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ORIGINAL ARTICLE

Comparison of stereotactic body radiotherapy versus metastasectomy outcomes in patients with pulmonary metastases

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Keywords
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Abstract

Background: We compared the treatment outcomes of stereotactic body radiotherapy (SBRT) and metastasectomy in patients with pulmonary metastases.

Methods: Twenty-one patients received SBRT (total radiation doses 60 Gy in 3 fractions or 48 Gy in 4 fractions) and 30 underwent metastasectomy, most (93.3%) with wedge resection. The patients were followed for a median of 13.7 months. The tumor size in the SBRT group was larger than in the metastasectomy group (median 2.5 vs. 1.25 cm; $P = 0.015$). Patients with synchronous metastases were more likely to be treated with SBRT than with metastasectomy ($P = 0.006$).

Results: There was no significant difference in the local control rates of the treatment groups ($P = 0.163$). Progression-free survival (PFS) was longer in the metastasectomy than in the SBRT group ($P = 0.02$), with one and two-year PFS rates of 51.1% and 46% versus 23.8% and 11.9%, respectively. The one and two-year overall survival (OS) rates were 95% and 81.8% in the metastasectomy group and 79.5% and 68.2%, in the SBRT group, respectively. In multivariate analysis, synchronous metastasis was related to poor PFS, and tumor size was the most significant factor affecting OS. There were no significant differences in PFS and OS between treatment groups after dividing patients according to the presence or absence of synchronous metastases.

Conclusions: SBRT is considered a suitable local modality against pulmonary metastases; however, patients with synchronous metastases are only likely to obtain a small benefit from local treatment with either SBRT or surgery.

Introduction

As cancer survival rates have improved commensurate with advancements made in cancer diagnosis and treatment methods, the number of patients with recurrent or metastatic cancer continues to increase.[1] The development of effective chemotherapy regimens and combinations of systemic and local treatments has improved the prognosis of metastatic cancer patients.[2,3] After the concept of

oligometastases was proposed, several studies have reported that aggressive local treatment of oligometastatic lesions may improve patient survival.[4–7] For example, the National Comprehensive Cancer Network guideline recommends local treatment for pulmonary metastases arising from colon cancer.[8]

However, the criteria for selecting the patients for whom local treatment is appropriate have not yet been defined, particularly as metastatic cancer patients usually experience distant site failure.[9–11] In some patients, local treatment may result in increased toxicity without improved therapeutic outcomes.[12] Therefore, the optimal local therapy remains unclear.[13–15] Surgery is considered the first choice among local treatment modalities, and several studies have shown good local control and survival outcomes in patients with hepatic and pulmonary metastases treated with surgery.[16,17] Although stereotactic body radiotherapy (SBRT) is usually recommended for medically inoperable patients, SBRT has shown treatment outcomes similar to surgery, exhibiting high local control and equivalent toxicity profiles.[18]

As is difficult to compare treatment outcomes of SBRT versus metastasectomy in prospective randomized trials, we retrospectively compared the efficacy of these methods as local treatment for pulmonary metastases. Additionally, we aimed to identify the patients who are most likely to benefit from local treatment.

Methods

Patients

The Institutional Review Board (IRB) of Gyeongsang National University Hospital (GNUH IRB 2017-08-009) approved the study. The inclusion criteria were as follows: (i) the presence of up to three pulmonary metastases arising from any non-hematological malignancy; (ii) Eastern Cooperative Oncology Group performance status (ECOG PS) 0–2; (iii) surgery or radiotherapy had been performed with ablative intent; and (iv) no previous history of thoracic radiotherapy. Between January 2010 and June 2016, 51 patients who satisfied the selection criteria were identified. Data on patients' clinical characteristics were obtained from electronic medical records. The characteristics of the pulmonary metastatic lesions including size, location, number, the interval from primary tumor diagnosis to the detection of pulmonary metastasis, whether the primary tumor and other metastatic lesions were controlled, and whether the pulmonary metastatic lesion was solitary, were recorded. Complications related to SBRT or surgery were also noted.

Treatment

A multidisciplinary tumor board decided the treatment modality for each patient. Twenty-one patients received SBRT for 29 pulmonary metastatic lesions. Three fiducial markers were implanted around the individual peritumoral area under computed tomography (CT)-guidance for daily set-up and tumor motion tracking. One week later, planning CT with contrast enhancement was obtained with a patient-specific immobilization device (Vac-lok, CIVCO Inc., Kalona, IA, USA) while maintaining regular breathing. Four-dimensional CT was performed using the Philips Brilliance 16 CT scanner while synchronizing the respiration signal obtained using a monitoring device (Philips pneumatic belt; Philips, Amsterdam, Netherlands). The gross tumor volume (GTV) was the metastatic lung tumor, and was delineated at maximum exhalation (referred to as a 50% phase in our CT scanning system). The clinical target volume (CTV) was the same as the GTV. The primary planning target volume (PTV) was generated by adding a 3 mm setup margin to the CTV. SBRT was performed using the CyberKnife system (Accuray, Sunnyvale, CA, USA); the radiation dose was prescribed to the isodose line covering the entire GTV and more than 95% of the PTV. The total radiation dose was 60 Gy/3 fractions for peripheral lesions and 48 Gy/4 fractions for central lesions. Thirty patients underwent surgical resection for 30 pulmonary metastatic lesions, 28 (93.3%) underwent wedge resection, and 2 (3.9%) underwent lobectomy. Under general anesthesia, a mini-thoracotomy or video-assisted thoracoscopic surgery was performed while the patient received single-lung ventilation using a double lumen endotracheal tube. After lung tissue resection, the chest tube was inserted into the pleural cavity until air leakage ceased and pleural fluid drainage decreased below 150 mL per day.

Statistics

Overall survival (OS) was defined as the period between the date of first SBRT or surgery and the date of death from any cause. Progression-free survival (PFS) was defined as the interval from the start of any local treatment to the date of tumor recurrence or death. For SBRT, local recurrence was defined as recurrence in or adjacent to the PTV; for surgery, it was defined as recurrence at or adjacent to the surgical bed. Chi-squared or Fisher's exact tests were used to compare categorical variables between the treatment groups, while the Mann–Whitney *U* test was used to compare continuous variables. We performed univariate and multivariate Cox proportional hazards analyses to evaluate the effect of variables on local control, PFS, and OS. The Kaplan–Meier method was used to calculate the OS and PFS rates, while differences in survival outcomes were assessed using the log-rank test. Toxicities were

recorded according to Common Terminology Criteria for Adverse Events version 4.0. All statistical analyses were performed using SPSS version 20 (IBM Corp., Armonk, NY, USA). $P < 0.05$ was considered significant.

Results

Patient and tumor characteristics

The patient and treatment characteristics are shown in Table 1. There were no differences between the treatment groups in terms of gender, age, smoking history, ECOG PS, comorbidities, pulmonary function, interval between primary diagnosis and detection of pulmonary metastases, or tumor location (central vs. peripheral). Comorbidities included hypertension (12 patients), diabetes mellitus (10 patients), cardiovascular disease (8 patients), hepatic disease (6 patients), and other cancer (5 patients). The median tumor size was larger in the SBRT than in the metastasectomy group (2.5 vs. 1.25 cm; $P = 0.015$). Patients with synchronous metastases were more likely to be treated with SBRT than with metastasectomy

Table 1 Patients and treatment characteristics

Characteristics	All	Surgery	SBRT	*P*
Patients number	51	30	21	—
Tx site number	—	30	29	—
Gender				
Male	28 (54.9%)	16 (53.3%)	12 (57.1%)	0.788
Female	23 (45.1%)	14 (46.7%)	9 (42.9%)	—
Age (years)	67 (28–85)	63 (28–78)	69 (35–85)	0.236
Smoking history				
None	37 (72.5%)	19 (63.3%)	18 (85.7%)	0.062
Ex-smoker	11 (21.6%)	9 (30%)	3 (14.3%)	—
Current smoker	2 (3.9%)	2 (6.7%)	0 (0%)	—
ECOG PS				
0	15 (29.4%)	9 (30%)	6 (28.6%)	0.436
1	30 (58.8%)	19 (63.3%)	11 (52.4%)	—
2	6 (11.8%)	2 (6.7%)	4 (19%)	—
Comorbidities				
None	18 (35.3%)	8 (26.7%)	10 (47.6%)	0.123
Yes	33 (64.7%)	22 (73.3%)	11 (52.4%)	—
Pulmonary function				
FEV1 (L)	2.39 (1.39–4.37)	2.42 (1.39–4.37)	2.2 (1.59–3.4)	0.640
FEV1/FVC (%)	76.3 (54–87)	75.6 (62–87)	79.4 (54–86)	0.596
Primary cancer				
Colorectal	18 (35.3%)	12 (40%)	6 (28.6%)	0.942
Hepatobiliary	7 (13.7%)	2 (6.7%)	5 (23.8%)	—
NSCLC	6 (11.8%)	4 (13.3%)	2 (9.5%)	—
Breast	4 (7.8%)	3 (10%)	1 (4.8%)	—
RCC	4 (7.8%)	2 (6.7%)	2 (9.5%)	—
Esophagus	3 (5.9%)	1 (3.3%)	2 (9.5%)	—
Stomach	2 (3.9%)	1 (3.3%)	1 (4.8%)	—
Others	7 (13.7%)	5 (16.7%)	2 (9.5%)	—
Time interval (months)	30 (1–204)	30 (1–135)	27 (5–204)	0.751
Location				
Central	9 (17.6%)	5 (16.7%)	4 (19%)	0.778
Peripheral	39 (76.5%)	24 (80%)	15 (71.4%)	—
Both	3 (5.9%)	1 (3.3%)	2 (9.5%)	—
Tumor size (cm)	1.5 (0.6–12.4)	1.25 (0.6–3.3)	2.5 (0.6–12.4)	0.015
Synchronous Other metastases				
None	33 (64.7%)	24 (80%)	9 (42.9%)	0.006
Yes	18 (35.3%)	6 (20%)	12 (57.1%)	—
Chemotherapy				
No	41 (80.4%)	21 (70%)	20 (95.2%)	0.034
Yes	10 (19.6%)	9 (30%)	1 (4.8%)	—

ECOG PS, Eastern Cooperative Oncology Group performance status; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma; SBRT, stereotactic body radiotherapy.

Table 2 Univariate and multivariate analyses of clinical factors associated with PFS and OS of patients receiving SBRT versus metastasectomy

	PFS				OS			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
Characteristics	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Gender								
Female								
Male	1.879 (0.938–3.765)	0.075	—	—	1.837 (0.517–6.525)	0.347	—	—
Age (years)	1.007 (0.98–1.035)	0.599	—	—	0.998 (0.949–1.050)	0939	—	—
ECOG PS								
0			—	—			—	—
1	1.367 (0.582–3.21)	0.473	—	—	2.45 (0.299–20.073)	0.404	—	—
2	2.571 (0.807–8.197)	0.110	—	—	2.599 (0.232–29.113)	0.439	—	—
Comorbidities								
None			—	—			—	—
Yes	1.612 (0.778–3.338)	0.199	—	—	0.883 (0.249–3.136)	0.848	—	—
Time interval (Months)	0.997 (0.988–1.005)	0.446	—	—	0.999 (0.985–1.014)	0.939	—	—
Tumor size (cm)	1.216 (1.082–1.367)	0.001	1.122 (0.982–1.281)	0.091	1.386 (1.107–1.735)	0.004	1.386 (1.107–1.735)	0.004
Synchronous metastases								
None								
Yes	3.461 (1.72–6.964)	0.001	3.461 (1.720–6.964)	0.001	3.894 (1.065–14.236)	0.040	2.520 (0.575–11.053)	0.220
Disease controlled								
No			—	—			—	—
Yes	0.484 (0.217–1.081)	0.077	—	—	0.492 (0.126–1.920)	0.307	—	—
Treatment								
SBRT			—	—			—	—
Metastasectomy	0.457 (0.232–0.90)	0.024	0.798 (0.354–1.798)	0.586	0.675 (0.194–2.349)	0.537	1.583 (0.313–8.000)	0.579
Chemotherapy								
No			—	—			—	—
Yes	0.673 (0.259–1.750)	0.417	—	—	1.86 (0.475–7.275)	0.373	—	—

CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; SBRT, stereotactic body radiotherapy.

(P = 0.006). There was no significant difference between the groups in terms of achieving control of the primary and metastatic lesions (P = 0.722). Systemic chemotherapy after local treatment was more frequently administered in the metastasectomy group (P = 0.034).

Treatment outcome

The patients were followed up for a median duration of 13.7 months (range: 7.8–75.5). Among the 51 patients, 6 (11.8%) experienced local recurrence, including 4 (19%) in the SBRT group and 2 (6.7%) in the metastasectomy group. The one and two-year local control rates were 83.5% and 75.2% in the SBRT group and 96.6% and 91.5% in the metastasectomy group, respectively; there were no significant differences between the groups (P = 0.163). PFS was significantly longer in the metastasectomy group than in the SBRT group (P = 0.02). The one-year PFS rates were 23.8% and 51.1% in the SBRT and metastasectomy groups, while the corresponding two-year PFS rates were 11.9% and 46%, respectively. Furthermore, the one and two-year OS rates were 79.5% and 68.2%, in the SBRT group and 95% and 81.8% in the metastasectomy group, respectively. However, the difference in OS between the treatment groups was not significant (P = 0.534).

Univariate analysis showed that age, gender, comorbidities, ECOG PS, interval between diagnosis and lung metastases, tumor size, other synchronous metastases, and treatment modality had no significant influence on local control. However, a larger metastatic mass and the presence of other synchronous metastases were related to poorer PFS (both P = 0.001) (Table 2). Patients treated with SBRT had poorer PFS rates than those who underwent metastasectomy (P = 0.024). Tumor size and the presence of synchronous metastases were also risk factors for poor OS (P = 0.004 and P = 0.040, respectively). The type of treatment modality did not influence OS (P = 0.537). The factors identified by univariate analysis and those suggested in previous studies to be related to PFS and OS were subjected to multivariate analysis. This analysis revealed that the presence of other synchronous metastases was the most significant factor associated with poor PFS (hazard ratio [HR] 3.461, 95% confidence interval [CI] 1.720–6.964; P = 0.001), while tumor size was the most significant factor associated with OS (HR 1.386, 95% CI 1.107–1.735; P = 0.004). However, the type of treatment (SBRT vs. metastasectomy) did not influence PFS or OS.

We performed stratification analysis of survival rates according to treatment modality and the presence of synchronous metastases. In patients who received SBRT, those with synchronous metastases tended to have poorer PFS rates (P = 0.062) (Fi1a), while in patients who underwent metastasectomy, the corresponding difference in PFS was significant (P = 0.038) (Fig 1b). Among patients with no synchronous metastases, there was no significant difference in PFS between the treatment modalities (P = 0.327) (Fig 1c). Similarly, patients with synchronous metastases exhibited no difference in PFS regardless of whether they underwent SBRT or metastasectomy (P = 0.727) (Fig 1d).

Among patients treated with SBRT, those with synchronous metastases exhibited significantly poorer OS than those without (P = 0.026) (Fig 2a); the difference in OS was not significant for those who underwent metastasectomy (P = 0.554) (Fig 2b). When stratified according to the presence of synchronous metastases, there was no significant difference in OS according to the type of treatment applied (P = 0.598 and P = 0.273 for SBRT and metastasectomy, respectively) (Fig 2c,d).

Toxicity

Radiation pneumonitis developed in 18 of the 21 patients who received SBRT (85.7%): grade 1 in 12 (57.1%), grade 2 in 5 (23.8%), and grade 3 in 1 (4.8%). Two patients each experienced grade 1 and 2 rib fractures, while one and two patients experienced grade 1 and 2 chest wall pain, respectively.

In the metastasectomy group, one patient experienced acute bleeding requiring surgical intervention. One patient had acute respiratory distress syndrome requiring intensive medical care; the patient improved after one month of hospitalization. One patient experienced grade 3 nausea and required fluid treatment.

Discussion

In this study, PFS was significantly longer in patients who had undergone metastasectomy than in patients who had received SBRT for pulmonary metastases. There were no significant differences in local control or OS between the treatment groups. Subgroup analysis showed that PFS rates varied depending on the presence or absence of synchronous metastases; however, the treatment method did not make a difference in either situation. OS rates showed similar trends to PFS. Multivariate analysis revealed that the presence of synchronous metastases significantly influenced PFS. No severe treatment-related toxicities were observed in this study.

Previous studies investigating treatment outcomes in patients with pulmonary metastases were retrospective reviews of patients treated with a single modality for primary cancers of diverse origins.[19–21] Surgery is initially recommended for the local treatment of pulmonary metastases.[14,22] The indications for treatment via metastasectomy have been relatively well studied compared to SBRT, and include good PS, long disease-free survival, and the absence

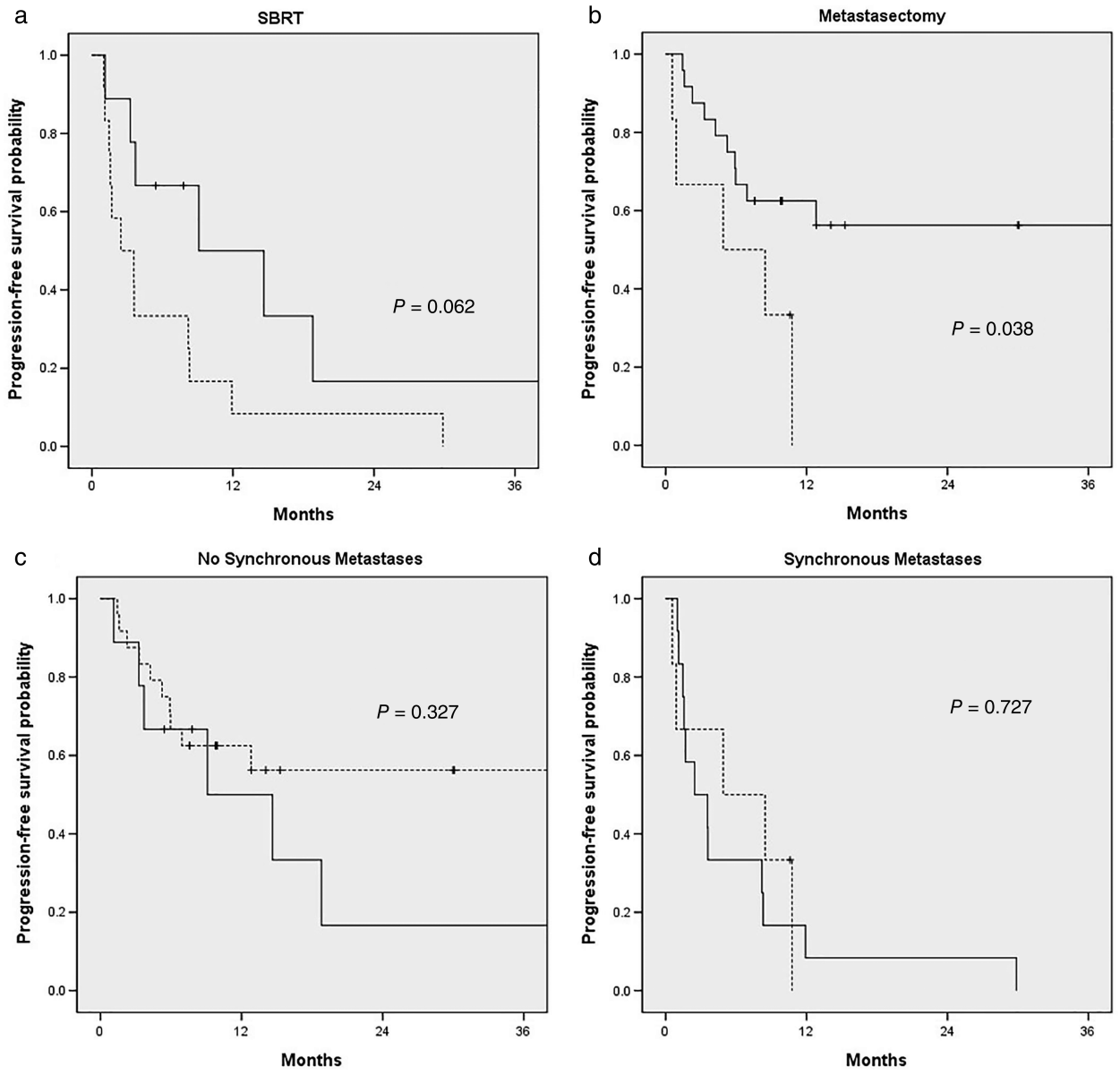

Figure 1 Kaplan–Meier curves showing progression-free survival (PFS) in patients treated with (**a**) stereotactic body radiotherapy (SBRT) or (**b**) metastasectomy according to the presence of synchronous metastases (⌐¬) no, (⌐¬) yes, (—) no-censored, and (—) yes-censored. (**c**) PFS in patients with absent or (**d**) present synchronous metastases according to whether they underwent SBRT or metastasectomy (⌐¬) SBRT, (⌐¬) metastasectomy, (—) SBRT-censored, and (—) metastasectomy-censored.

of synchronous metastases.[23] Surgery is not recommended when incomplete resection is predicted, the primary tumor is not locoregionally controlled, widespread metastatic cancer is present, and/or pulmonary function is inadequate. A systematic review found that the two-year OS for patients who undergo complete resection ranges from 64–88% and that the survival outcome is good.[13] The patients in our study who underwent metastasectomy showed a two-year OS rate of 81.8%, which was consistent; however, OS rates were poor when synchronous metastases were present.

Stereotactic body radiotherapy is increasingly being used as a local treatment for pulmonary metastases because of its noninvasiveness and lower morbidity. This modality is also considered for metastatic lesion control and disease progression delay during breaks from chemotherapy. However, studies of SBRT are subject to selection bias as they often include older patients with poor PS and pulmonary function, and higher metastatic burdens compared to patients who undergo surgery. Nevertheless, the one-year local control rates reportedly range from 70% to 95%,

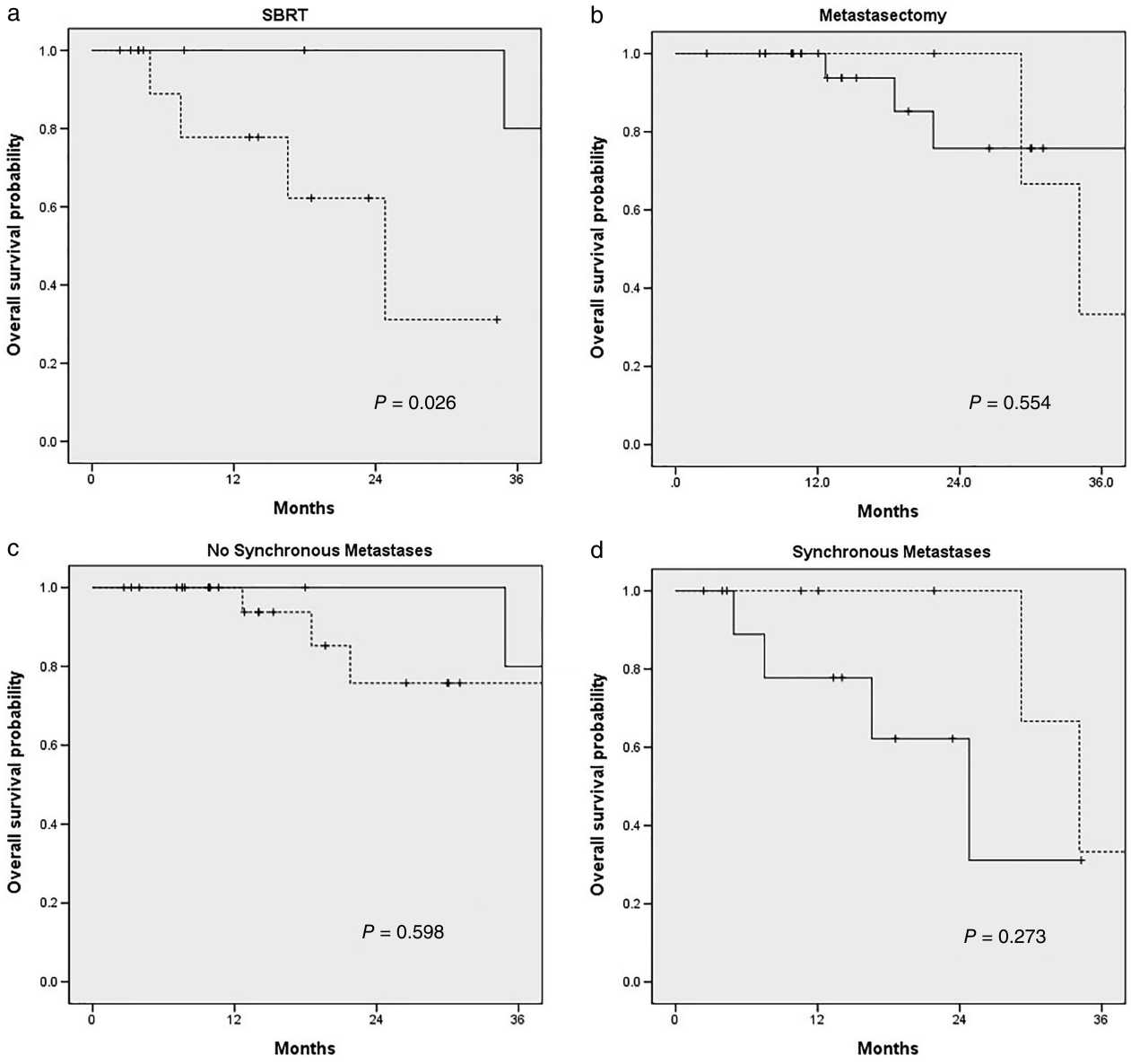

Figure 2 Kaplan–Meier curves showing overall survival (OS) in patients treated with (**a**) stereotactic body radiotherapy (SBRT) or (**b**) metastasectomy according to the presence of synchronous metastases (⌐¬) no, (⌐¬) yes, (—|—) no censored, and (—|—) yes-censored. (**c**) OS in patients with absent or (**d**) present synchronous metastases according to whether they underwent SBRT or metastasectomy (⌐¬) SBRT, (⌐¬) metastasectomy, (—|—) SBRT-censored, and (—|—) metastasectomy-censored.

which are favorable.[24] Patients in our study also showed good one and two-year local control rates of 83.5% and 75.2%, respectively.

Conversely, the two-year OS rates vary in the literature, ranging from 33% to 80%.[19] In our study, the two-year OS was 68.2%, which is consistent with previous results despite the heterogeneous primary tumors in our patients.

Comparative retrospective investigations that compare pulmonary metastasectomy to SBRT are rare, with only two such studies published. Widder *et al.* compared metastasectomy to SBRT in patients treated in a university hospital-based multidisciplinary setting.[14] Patients with favorable prognoses were offered metastasectomy, while SBRT was the second treatment of choice; however, survival rates were comparable in both populations. The one, three, and five-year OS rates were 87%, 62%, and 41% for metastasectomy, and 98%, 60%, and 49% for SBRT, respectively. The other study compared the survival outcomes of surgery versus SBRT in patients with pulmonary

oligometastases from colorectal cancer.[22] The one and two-year OS rates were 89% and 77% for SBRT and 96% and 82% for surgery, respectively, with no significant differences. Patients who received SBRT in our study also showed comparable survival outcomes at two years to those who underwent metastasectomy. Additionally, despite the prevalence of larger-size metastatic lesions and the presence of synchronous metastases (which are usually considered relative contraindications for metastasectomy) in the SBRT group, the survival outcomes in these patients were comparable to those in the surgery group.

Randomized trials are required to determine whether SBRT improves local control, PFS, and OS in patients with pulmonary metastases. Recently, a multicenter, randomized phase II study was performed to assess the effect of local consolidative therapy in oligometastatic non-small cell lung cancer patients.[25] Although the primary treated lesion was in the lung, local consolidative therapy (mainly radiotherapy) extended patients' PFS rates. To the best of our knowledge, no studies have compared active monitoring and SBRT for pulmonary metastases; however, a randomized trial comparing the outcomes of colorectal cancer patients receiving active monitoring versus those undergoing pulmonary metastasectomy has been ongoing since 2010 (NCT01106261), with the results pending.

Tanadini-Lang *et al.* evaluated prognostic factors for OS and developed a nomogram aimed at predicting OS after SBRT for pulmonary metastases.[11] According to their study, OS was influenced by the size of the pulmonary metastatic lesion, whether synchronous metastasis was present, and whether the primary lesion was controlled. Although patients with large metastatic lesions and synchronous metastases (which are considered contraindications to metastasectomy) were more prevalent in the SBRT group in our study, their OS rates were comparable to those in the surgery group. Thus, SBRT is considered a good local treatment modality with a broader indication than metastasectomy.

It has been suggested that SBRT may produce antitumor effects not only through direct DNA damage but also via immunologic modulation. The effect of SBRT in the tumor stroma or outside the treatment field, referred to as the abscopal effect, is currently undergoing rigorous research.[26] Widder *et al.* unexpectedly showed that although patients with good prognoses were included in the surgery instead of the SBRT group, survival outcomes were not superior in the former group.[14] The authors explained that the high local control attained with both treatments may contribute to achieving comparable survival outcomes; however, immunologic responses may also promote favorable outcomes in patients receiving SBRT. Likewise, patients with poor prognostic factors in our study who were treated with SBRT may have benefited from immunologic responses that may have improved the survival outcomes to the extent that they were on par with those in the surgery group.

The present study had inevitable limitations as a result of its retrospective design. Additionally, the number of patients included in each treatment group was small, and the follow-up period was short. There was also an imbalance in patient characteristics and toxicity profiles that could have biased the results.

Our study showed that local treatment of pulmonary metastases with SBRT or metastasectomy produced similar local control and OS rates. SBRT is considered a suitable local modality, and a wide patient pool is eligible for this treatment. However, patients with synchronous metastases are only likely to obtain a small benefit from local treatment, whether via SBRT or surgery.

Disclosure

No authors report any conflict of interest.

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