Likewise, 96 lung oligometastases patients were investigated in 2016 (5), and this larger population study reported the same results.

However, we do not consider 100 patients to be a sufficient sample size; therefore, larger nationwide population database studies are required. Thus, the primary purpose of this study was to statistically reveal the OS superiority of lung oligo-recurrence compared to lung sync-oligometastases using univariate and multivariate analyses and to evaluate this comparison quantitatively using hazards ratios (HRs). The primary endpoint of this large database study was to determine the superiority or inferiority HR of sync-oligometastases *vs.* oligo-recurrence in a multivariate analysis.

Patients and Methods

Patient eligibility. The patient inclusion criteria were as follows: Patients with 1 to 5 lung metastases at the start of stereotactic body radiation therapy (SBRT) targeting the tumors (regardless of whether the primary lesions were controlled) were included. However, because patients under the Japanese Social Insurance System were included in this study, the primary lesion was controlled and other detectable lesions were limited in the lungs before beginning SBRT. The SBRT was performed between January 2004 and June 2015, and the biological effective dose (BED) of SBRT was ≥75 Gy with a dose per fraction of ≥4 Gy. BED_{10} was calculated using the following formula: $BED=nd\ [1+d/(\alpha/\beta)]$, where n is the number of fractions, d is the dose per fraction, and the α/β ratio is applied for 10 Gy for the tumors. Pulmonary metastases were defined as the appearance of a solid tumor in the lung simultaneously or after treatment of the primary tumor; local recurrence of a thoracic primary tumor was excluded.

Data acquisition and opt-out consents. For the purpose of the retrospective, observational, multicenter study, recruitment questionnaire was sent to the institutions registered in the Japanese Society for Radiation Oncology (JASTRO) database. Among the 426 institutions, 83 joined, but 15 had no eligible patients or later refused to participate. Finally, this study was conducted in 68 institutions in Japan. This study was approved by the Ethics Committee of Toho University Omori Medical Center, reference number, (reference number: 27-148), and all participating institutions guaranteed the chance to opt-out of participation in this study by providing information of this study *via* the internet or posters. Opt-out consents were obtained from all included patients.

Definitions. The disease-free interval (DFI) was defined as the interval between the date that the primary lesion was controlled and the date that the first metastasis was confirmed. The DFI start date was the date that surgery or radiofrequency ablation, *etc.*, was performed, or the last date of radiotherapy or particle therapy. Adjuvant therapy (chemotherapy or hormonal therapy) was not considered. The DFI of oligo-recurrences, sync-oligometastases, and unclassified oligometastases was defined as a DFI ≥6, 0, and <6 months, respectively. Local failure was defined as enlargement of the irradiated tumor, and local control (LC) was defined as freedom from local failure. Relapse-free survival (RFS) was defined as freedom from any metastases, any recurrences, or death.

Statistical analysis. The time to an event was calculated from the first day of SBRT to the day an event was confirmed. The Kaplan–Meier method was used to calculate the cumulative LC rate, RFS rates, and OS rates, and Greenwood's formula was used to calculate 95% confidence intervals (95% CIs). A log-rank test was used to compare Kaplan–Meier curves. The Cox proportional hazards model was used to perform the multivariate analyses. A stepwise backward elimination/forward addition approach using the Akaike information criterion was applied to build the best multivariate analysis model. A *p*-value less than 0.05 was defined as significant. EZR, version 1.37 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a modified version of R commander (R Foundation for Statistical Computing, Vienna, Austria), was used for the analyses (6). The National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 was used to grade adverse events.

Results

Acquisition results and treatment results. A total of 1,378 patients with 1,547 tumors were enrolled in this study. This large database study included all registered patients with or without missing values to avoid selection bias. The characteristics of the patients and tumors are listed in Table I. The oligometastatic states were distributed as follows: oligo-recurrence in 1,016 patients, sync-oligometastases in 118 patients, and unclassified oligometastases in 121 patients. The median follow-up period for all patients was 24.2 months

(range=0.1-143.7) and that for living patients was 26.9 months (range=0.1-143.7). During follow-up, 375 patients died from the primary disease, 109 died from other causes, and 52 died from unknown causes. There were 222 local failures, and the median interval to local failure was 12.4 months (range=3.0-98.7). The 1-, 3-, and 5-year OS rates were 90.1% (95% CI=88.3%-91.6%), 60.3% (95% CI=57.1%-63.3%), and 45.5% (95% CI=41.8%-49.1%), respectively (Figure 1). The 1-, 3-, and 5-year RFS rates were 55.2% (95% CI=52.4%-57.9%), 28.3% (95% CI=25.7%-31.0%), and 19.5% (95% CI=16.9%-22.3%), respectively. The median OS and the median RFS were 51.4 months (95% CI=45.0-55.7) and 14.2 months (95% CI=12.7-15.7), respectively. The 1-, 3-, and 5-year LC rates were 92.1% (95% CI=90.4%-93.4%), 81.3% (95% CI=78.8%-83.6%), and 78.6% (95% CI=75.6%-81.2%), respectively. Adverse events were reported in 1,040 patients, and grade 2, 3, 4, and 5 pneumonitis occurred in 96 (9.2%), 14 (1.3%), 2 (0.1%), and 7 (0.6%) patients, respectively. Grade 5 hemoptysis occurred in 3 patients (0.2%).

Univariate and multivariate analyses. In the univariate analyses (log-rank tests), significant differences in OS were found according to gender ($p<0.001$), Eastern Cooperative Oncology Group performance status (ECOG PS, $p<0.001$), primary lesion ($p<0.001$), pathology ($p<0.001$), oligometastatic state ($p<0.001$), chemotherapy after SBRT ($p=0.033$), and maximum tumor diameter ($p<0.001$) (Table II). The three-year OS was 64.0% (95% CI=60.3%-67.4%) for oligo-recurrence, 47.5% (95% CI=36.2%-58.0%) for sync-oligometastases, and 53.3% (95% CI=42.6%-62.8%) for unclassified oligometastases.

The results of the multivariate analyses (Cox regression) are shown in Figure 2. The following factors were revealed to significantly negatively affect OS: ECOG PS 1 (PS 1 *versus* PS 0, HR=1.415, 95% CI=1.116-1.795, $p=0.004$), ECOG PS 2-3 (PS 2-3 *versus* PS 0, HR=2.186, 95% CI=1.469-3.253, $p<0.001$), primary lesion pathology of squamous cell carcinoma (squamous cell carcinoma *versus* adenocarcinoma, HR=1.440, 95% CI=1.024-2.026, $p=0.036$), primary lesion of esophagus (esophagus *versus* colorectum, HR=1.676, 95% CI=1.003-2.801, $p=0.048$), sync-oligometastases (sync-oligometastases *versus* oligo-recurrence, HR=1.601, 95% CI=1.097-2.336, $p=0.014$), unclassified oligometastases (unclassified oligometastases *versus* oligo-recurrence, HR=1.457, 95% CI=1.039-2.043, $p=0.029$), and maximum tumor diameter (≥1.5 cm *versus* <1.5 cm, HR=1.447, 95% CI=1.151-1.819, $p=0.001$).

Table I. *Patient and treatment characteristics*.

Factors	n (%) N=1,378
Gender	
Male	894 (64.9)
Female	484 (35.1)
Age (years)	
Median, range	72, 16-93
ECOG performance status	
0	744 (56.3)
1	475 (35.9)
2-3	103 (7.8)
Clinical stage; pathological stage	
1	187 (29.4); 222 (35.9)
2	130 (20.4); 133 (21.5)
3	162 (25.5); 173 (28.0)
4	157 (24.7); 90 (14.6)
Primary lesion	
Lung	422 (30.6)
Colorectum	345 (25.0)
Head and neck	114 (8.3)
Esophagus	114 (8.3)
Others	383 (27.8)
Pathology	
Adenocarcinoma	760 (55.8)
Squamous cell carcinoma	392 (29.3)
Others	185 (13.8)
Oligometastatic state	
Oligo-recurrences	1016 (81.0)
Sync-oligometastases	118 (9.4)
Unclassified oligometastases	121 (9.6)
DFI (months) median, range	
Oligo-recurrences	23.2, 6.0-424
Sync-oligometastases	0
Unclassified oligometastases	3.8, 0.3-5.9
Chemotherapy before SBRT	
Yes	503 (36.8)
No	865 (63.2)
Chemotherapy concurrent SBRT	
Yes	29 (2.1)
No	1349 (97.9)
Chemotherapy after SBRT	
Yes	190 (17.7)
No	882 (82.3)

Eastern Cooperative Oncology Group; DFI, disease-free interval; SBRT, stereotactic body radiotherapy.

Discussion

This retrospective nationwide study was selected by the JASTRO. As the primary endpoint, this study hypothesized that the HR for OS in patients with oligo-recurrence was superior to that of patients with sync-oligometastases. The HR was 1.601, suggesting that our hypothesis was supported in this nationwide survey. Furthermore, the 1-, 3-, and 5-year OS rates of 90.1%, 60.3%, and 45.5%, respectively, and the limited adverse events indicated that this technique of using BED in SBRT was effective and feasible for pulmonary oligometastases.

In a previous study investigating a similar hypothesis, Niibe *et al*. reported that the 2-year OS of lung oligo-recurrence was significantly higher than that of sync-oligometastases (68.8%

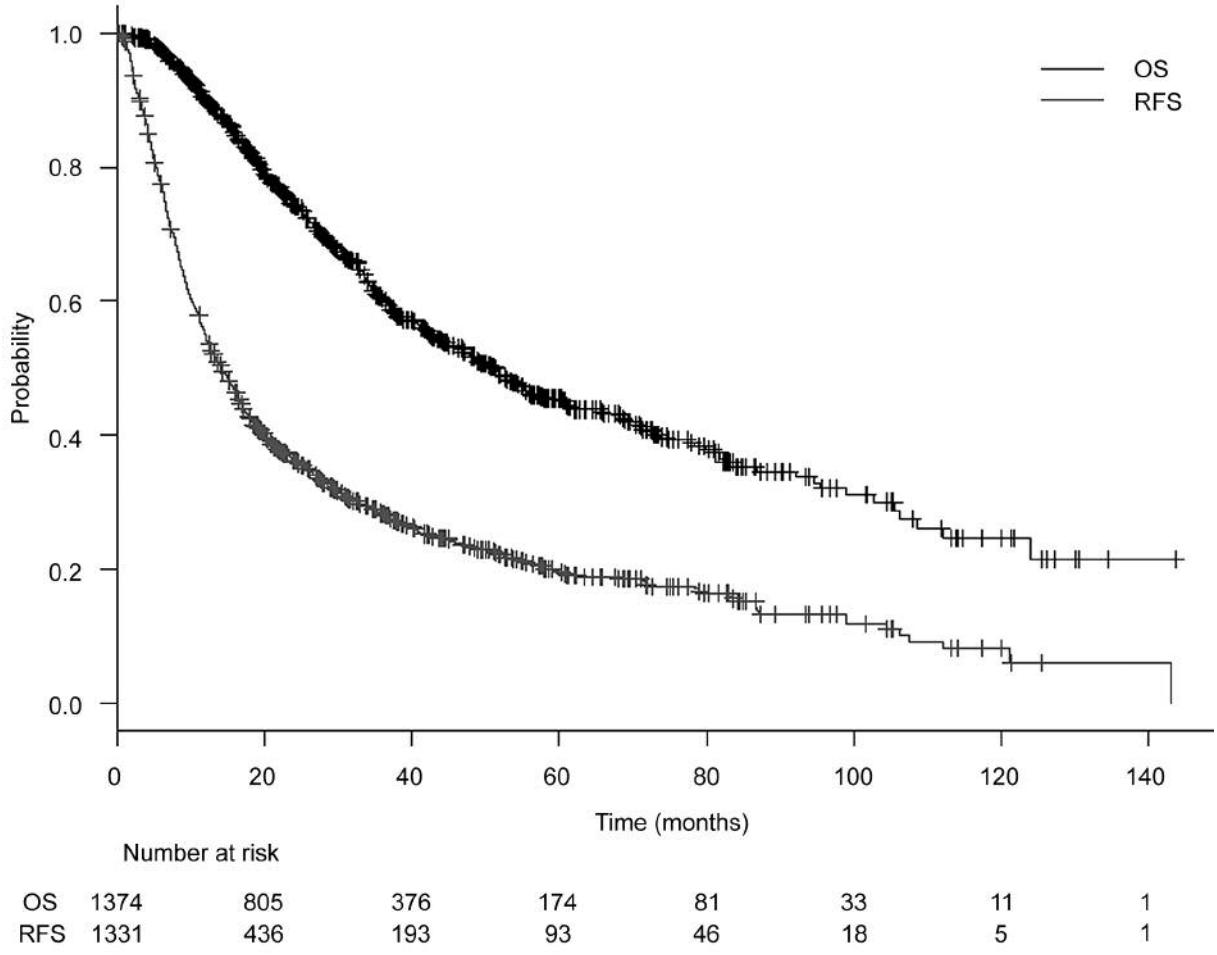

Figure 1. *Kaplan–Meier estimate of overall survival (OS) and relapse-free survival (RFS).*

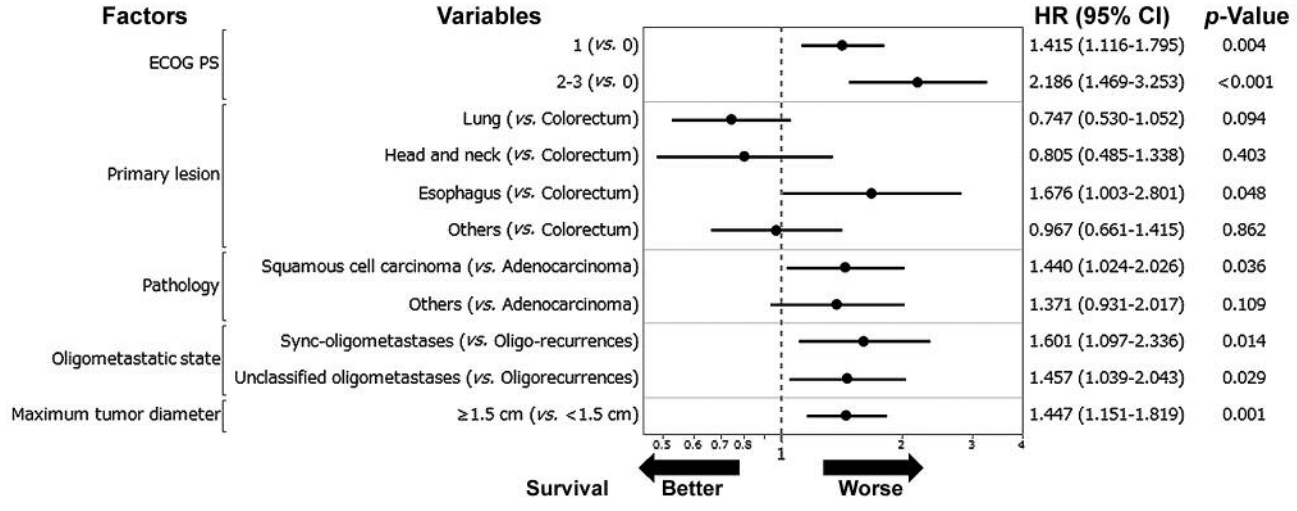

Figure 2. *Multivariate analysis of overall survival. ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; CI, confidence interval.*

Table II. *Tumor and treatment characteristics*.

Factors		n (%) N=1,547
SBRT date	2004-2009	468 (34.0)
	2010-2015	910 (66.0)
Maximum tumor diameter (cm)	Median, range	1.5; 0.3-6.5
Number of metastases	1	1012 (73.9)
	2-5	358 (26.1)
Field coplanarity	Coplanar field	404 (26.2)
	Non-coplanar field	1139 (73.8)
Dose prescription	IC	1103 (71.3)
	D95 of PTV	317 (20.5)
	Others	127 (8.2)
BED_{10} dose of IC (Gy)	Median, range	105.6, 75.0-289.6
	<100 Gy	173 (13.7)
	≥100 Gy	1093 (86.3)
OTT of SBRT (days)	Median, range	7, 3-81

SBRT, Stereotactic body radiotherapy; IC, isocenter; D95 of PTV, dose covering 95% of planning target volume; BED, biological effective; OTT, overall treatment time.

and 50.0%, respectively) (7). Similarly, Yamashita *et al*. demonstrated that the median OS of lung oligo-recurrence was significantly higher compared to 66.6 that of sync-oligometastases (66.6 *vs*. 23.9 months). Furthermore, in the same study, multivariate analysis indicated that lung oligo-recurrences had significantly improved OS compared to that of sync-oligometastases (5). In a study that included 61 patients with brain NSCLC, pateients with oligometastases achieved a better OS comopared to patients with sync-oligometastases. Moreover, a multivariate analysis indicated oligo-recurrence as a predictive factor for favorable prognosis (HR=0.253, 95% CI=0.082-0.043, p=0.025) (4). The current nationwide survey is consistent with these previous reports even with a large oligometastases population. A possible explanation for the superior OS of oligo-recurrence compared to that of sync-oligometastases, as reported in the aforementioned studies and the current one, is that patients with oligo-recurrence had controlled primary lesions and did not require further local therapy for their primary lesions. On the other hand, patients with sync-oligometastases must receive local therapy for both metastatic lesions and primary lesions. In general, primary lesions often invade the surrounding tissues and associated with metastases to the regional lymph nodes, thus, their LC is more difficult than that metastatic lesion (4-7).

Favorable prognostic factors to indicate surgery for pulmonary oligo-recurrence include a lung oligo-recurrence of osteosarcoma DFI ≥12 months, 1 to 3 lung recurrent sites, and a total surgery lesion size of less than 30 mm (8). He *et al*. reported that in cancer patients with lung oligometastases from NSCLC, the median survival time of patients treated by

Table III. *Univariate analyses for overall survival*.

Factors	N	MST	p-value
Age			
<72	683	49.3	
≥72	691	52.9	0.789
Gender			
Male	891	37.0	
Female	483	53.7	<0.001
ECOG PS			
0	742	60.3	
1	473	42.0	
2-3	103	33.1	<0.001
Primary lesion			
Lung	422	61.5	
Colorectum	343	51.7	
Head and Neck	113	52.8	
Esophagus	113	27.1	
Others	383	54.5	<0.001
Pathology			
Adenocarcinoma	757	60.8	
Squamous cell carcinoma	360	37.4	
Others	186	56.0	<0.001
Oligometastatic state			
Oligo-recurrence	1013	60.3	
Sync-oligometastases	118	35.1	
Unclassified oligometastases	120	37.6	<0.001
SBRT date			
2004-2009	468	51.3	
2010-2015	906	53.6	0.762
Chemotherapy before SBRT			
Yes	501	47.9	
No	863	51.6	0.175
Chemotherapy concurrent SBRT			
Yes	29	34.0	
No	1345	51.7	0.102
Chemotherapy after SBRT			
Yes	190	37.9	
No	878	56.0	0.033
Maximum tumor diameter, cm			
<1.5	595	61.5	
≥1.5	716	40.9	<0.001
Number of metastases			
1	1009	51.7	
2-5	357	48.7	0.495
Field coplanarity			
Coplanar field	385	46.2	
Non-coplanar field	985	52.6	0.421
Dose prescription			
IC	1011	48.8	
D95 of PTV	252	60.9	
Others	111	NR	0.433
BED10 dose of IC, Gy			
<100 Gy	172	68.8	
≥100 Gy	1090	49.3	0.088
OTT of SBRT, day			
<7	485	50.3	
≥7	580	56.0	0.994

MST, Median survival time; ECOG, Eastern Cooperative Oncology Group; IC, isocenter; D95 of PTV, dose covering 95% of planning target volume; NR, not reached; BED, biological effective dose; OTT, overall treatment time.

surgery was higher than that of patients treated by systemic chemotherapy (18.2 *vs*. 9.1 months, $p<0.05$), although only 21 patients were included in that study (9). In another study of 7 patients who underwent hepatic resection for oligo-recurrence of NSCLC in the liver, the median survival time was 24.0 months (range=15.2-30.2), and 4 patients remained alive at the end of follow-up (23.4-30.2 months) (10). Lodeweges *et al*. reported that the 5-year OS of patients with pulmonary oligometastaes who underwent surgery for LC was similar to that of patients who underwent stereotactic ablative radiation therapy (SABR) (41% and 45%, respectively), suggesting SABR as a more effective and less invasive treatment method for pulmonary oligometastases; however, this was a small population-based retrospective study (11). Furthermore, a randomized phase II trial has suggested that OS of patients with oligometastastatic cancer treated by SABR was better than that of patients treated with palliative radiation therapy; however, only 99 patients were included in that study (12).

In the present nationwide survey of pulmonary oligometastases, oligo-recurrence, ECOG PS 0, adenocarcinoma pathology of the primary cancer, colorectal origin, and a smaller maximum tumor diameter (<1.5 cm) resulted in a significantly favorable prognosis for OS in the multivariate analysis. Although Niibe *et al*. (4) have previously shown that 5-year OS rate was 0% in NSCLC patients with sync-oligometastases treated with stereotactic radiosurgery or stereotactic radiotherapy, the current study indicated that patients with sync-oligometastases reached the 5-year OS. Despite the fact that the OS rate of the sync-oligometastases group was inferior to that of the oligo-recurrences group. The present result encourages patients, radiation oncologists, oncologic surgeons, medical oncologists and medical staff to treat sync-oligometastases aiming at cure or long-term survival.

The main limitation of the current study is its retrospective, non-randomized nature. The patients included were treated only in Japan. However, this is the first study to examine a large population database of 1,378 patients with pulmonary oligometastases.

In conclusion, this nationwide study as well as the studies mentioned above indicate that the OS of pulmonary oligo-recurrence is better than that the OS of sync-oligometastases. The HR of sync-oligometastases *vs*. oligo-recurrence was 1.601 (95% CI=1.097-2.336, $p=0.014$), and the adverse effects were manageable. Further studies, particularly large population-based prospective studies, will be required to construct more evident results supporting this hypothesis.

Conflicts of Interest

HO has grants from Accuray Japan, Cannon, present or during 36 months prior to publication.

Author's Contributions

NY drafted the protocol of this study, performed statistical analyses, wrote this manuscript and collected patients. TY revised protocol and performed statistical analyse, revised manuscript and collected patients. KJ, HO, HY, KK, AT revised protocol, revised manuscript and collected patients. YM, R-JO, MA, TS, KY, MK, MO, YM, KY, AN, HK, KY, TI, YT, KN, OS revised manuscript and collected patients.

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