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Stereotactic Body Radiotherapy Provides Excellent Long-Term Local Control of Very Few Lung Metastases

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Abstract. *Aim: To evaluate treatment outcomes after stereotactic body radiotherapy (SBRT) for a limited number of lung metastases mainly focusing on local control. Patients and Methods: Forty-six patients receiving SBRT for 1-3 lung metastases were retrospectively evaluated. Local control, freedom from distant progression and overall survival were evaluated in the entire series. In addition, nine factors (gender, age, performance status, interval between cancer diagnosis and SBRT, primary tumor type, other metastases, main site and number of lesions, irradiated volume, SBRT dose) were evaluated for local control. Results: Local control rates at 1, 2 and 3 years were 93%, 93% and 78%, respectively. Rates of freedom from distant progression were 57%, 38% and 29%, respectively, and overall survival rates were 66%, 56% and 36%, respectively. Only one patient (2%) experienced radiation-induced pneumonitis. Conclusion: SBRT administered for very few lung metastases resulted in excellent long-term local control rates and was associated with very little toxicity.*

Patients with disseminated lung metastases generally have a poor prognosis, whereas patients with a very limited number of lesions may live much longer. This raises the question of whether the latter group of patients would benefit from a more aggressive local treatment approach including thoracic surgery or stereotactic body radiotherapy (SBRT) (1, 2). In many institutions, patients presenting in a more favorable general condition preferably undergo surgical resection, whereas elderly patients or those with a poorer performance status are more likely considered for non-invasive SBRT (1). This selection bias may lead to the conclusion that SBRT is less effective than thoracic surgery. The present study was performed on a less selected series of patients. Out of patients included in this study, 72% had a good performance status, *i.e.* an Eastern Cooperative Oncology Group (ECOG) performance score of 0-1, and 63% were younger than 70 years. However, the patients still had less favorable characteristics than patients generally selected for thoracic surgery. Since SBRT is a local treatment, the study focused mainly on the local control of the irradiated lung metastases.

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Patients and Methods

In this retrospective study, 46 patients treated with SBRT for 1-3 lung metastases were analyzed for local control of the irradiated lesions. SBRT doses were prescribed to the margins of the metastatic lesions and ranged from 48 to 80 Gy given as EQD2 (equivalent dose in 2Gy fractions). The EQD2s were obtained from the equation: EQD2=TD×(DFx+α/β /2 Gy+α/β), where TD=total dose, DFx=dose per fraction, α/β=10 Gy (3).

The most common SBRT program was 8×6 Gy (EQD2=64 Gy), which was administered to 28 patients (61%). Other programs included 6×6 Gy (EQD2=48 Gy, n=7), 15×3.3 Gy (54.9 Gy, n=1), 12×4 Gy (56 Gy, n=1), 5×8 Gy (60 Gy, n=1), 3×12.5 Gy (70.3 Gy, n=3), 5×9 Gy (71.3 Gy, n=1), 6×8 Gy (72 Gy, n=3) and 10×6 Gy (80 Gy, n=1). Local control of the irradiated lung metastases, freedom from distant progression and overall survival were evaluated in the entire series. In addition, 10 factors, namely gender, age (≤65 *vs.* ≥66 years, median=65 years), ECOG performance score (0-1 *vs.* 2), interval between cancer diagnosis and SBRT of the lung metastases (≤12 *vs.* >12 months), primary tumor type [non-small cell lung cancer (NSCLC *vs.* colorectal cancer *vs.* melanoma *vs.* other], other metastases (no *vs.* yes), main site of lung metastases (upper lobe *vs.* lower lobe *vs.* other), number of lesions (1 *vs.* 2-3), irradiated volume (≤16 *vs.* >16 ml, median=16 ml) and EQD2 (≤60 Gy *vs.* >60 Gy) were evaluated for local control. For the univariate analysis, the Kaplan–Meier method and the log-rank test were applied; for the multivariate analysis, Cox regression analysis was used (4).

Table I. *Local control rates at 1, 2 and 3 years following stereotactic body radiotherapy (SBRT).*

Factor	At 1 year (%)	At 2 years (%)	At 3 years (%)	*p*-Value†	*p*-Value‡
Gender					
Female (n=18)	92	92	92		
Male (n=28)	92	92	71	0.81	0.97
Age					
≤65 Years (n=24)	100	100	67		
≥66 Years (n=22)	82	82	82	0.36	0.98
ECOG performance score					
0-1 (n=33)	96	96	77		
2 (n=13)	86	86	86	0.60	0.97
Interval between cancer diagnosis and SBRT					
≤12 Months (n=18)	91	91	91		
>12 Months (n=28)	95	95	71	0.94	0.97
Primary tumor type					
NSCLC (n=16)	90	90	90		
CRC (n=13)	90	90	60		
Melanoma (n=5)	100	100	100		
Other (n=12)	100	100	100	0.69	0.93
Other metastases					
No (n=24)	88	88	88		
Yes (n=22)	100	100	67	0.67	0.78
Main site of lung metastases					
Upper lobe (n=18)	93	93	75		
Lower lobe (n=9	88	88	88		
Other (n=4)	100	100	100	0.58	0.94
Number of lesions					
1 (37)	91	91	76		
2-3 (9)	100	100	100	0.43	0.97
Irradiated volume					
≤16 ml (n=24)	100	100	75		
>16 ml (n=22)	85	85	85	0.34	0.97
EQD2					
≤60 Gy (n=10)	100	100	100		
>60 Gy (n=36)	91	91	68	0.29	0.94

SBRT: Stereotactic body radiation therapy, ECOG: Eastern Cooperative Oncology Group, NSCLC: non-small cell lung cancer, CRC: colorectal cancer, EQD2: equivalent dose in 2 Gy fractions. †Univariate analysis, ‡multivariate analysis.

Results

Local control rates for the entire cohort at 1, 2 and 3 years were 93%, 93% and 78%, respectively. Rates of freedom from distant progression were 57%, 38% and 29%, respectively. Overall survival rates were 66%, 56% and 36%, respectively. On both univariate and multivariate analyses, none of the investigated factors had a significant association with local control. The data of analyses of local control are given in Table I.

SBRT was well tolerated. Only one patient (2%) experienced radiation-induced pneumonitis. In addition, 17 patients (37%) complained about mild to moderate fatigue.

Discussion

Due to improved treatment of primary tumors and regional lymph nodes, the survival times of patients with cancer have become considerably longer over the past decades. Since the risk of developing metastatic disease increases with lifetime, the number of patients living long enough to experience the occurrence of distant metastases is constantly growing. This applies also to patients developing lung metastases. In cases with very few pulmonary lesions, more aggressive treatment regimens including surgical resection and SBRT have gained importance. In many centers, thoracic surgery is the first choice for these patients if they are considered able to withstand this procedure (1,

5). Patients with a reduced general condition and elderly patients are at a higher risk of experiencing surgery-related and anesthesia-related complications, including infections, pneumonia and thromboembolic events. Many such patients are referred for SBRT (2, 6). These selection processes likely led to biases in the past and have given the impression that SBRT is less effective than surgical resection. The present study of SBRT for 1-3 lung metastases included a considerable proportion of patients with a good performance status (ECOG 0-1) and patients younger than 70 years. According to the results, SBRT resulted in excellent long-term local control rates. At 2 and 3 years following SBRT, local control rates were still 93% and 78%, respectively. The 2-year local control rate of the present study was better than the local control rates of 64% and 86% observed in two previous studies (2, 6). This difference was likely due to the number of lesions and the primary tumor types included. In one previous study, up to five lung metastases were treated (2), and the other previous study focused on lung metastases from sarcomas that are considered less radiosensitive than many other solid tumor types (6). In the present study, the high local control rates did not translate into high overall survival rates. The 2-year overall survival rate of 56% was in the range of 49% to 66% of the previous studies (2, 6).

In the present study, the relatively low survival rates (in comparison to the high local control rates) can be explained by the fact that a considerable number of the patients showed progression of their disease distant from the irradiated lung metastases. At 2 and 3 years following SBRT, only 38% and 29% of patients, respectively, had no distant progression. This demonstrates that the patients included in this study still had less favorable characteristics than most patients included in studies investigating surgical resection of lung metastases. Despite the less favorable characteristics of the patients in the presents study, SBRT resulted in high long-term local control rates and can therefore be considered a reasonable option for all patients with very few lung metastases, not only for elderly patients aged 70 years or more and those patients with a poor performance status. Furthermore, SBRT for lung metastases was very well tolerated in the present series, with a comparably low pneumonitis rate (7). The results of SBRT, in particular regarding freedom from distant progression and overall survival, may be further improved with the addition of concurrent and sequential chemotherapy. The combination of SBRT and concurrent chemotherapy was recently presented as a new and feasible treatment option for metachronous primary lung cancer (8).

In conclusion, when administered for a very limited number of lung metastases SBRT resulted in excellent long-term local control rates and was associated with very little toxicity. Therefore, SBRT can be considered a reasonable alternative to thoracic surgery, not only for elderly patients and those with a limited general condition.

Conflicts of Interest

On behalf of all Authors, the corresponding Author states that there is no conflict of interest related to this study.

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