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# Stereotactic body radiation therapy for lung metastases

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ABSTRACT

*Introduction:* Stereotactic body radiation therapy (SBRT) has an emerging role in patients affected with pulmonary metastases. Purpose of this study was to evaluate efficacy and tolerability of SBRT in a cohort of patients treated between 2003 and 2009 at our institution.
*Methods:* A total of 61 patients with oligometastatic lung tumors (single pulmonary nodules in 73.7%) were included in the study. SBRT was performed with a stereotactic body frame and a 3D-conformal technique. Fifty-one patients received 26 Gy in 1 fraction, 22 a dose of 45 Gy in 3 fractions and 3 a dose of 36 Gy in 4 fractions. Primary tumor was lung cancer in 45.7% of patients, colorectal cancer in 21.3% and a variety of other origins in 33%. The primary endpoint was local control, secondary endpoints were survival and toxicity.
*Results:* After a median follow-up interval of 20.4 months, local control rates at 2 and 3 years were 89% and 83.5%, overall survival 66.5% and 52.5%, cancer-specific survival 75.4% and 67%, progression-free survival 32.4% and 22.3%. Tumor volume was significantly associated to survival, with highest rates in patients with single small tumors. Median survival time was 42.8 months, while median progression-free survival time was 11.9 months. Toxicity profiles were good, with just one case of grade III toxicity (pneumonitis).
*Conclusion:* This study shows that SBRT is an effective and safe local treatment option for patients with lung metastases. Definitive results are strictly correlated to clinical selection of patients.


## 1. Introduction

The lung is a main site of metastatic disease for most solid tumors and local treatments have an emerging role in combination with systemic therapies. In oligometastatic (1–3 pulmonary nodules) and clinically selected patients (good performance status and absent or stable extra-thoracic disease), surgery can be considered as the standard option, with good results in terms of local control and survival [1].

Stereotactic body radiation therapy (SBRT) represents a potentially effective alternative treatment modality, with recent studies reporting high local control rates, a good toxicity profile and survival outcomes comparable to surgical series when high doses are delivered in one or more fractions [2,3], as previously shown for patients affected by stage I NSCLC not amenable with surgery [4–6].

Aim of the present study was to investigate feasibility, toxicity and effectiveness of SBRT in the treatment of lung metastases.

## 2. Materials and methods

### 2.1. Patients

We performed a retrospective analysis of 61 patients with 77 metastases treated with SBRT between July 2003 and March 2009 at our institution. Selection criteria for SBRT were: 1–3 lung metastases (the current definition of oligometastatic disease includes 1–5 metastatic sites, but when we started our SBRT program in metastatic lung tumors the majority of clinical series was limited to 3 lesions), maximum tumor diameter smaller than 50 mm, absent or controlled extra-thoracic disease (at CT and CT-PET scans performed prior to SBRT), adequate pulmonary function ($FEV_1$ higher than 40% predicted and DLCO higher than 40% predicted), no prior

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**Table 1**
Patients' characteristics.

| | |
|---|---|
| Patients characteristics | |
| No. of patients | 61 |
| No. of lesions | 77 |
| Age (years) | |
| Median | 70 |
| Range | 46–86 |
| Male:female proportion | 2.34:1 |
| Primary tumor | |
| NSCLC adenocarcinoma | 10 (16.4%) |
| NSCLC squamous | 8 (13.1%) |
| NSCLC NOS/other | 16 (26.2%) |
| CRC | 13 (21.3%) |
| Pancreas | 2 (3.4%) |
| HCC | 2 (3.4%) |
| Head and neck | 2 (3.4%) |
| Melanoma | 1 (1.6%) |
| Liposarcoma | 1 (1.6%) |
| Breast | 1 (1.6%) |
| Kidney | 1 (1.6%) |
| Prostate | 1 (1.6%) |
| Timoma | 1 (1.6%) |
| Uterus | 1 (1.6%) |
| Esophagus | 1 (1.6%) |
| Disease-free interval (months) | |
| Median | 28.2 |
| Range | 1–174 |
| Prior systemic therapy regimens for metastatic disease | |
| Yes | 7 (11.5%) |
| No | 54 (88.5%) |
| Presence of extrathoracic disease | |
| Yes | 3 (5%) |
| No | 58 (95%) |
| No. of thoracic metastases | |
| 1 | 45 (73.7%) |
| 2 | 16 (26.3%) |
| Tumor size (mm) | |
| Median | 20 |
| Range | 7–45 |
| Gross tumor volume ($cm^3$) | |
| Median | 3.3 |
| Range | 0.2–19 |
| <3.3 $cm^3$ | 44 (57.1%) |
| >3.3 $cm^3$ | 33 (42.9%) |
| Radiation doses at 80% isodose (Gy) | |
| 26/1 fr | 51 |
| 45/3 fr | 22 |
| 36/3 fr | 4 |

*Abbreviations*: NSCLC (non-small cell lung cancer), CRC (colo-rectal cancer), HCC (hepatocarcinoma).

radiotherapy, performance status ECOG 0-1. Patients with any primary tumor histology were eligible (except those with germ cell tumors or hematological malignancies). All patients were mandatorily restaged according to clinical guidelines for their primary tumor prior to SBRT; a PET-CT scan was always requested to complete restaging when not previously performed (the interval between PET scan and SBRT was in the range 20–60 days, less than 45 days in 85.2% of patients). Lung metastases were clinically diagnosed without a histological confirmation in the majority of patients (88.5%). Metastatic lesions were defined as the onset of new lung nodules $\geq$8 mm of diameter, with $^{18}$FDG uptake and a Standard Uptake Value > 4.5, during the regular follow-up of a previous cancer disease.

Patient's characteristics are summarized in Table 1. Forty-five patients had single metastasis (73.7%) and sixteen 2 metastases (26.3%). In 34 patients (55.7%) the primary tumor was lung cancer. Out of a total of 61 patients, 7 (11%) received chemotherapy (for metastatic disease) prior to SBRT and 9 (14.7%) underwent previous pulmonary metastasectomy at the time of their first event of lung metastatic disease.

Written informed consent for the use of SBRT was obtained in every case and the Institutional Review Board approved the study.

### 2.2. Treatment technique

Treatment technique was previously described by our group [6]. In this series the vast majority of treatments were planned without employing 4D-CT, introduced in our clinical routine for SBRT since July 2008; briefly, each patient was immobilized in supine position with a stereotactic body frame (SBF-ELEKTA® Oncology Systems). Set-up was checked using a laser system and permanent chest and legs skin markers. Tumor's movements secondary to breathing were checked by fluoroscopy and measured with a 10 mm grid; in case of tumor movements exceeding 10 mm a diaphragm compression device was used to reduce motion below the previous accepted limits. A planning CT scan of the entire thorax (2.5 mm thick slices) without intravenous contrast media was obtained for every patient. Each CT slice was scanned with an acquisition time of 3 s to include all phases of one respiratory cycle. The target was outlined in sequential axial CT images and the gross tumor volume (GTV) contoured using a CT lung window setting (1600–400 Hounsfield units). Clinical target volume (CTV) corresponded to GTV, as previously reported. The planning target volume (PTV) was generated adding a 5 mm margin in the axial plane and a 10 mm margin in the longitudinal direction, in order to compensate for set-up errors and organ motion. A Multi-Leaf Collimator – PTV distance of 3–5 mm was employed to adequately cover PTV within 80% isodose. Adjacent organs-at-risk (esophagus, heart, spinal cord, both lungs, trachea-main bronchi) were then outlined. OTP version 1.5 software was employed for treatment planning and SBRT was delivered with an Elekta Precise® Linear Accelerator, using 6–8 static non-opposing, non-coplanar shaped fields, with 6–10 MV photons. Dose limits to organs-at risk were as follows (converted in 2 Gy-equivalent according to Linear Quadratic Model): ipsilateral mean lung dose < 15 $Gy_2$ (radiation pneumonitis, alfa/beta = 3.5 Gy), spinal cord <36 $Gy_2$ (alfa/beta = 2 Gy), skin < 56 $Gy_2$ (necrosis, alfa/beta = 2.5 Gy), trachea/main bronchi < 78 $Gy_2$ (stenosis/fistula, alfa/beta = 3 Gy), heart <70 $Gy_2$ (pericarditis, alfa/beta = 4 Gy).

Radiation doses were prescribed to the PTV encompassing 80%-isodose, with normalization to 100% at the isocenter; convolution superposition algorithm (collapsed cone) was employed for dose calculation. Orthogonal anterior (0°) and lateral (90°) digital portal images were obtained and compared to digitally reconstructed radiographs (DRRs) before each treatment session. Patients were repositioned and portal images were taken and re-checked if set-up error was estimated to be 3 mm or more in any direction. This measure was obtained by online comparison of 4 cm × 4 cm field size AP and LL digitally reconstructed radiographs to portal images with the help of an electronic grid and a specific fusion software.

Initially, when treating metastatic tumors, we employed a schedule of 45 Gy/3 fractions in 3 days, as we usually did in SBRT for primary NSCLC; afterwards, we started to deliver single fractions of 26 Gy in order to improve patients compliance and to optimize department workload; this dose level, originally employed by Wulf et al. [7] in metastatic tumors, corresponds to a minimal biologically effective dose of 94 Gy at the tumor periphery with an alfa/beta ratio of 10 Gy ($BED_{10}$), slightly lower than the previous fractionation schedule.

Seventy-seven treated tumors (in 61 patients) received the following doses: 26 Gy/1 fraction (51 tumors, minimal $BED_{10}$ 94 Gy), 45 Gy/3 fractions (22 tumors, minimal $BED_{10}$ 112.5 Gy), 36 Gy/3 fractions (minimal $BED_{10}$ 79.2 Gy, in 4 tumors when normal tissues dose constraints, mainly Mean Lung Dose, did not allow the safe delivery of standard 45 Gy in 3 fractions).

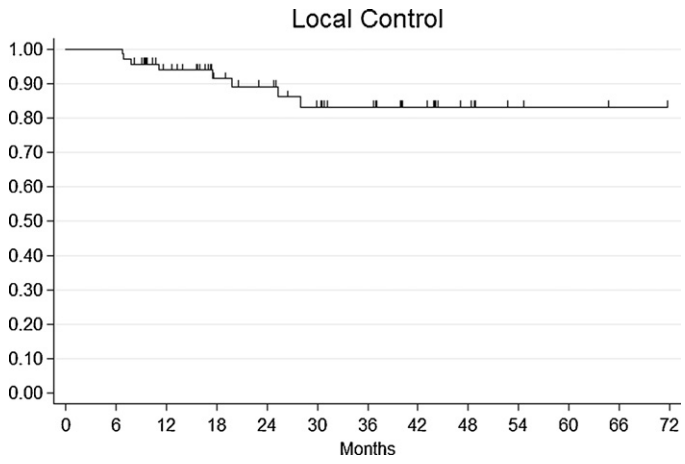


**Fig. 1.** Actuarial local control.

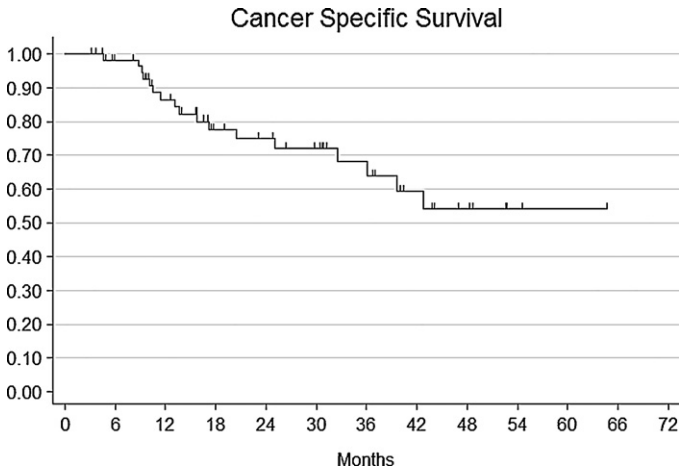


**Fig. 3.** Cancer-specific survival.

### 2.3. Follow-up and statistics

Primary endpoint of this clinical study was local control; secondary endpoints were overall, cancer-specific, progression-free survival (OS, CSS, PFS) and treatment-related toxicity.

All patients underwent clinical examination and CT scan for evaluation of treatment results and side effects 6 weeks after SBRT, and were then prospectively followed with clinical examination and CT scans every 3 months. CT-PET was employed in follow-up only in case of differential diagnosis between radiation fibrosis and tumor progression.

Lung toxicity was graded according to the RTOG acute radiation toxicity score (for events occurring between day 1 and day 90 from the start of radiation treatment) and to the RTOG late radiation toxicity score (for events occurring after day 90) (http://www.rtog.org/members/toxicity).

Local tumor control was defined as the absence of local progression, evidenced by tumor growth or re-growth after initial shrinkage. Although it is occasionally difficult to differentiate tumor re-growth from radiation-induced lung injury, tumor recurrence was considered if a solid homogeneous mass increasing in size during follow-up was evident.

Cox proportional hazards model was used to calculate the hazard ratios (HRs) and their 95% confidence interval in multivariate analysis. All $p$ are two-sided and <0.05 was considered for statistical significance. The proportionality assumption was investigated using a test based on the Schoenfeld residuals. Factors investigated for prognostic value with respect to clinical outcome parameters were: age, gender, histology of primary tumor, disease-free interval (median time from primary tumor diagnosis and lung systemic spread), prior systemic therapy (for metastatic disease), size and number of lesions (for size, the median value of 3.3 $cm^3$ was considered as cut-off; for patients with 2 lesions the larger lesion was considered for multivariate analysis for potential correlation to survival), control of primary tumor, presence of extra-thoracic metastatic disease, radiation doses (BED equivalent). Performance status was not considered since patients were strictly selected from a clinical point of view (only ECOG 0-1).

Survival curves were generated using the method of Kaplan and Meier starting from time of SBRT, and were defined as follows: overall survival (end-point: death from any cause), cancer-specific survival (end-point: cancer-related death), progression-free survival [end-point: local and/or regional (nodal) and/or systemic failure]; the log-rank test was used to test for survival differences.

STATA Statistical Software (10.0 release, STATA Corporation, College Station, TX, 2007) was employed for data analysis.

## 3. Results

All patients were assessable for local control and survival. The median follow-up time was 20.4 months (range 3–77.4).

Actuarial local control at 2 years was 89% (Fig. 1). Nine events of local failure were recorded; multivariate analysis did not show a

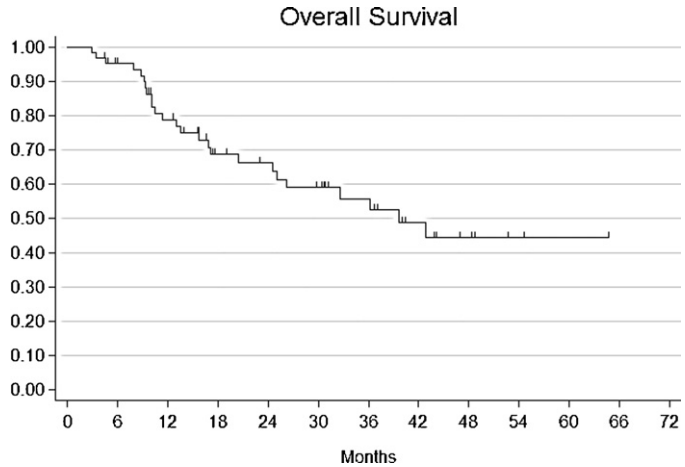


**Fig. 2.** Overall survival.

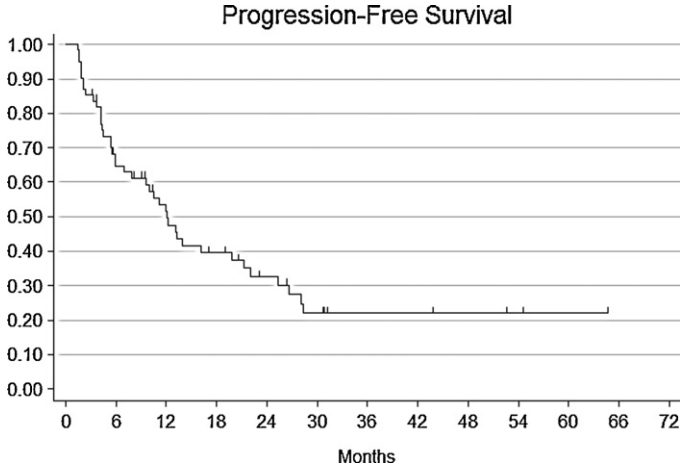


**Fig. 4.** Progression-free survival.

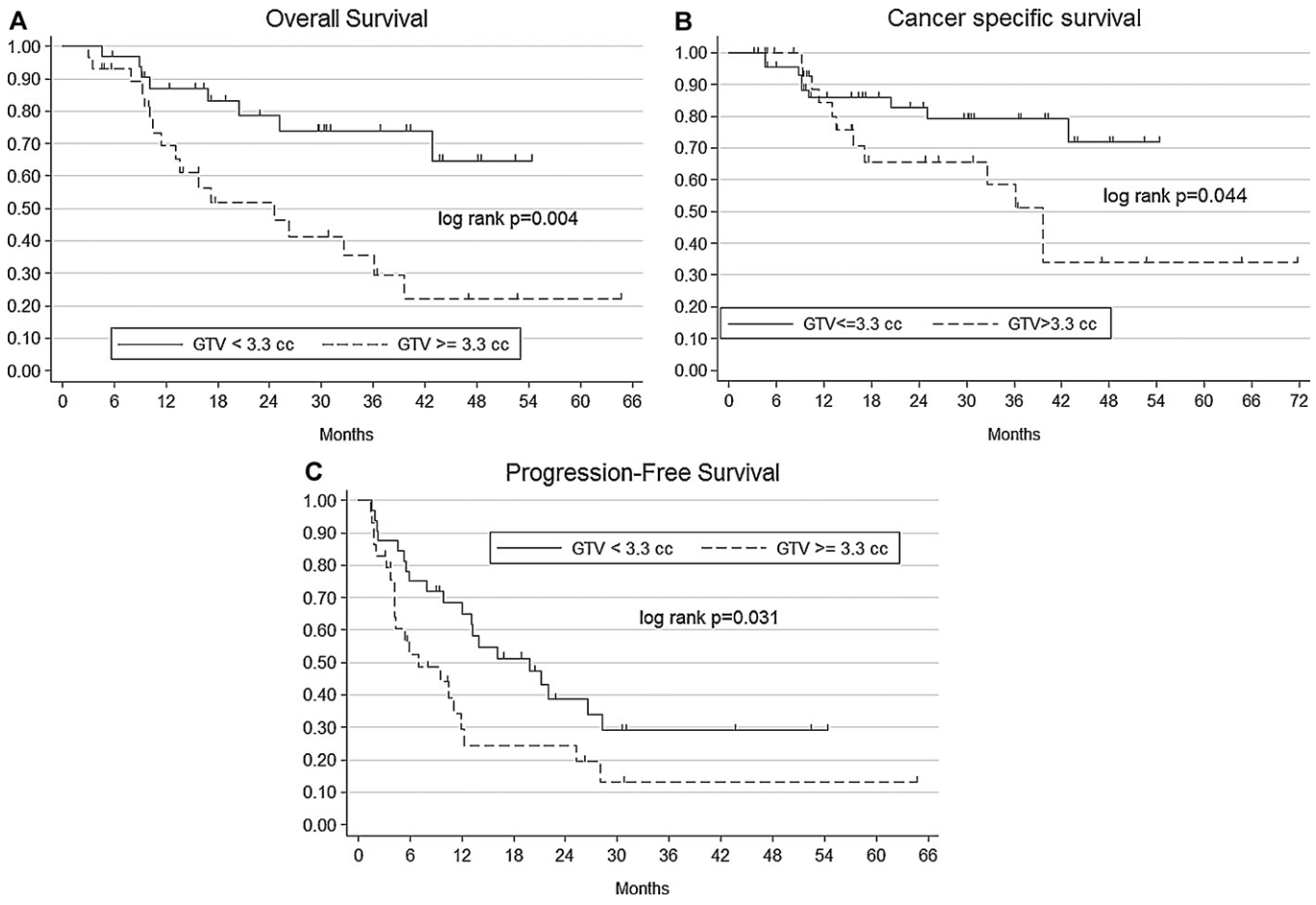


**Fig. 5.** (a) Overall survival by gross tumor volume, (b) cancer-specific survival by gross tumor volume and (c) progression-free survival by gross tumor volume.

significant correlation between selected variables and local control probability (Table 2).

Overall survival, cancer-specific survival and progression-free survival rates at 2 years were respectively 66.5, 75.4 and 32.4% (Figs. 2–4). Median survival time was 42.8 months and median progression-free survival time was 11.9 months.

GTV was significantly correlated to OS, CSS and PFS on multivariate analysis (Table 2); log-rank tests performed on Kaplan–Meier survival estimates confirmed this finding as shown in Fig. 5(a)–(c).

The selected group of patients ($n = 24$) with small (<3.3 $cm^3$) single metastasis had the more favorable outcome in terms of progression-free survival, with a PFS rate of 70% at 1 year and of 52.8% at 2 and 3 years (Fig. 6).

The number of metastatic lesions was not correlated to PFS at multivariate analysis but a trend was evident (Table 2). Pattern of disease progression is reported in details in Table 3.

Fifteen patients received chemotherapy after SBRT at the time of systemic progression (24.6%) and 10 (16.4%) were treated after SBRT with surgery, radio-surgery and/or thermo-ablation for isolated metastatic lesions diagnosed during follow-up.

No cases of grade 4 acute or late toxicity were recorded. One case of grade 3 acute pulmonary toxicity (severely interfering with daily activities and requiring treatment) and 2 cases of grade 2 were observed, with most of the patients experiencing no toxicity at all.

**Table 2**
Multivariate analysis.

| Factors | OS | | CSS | | LC | | PFS | |
|---|---|---|---|---|---|---|---|---|
| | HR | *p* | HR | *p* | HR | *p* | HR | *p* |
| Age (years) | 1.02 | 0.385 | 1.04 | 0.144 | 0.92 | 0.112 | 1.01 | 0.557 |
| Gender | 0.62 | 0.340 | 0.40 | 0.107 | 0.56 | 0.557 | 1.12 | 0.772 |
| Position | 1.24 | 0.584 | 1.02 | 0.963 | 0.60 | 0.587 | 0.76 | 0.381 |
| Tumor volume | 1.10 | 0.012 | 1.17 | 0.001 | 0.65 | 0.645 | 1.11 | 0.012 |
| Disease-free interval | 0.99 | 0.824 | 0.99 | 0.385 | 1.01 | 0.139 | 1.00 | 0.320 |
| *n* Lung mets | 0.79 | 0.609 | 0.77 | 0.617 | 0.06 | 0.927 | 1.65 | 0.068 |
| Prior chemotherapy | 0.56 | 0.335 | 0.70 | 0.583 | 0.01 | 0.999 | 1.17 | 0.109 |
| Biologically effective dose | 0.99 | 0.805 | 0.98 | 0.204 | 1.00 | 0.778 | 0.99 | 0.749 |

*Abbreviations*: OS (overall survival), CSS (cancer-specific survival), LC (local control), PFS (progression-free survival), HR (hazard ratio).

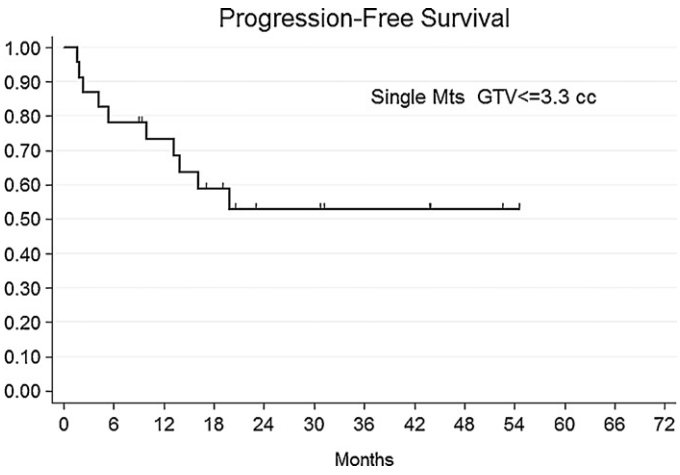


**Fig. 6.** Progression-free survival in patients with single and small metastases.

**Table 3**
Pattern of disease progression (a total of 38 failures in 33 patients).

| Pattern | *n* |
|---|---|
| New pulmonary metastasis | 10 |
| Regional lymph node metastasis | 7 |
| Local recurrence at SBRT site | 9 |
| Recurrence of primary lesion | 3 |
| Adrenal gland metastasis | 1 |
| Liver metastasis | 5 |
| Brain metastasis | 1 |
| Bone metastasis | 2 |

## 4. Discussion

We herein report the results of a clinical mono-institutional study investigating the role of SBRT in patients affected with 1–3 lung metastases. Previous published series, including various disease presentations and different radiation doses, show LC values at 2 years in the range of 67–100%, as well shown in a recent review by Siva et al. [8]. Although it is hard to make a correct comparison between different published experiences (different fractionation schedules and dose prescription modalities, LC rates reported at different times, different clinical characteristics and patients selection criteria), results of our study, with the majority of patients receiving 1 single fraction of 26 Gy or 45 Gy/3 fractions, appear quite similar. Tumor volume does not significantly correlate with local control probability, differently to what we observed with SBRT in primary lung tumors [6]; in some series there is a trend towards a worse clinical outcome, also in terms of local control, for larger lesions [2], while, according to our experience, this correlation emerges only for survival (OS, CSS and PFS). Overall, our treatment regimen (with BED slightly lower than values reported by other groups), appears to be adequate to control at 2 years at least 85% of metastatic tumors, without any difference in terms of local control between 26 Gy/1 fraction (minimal $BED_{10}$ of 94 Gy–maximal 138 Gy when considering 100% isodose) and 45 Gy/3 fractions (minimal $BED_{10}$ 112.5 Gy–maximal 161.7 Gy when considering 100% isodose).

Survival results of the present study are globally comparable to published experiences. In the review by Siva et al. [8], the 2-year weighted overall survival estimation from the largest studies is 54.5%, ranging from higher rates in selected series, such as the study by Norihisa et al. [9], reporting an OS rate at 2 years of up to 84%, to lower rates (39%) in the multi-institutional trial conducted by Rusthoven and colleagues [3] (it has to be underlined that this trial considers a general population of non-surgical unselected patients, with 39.5% presenting with 2 metastases, 28.9% receiving more than 1 previous chemotherapy lines, median volume of 4.2 $cm^3$ and roughly 30% of tumors >10 $cm^3$). Median overall survival (42.8 months) of our cohort is higher than expected for metastatic patients, the majority of them affected with primary lung tumors. A possible explanation could be that clinical characteristics of our patients are generally favorable in terms of tumor volume (in our series smaller than in other reports, with a median volume of 3.3 $cm^3$ and 86% < 10 $cm^3$), number of patients with single metastases (45/61, 73.7%), previous chemotherapy (11.5%), absence of extra-thoracic metastatic disease (95%). With regard to patients with lung cancer ($n = 34$), it has to be noticed that 27 (79.4%) had single metastases, diagnosed as small single nodules during regular follow-up. Moreover, we have a relatively high percentage of patients who received chemotherapy (24.6%) or other local treatments (16.4%) after SBRT, resulting in increased disease control after systemic progression.

Long-term results of metastasectomy from the International Registry of Lung Metastases show an OS rate of 70% at 2 years and 36% at 5 years [1]. As pointed out by different authors, it is difficult to compare SBRT data to historical surgical series. However, the results of the present study and of previous trials investigating the role of SBRT appear promising also considering issues such as patients compliance to treatment, toxicity profile, and cost-effectiveness parameters, even in the absence of histological confirmation of malignancy in SBRT series.

## 5. Conclusion

This study confirms that SBRT is a safe and effective procedure to locally control lung metastases, to prolong disease control, and to result in longer life, providing the possibility of cure in highly selected clinical subgroups.

## Conflict of interest statement

None declared.

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