

# Radiosurgery and fractionated stereotactic body radiotherapy for patients with lung oligometastases

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## Research article

**Keywords:** oligometastases, SBRT, radiosurgery, lung metastases, CyberKnife

**Posted Date:** August 2nd, 2019

**DOI:** <https://doi.org/10.21203/rs.2.12297/v1>

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**Version of Record:** A version of this preprint was published at BMC Cancer on May 11th, 2020. See the published version at <https://doi.org/10.1186/s12885-020-06892-4>.

# Abstract

**Background** Patients with oligometastatic disease can potentially be cured by using an ablative therapy for all active lesions. Stereotactic body radiotherapy (SBRT) is a non-invasive treatment option that lately proved to be as effective and safe as surgery in treating lung metastases (LM). However, it is not clear which patients benefit most and what are the most suitable fractionation regimes. The aim of this study was to analyze treatment outcomes after single fraction radiosurgery (SFRS) and fractionated SBRT in patients with lung oligometastases and identify prognostic clinical features for better survival outcomes.

**Methods** Fifty-two patients with 94 LM treated with SFRS or fSBRT (Cyberknife, Novalis) between 2010 and 2016 were analyzed. The characteristics of primary tumor, LM, treatment, toxicity profiles and outcomes were assessed. Kaplan-Meier and Cox regression analyses were used for estimation of local control (LC), overall survival (OS), progression free survival and distant metastases free survival (DMFS).

**Results** Ninety-four LM in 52 patients were treated using SFRS/fSBRT with a median of 2 lesions per patient (range: 1–5). The median prescription dose for SFRS was 24 Gy (range: 17-26) compared to 48 Gy (range: 24-75) in 2-12 fractions in fSBRT. The median follow-up time was 21 months (range: 3-68). LC rates at 1 and 2 years for SFRS vs. fSBRT were 89% and 83% vs. 75% and 59%, respectively ( $p=0.026$ ). LM treated with SFRS were significantly smaller ( $p=0.001$ ). The 1 and 2-year OS rates for all patients were 84% and 71%, respectively. In univariate analysis treatment with SFRS, an interval of  $\geq 12$  months between diagnosis of LM and treatment, non-colorectal cancer histology and BED  $<100$  Gy were significantly associated with better LC. However, none of these parameters remained significant in the multivariate Cox regression model. OS was significantly better in patients with negative lymph nodes (N0), Karnofsky performance status (KPS)  $> 70\%$  and DMFS  $\geq 12$  months. There was no grade 3 acute or late toxicity.

**Conclusions** We observed good LC and low toxicity rates after SFRS for small lung metastases. Long DMFS, good KPS and N0 predicted longer OS in patients with lung oligometastases.

## Background

Metastatic progression of cancer is linked to poor prognosis and is the leading cause of cancer-related deaths (1). Few decades ago, the diagnosis of metastatic disease was related with lethal outcomes. This paradigm has changed after Hellman and Weichselbaum introduced the concept of oligometastases: the intermediate state between non-metastatic cancer and highly palliative disseminated metastatic disease (2). Patients with an initially limited number of metastases or with progression of only few lesions after cytoreductive therapy might be potentially cured or reach long-term survival when treated with local ablation therapy for all lesions. The search for prognostic biomarkers for discrimination of potentially oligometastatic patients is still ongoing. In some small prospective studies circulating tumor cells as well as circulating tumor DNA in liquid biopsies were able to predict treatment outcomes and response to ablative therapy (7). However, until prognostic biomarkers will be established for routine application, the selection of patients that could benefit from local ablative therapy rather than from palliation will be based on clinical features.

The lungs are one of the most common metastatic sites for various solid tumors (3, 4). Stereotactic body radiotherapy (SBRT) and surgical resection are frequently used treatment options for patients with a limited number of pulmonary lesions. Although SBRT compared to surgery for lung metastases have not been studied in a prospective randomized trial, retrospective data suggest that both methods achieve equal results in terms of local control and overall survival (5, 6). Single fraction radiosurgery (SFRS) is especially attractive as an outpatient procedure in terms of patients' compliance, cost effectiveness and limited treatment time. However, up to now there is no recommendation when to administer SFRS over fractionated SBRT (fSBRT). The aim of this study was to analyze local control (LC) after SFRS and fSBRT in patients with lung oligometastases and identify prognostic clinical features for better survival outcomes.

## Methods

### Study Design

This retrospective study was approved by the institutional medical ethics committee of the Charité - Universitätsmedizin Berlin (EA1/214/16). We identified all patients with lung metastases treated with curative intended SFRS or fSBRT between January 2010 and December 2016. Cases with an initially limited number of lung metastases from various solid tumors or with oligo-progression after systemic therapy were selected for the study. Patients with disseminated disease or with a second malignancy were excluded. The data on patients' demographics, e.g. primary tumor and metastases, disease stage as determined by computed tomography, magnetic resonance imaging or positron emission tomography, treatment parameters, follow-up and overall survival (OS), LC, progression-free survival (PFS), distant metastases-free survival (DMFS) were calculated. We determined a total tumor diameter (TTD) by summing up the longest diameter of each existing metastasis. Clinical follow-up was performed at 6 weeks after SFRS/fSBRT and at 3, 6, 12, 18, and 24 months after treatment and annually thereafter. Acute and late adverse events were scored using NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

### Treatment planning and delivery

SBRT was delivered using CyberKnife and Novalis systems, both dedicated stereotactic linear accelerators. For respiratory motion compensation, the CyberKnife Synchrony® Respiratory Motion Tracking System was used. In general, one gold fiducial (1.0 mm x 5.0 mm) was placed centrally within the lung metastasis under CT-guidance in local anesthesia. For lesions larger than 2 cm feasibility of X-sight lung tracking was evaluated. If motion compensation was not possible (e.g. due to patients' comorbidities or technical limitations) an internal gross tumor volume (IGTV), defined as the gross tumor volumes of all respiratory phases on a 4D CT was constructed. In these cases, patients were aligned on

the spine. High-resolution thin-slice native planning CT of the chest with 1.0 to 2.0 mm slice thickness in supine position was performed.

The gross tumor volume (GTV) was delineated on all axial slices including spiculae in the lung window. The clinical target volume (CTV) was equal to the GTV. The planning target volume (PTV) was obtained by adding a 5-8 mm margin to the CTV (Figure 1).

Prescription dose was 17-26 Gy for SFRS or 24-75 Gy in 2-12 fractions for fSBRT. For CyberKnife treatments, doses were prescribed to the 70% isodose covering the PTV. Novalis treatment was planned with less inhomogeneous dose distributions with the 80% isodose line of the prescribed 100% dose encompassing the PTV.

The linear-quadratic model, assuming an alpha/beta ratio of 10 Gy for tumor, was used to calculate the biologically equivalent dose (BED) and the equivalent dose in 2 Gy fractions (EQD2). Dose constraints to organs at risk for single fraction treatment are shown in Table 1. Treatment planning was performed in Multiplan® (Accuray) using the Ray-Trace or Monte Carlo algorithm and in iPlan® (BrainLAB) using the pencil-beam algorithm.

## **Endpoints and statistical considerations**

LC was defined as time from SFRS/fSBRT to tumor progression within the irradiation field or absence of progression at last available follow-up. LC was assessed using routinely CT scans every 3 months. PET-CT and/or biopsy of irradiated metastasis was performed in cases of uncertain progression detected on CT images. OS survival was calculated from the beginning of SFRS or fSBRT until the death of any cause or the date of last follow-up. The time to new metastases in the lung outside of the SFRS/fSBRT field or in other organs and was defined as DMFS and was calculated from the start of SFRS/fSBRT. PFS was defined as the time from the start of SFRS/fSBRT until progression of the primary tumor, development of new metastases or local failure.

LC was compared between LM treated with SFRS and fSBRT. The different fractionation regimes in the same patient were allowed, thus fractionation impact on OS, PFS and DMFS could not be assessed.

OS, LC, DMFS and PFS after SFRS/fSBRT for lung metastases were calculated using the Kaplan-Meier method. Cox-regression analysis was used to obtain the Hazard Ratio (HR) and 95% confidence intervals (CI) for various covariates. Covariates with a p-value of 0.1 were included into the multivariate analyses carried out with a Cox proportional hazards model with a threshold of  $p < 0.05$ . The chi-squared test was performed in order to compare variables between groups. A p-value of  $< 0.05$  was considered as statistically significant. The data processing and statistical analyses were accomplished using FileMaker Pro 15 Advanced, Excel 2010 and IBM SPSS Statistics 24 (SPSS Inc., Chicago, IL, USA).

# Results

## Patient and tumor characteristics

The clinical, treatment and follow-up data of 52 eligible patients were assessed. Thirty-two patients were male (61.5%) and 20 were female (38.5%) with a median age of 66 years (range: 26-84) and a median Karnofsky performance status (KPS) of 80% (range: 60-100). The most prevalent primary tumor was colorectal cancer (CRC) in 17 patients (32.7%). PET-CT staging before the SBRT for lungs was performed in 7 (13.5%) patients. Twelve patients (23.1%) had oligometastases at the time of tumor diagnosis. The median time from the diagnosis of primary tumor and first metastases was 19.5 months (range: 0–37.9). In 37 patients (71.2%) metastases were limited to the lungs. Eight patients (15.4%) had additional liver metastases and 3 patients (5.8%) had brain metastasis. Forty-six patients (88.5%) had systemic therapy prior to lung SBRT and 15 (28.8%) after lung SBRT. Seventeen patients (32.7%) received immunotherapy at any time during the disease course. Patients' and primary tumor characteristics are shown in Table 2.

## Treatment characteristics

Overall 94 lung metastases were treated using SFRS/fSBRT with a median of 2 lesions per patient (range: 1–5). Metastases and SFRS/fSBRT characteristics are shown in Table 3 and 4. Forty-five metastases (47.9%) were treated with SFRS of which only 12 were located centrally. Metastases treated with fSBRT were almost equally distributed with respect to location (25 central vs. 22 peripheral). Median diameter of metastases was 14.5 mm (range: 5-70), with no significant difference between centrally and peripheral located lesions. The median time from the diagnosis of lung metastases to the start of SFRS/fSBRT was 4.5 months (range: 0-61). Before the therapy with CK a gold fiducial was implanted in 51 metastases, whereof 37 were treated with SFRS and 14 with fSBRT using the Synchrony tracking method. A total of 14 lung metastases were treated using the X-sight lung tracking method. IGTV was used for all 29 metastases treated with Novalis. The median prescription dose for SFRS was 24 Gy (range: 17-26) compared to fSBRT with 48 Gy (range: 24-75) delivered in 2-12 fractions. The median diameter and PTV-volume were significantly smaller in metastases treated with SFRS compared to fSBRT: 12 mm (range: 5-35) and 9.9 cm<sup>3</sup> (range: 2.4-90.8) vs. 16 mm (range: 5-70) and 24.0 cm<sup>3</sup> (range: 5.8-164.5), respectively.

## Patient outcomes

The median follow-up time was 21 months (range: 3-68). The 1-year and 2-year LC rates for SFRS vs. fSBRT were 89% and 83% vs. 75% and 59%, respectively ( $p=0.026$ ). One and 2-year LC rates for

metastases from CRC vs. non-CRC were 59% and 46% vs. 90% and 80%, respectively ( $p=0.001$ ). In 5 out of 22 metastases with local progression relapse was confirmed using PET-CT and in 2 after histological examination. Eleven lesions were repeatedly treated with local therapy: either with repeated SBRT or with surgery. One and 2-year OS and PFS rates were 84%, 71% and 26%, 15%, respectively. At the time of analysis 21 patients (41.4%) were dead. Disease progression occurred in 42 patients (80.8%), of which 19 patients (36.5%) developed metastases in new organs. The Kaplan-Meier LC, OS and PFS curves are shown in Figure 2.

Treatment with SFRS, an interval of < 12 months between diagnosis of metastases and the beginning of SFRS/fSBRT as well as non-colorectal histology were significantly associated with better LC in univariate analysis (Tab. 5). However, none of these parameters remained significant in multivariate analysis. N0, KPS >70% and DMFS  $\geq$ 12 months were significantly associated with improved OS. PFS was significantly better in patients with KPS >70% and with maximum 3 metastases at the time of SBRT (Tab. 6). There was no difference regarding survival outcomes between patients with oligorecurrence and oligometastases.

### **Treatment related toxicity**

The SFRS and fSBRT were safe and very well tolerated. No treatment-related deaths and grade  $\geq$ 3 toxicities occurred. Six patients (11.5%) developed asymptomatic grade 1 pneumonitis (2 patients after SFRS and 4 patients after fSBRT) and one patient had grade 1 pulmonary fibrosis. Symptomatic and medical intervention requiring grade 2 pneumonitis was diagnosed in one patient (1.9%) after SFRS with 25 Gy.

## **Discussion**

This analysis represents a single-center experience in treating oligometastatic lung lesions with curative intended SFRS and fSBRT. The 1-, 2-year LC and OS rates for the entire cohort were 82%, 70% and 84%, 71%, respectively. Our findings are comparable with the current findings in the literature (Tab. 7) (7-15).

It has been postulated by others that a BED > 100 Gy, smaller tumor size, shorter interval between diagnosis and treatment of metastases are favorable prognostic factors influencing the local control of lung metastases after SBRT (8, 16-18). The existing data on fractionation schedules as well as dosage of SBRT for lung metastases is limited by retrospective nature. Therefore, no standardized treatment regimens are yet available. The primary results of TROG 13.01 SAFRON II Phase II study which compares SFRS to fSBRT for lung metastases are expected soon (19). Meanwhile, fractionation schedules for small (T1-T2, N0, M0) NSCLC tumors were investigated in several Phase 2 trials. RTOG 0618 trial reported 54 Gy

delivered in 3 fractions for operable peripheral tumors to be safe and effective (LC at 4-years 96%, with 8% grade 3 adverse events) (20). Timmerman et al. concluded that dose escalation up to 3 x 20/21 Gy for central lesions in inoperable patients should not be applied due to high toxicity rates (21). Furthermore, Videtic and colleagues compared grade  $\geq 3$  adverse event rates after SBRT with 34 Gy in 1 fraction vs. 48 Gy in 4 fractions for inoperable NSCLC. Analyzing a cohort of 94 patients they found that SFRS with 34 Gy is superior compared to fSBRT regarding safety (10.3 % vs. 13.3%) and 1-year LC rates (97% vs 92.7%) (22). According to our data, small lung metastases (median PTV  $\leq 9.9$  cm<sup>3</sup>) might safely be treated with SFRS applying 24-26 Gy at the surrounding 70% isodose (median Dmax of 53 Gy and a median BED of 81 Gy) with excellent 1- and 2-year LC rates of 89% and 83%. This finding suggests that a BED <100 Gy using SFRS might be sufficient for durable control in some lung metastases. Previous studies rarely investigated SFRS regimes for different tumor volumes especially for small lesions. In accordance with our data, Filippi and colleagues reported excellent 1- and 2-year LC rates (93.4% and 88.1% respectively) after SFRS with 26 Gy (80% surrounding isodose) for lung metastases with a median tumor diameters of 17 mm (7-38 mm) in 67 patients with 90 lung lesions mainly from NSCLC and CRC primaries (14). Siva et al. observed no difference in LC, OS and distant progression between 65 patients with mainly NSCLC or CRC treated with either SFRS (26 Gy for peripheral LM or 18 Gy for central LM) or multifractionated SBRT (48Gy/4 and 50Gy/5 for peripheral targets or 50Gy/5 for central targets) for 1 to 3 lung oligometastases (23). Randomized, prospective studies are needed to determine which fractionation schedule is optimal in terms of therapy outcomes, treatment related costs as well as patient's compliance.

Recently, Hong et al. developed a prognostic tool for the discrimination of oligometastatic patients with extracranial lesions who benefit most from SBRT. The authors found that primaries from breast, kidney and prostate cancer lead to long-term survival with 3-year OS rates of 75% (24). Furthermore, a retrospective analysis of 700 patients with lung metastases found that breast cancer and CRC were positive prognostic factors for superior OS (8). Newly, Sharma and colleagues reported 38% lower mortality risk in patients with lung oligometastases from CRC compared with non-CRC histology. This OS improvement might be explained by the broad arsenal of effective systemic therapeutic agents and radical ablative treatment for the primary tumor while breast cancer is associated with less aggressive tumor biology (10). Our cohort consisted of patients with 10 different tumor entities with the leading diagnosis of CRC. There was no significant OS difference regarding the primary cancer most likely due to the heterogeneous cohort and small sample size. Nonetheless, our data suggest that metastases from CRC have a higher risk of local failure compared to other histologies. One and 2-year LC rates for metastases from CRC vs. non-CRC were 59% and 46% vs. 90% and 80%, respectively. Recently, systematic review and meta-analysis have been published in which the prognostic value of CRC histology after SBRT for lung lesions was investigated. Analysis of 1920 patients (619 with CRC, 1301 non-CRC) showed that LC was significantly inferior in the CRC group ( $p < 0.00001$ ). Furthermore, the dose escalation (BED >130 Gy) was associated with decreased local recurrences ( $p < 0.00001$ ) (25). Ahmed et al. found that lung metastases from rectal carcinoma, soft-tissue sarcoma, renal cell carcinoma and melanoma are related with increased radio-resistance and thus reached significantly worse LC after SBRT. The authors

recommend a BED beyond 100 Gy for radio-resistant lung metastases in order to improve LC rates (26). In the present study, 75.9% pulmonary metastases from CRC originated from primary rectal tumors. The median BED for relapsed pulmonary lesions from rectal carcinoma was 87.5 Gy (range: 56-124.8). We hypothesize that median BED less than 100 Gy for radio-resistant metastases might be associated with high local relapse rates in patients with rectal cancer observed in our cohort.

According to our data, N0 stage and long DMFS from the diagnosis of primary tumor seems to play an important role in predicting OS for patients with lung oligometastases. Therefore, assessment of these potentially prognostic factors might be useful for selecting patients with stage IV cancer for curative SBRT. In the present study, patients with N0 and DMFS  $\geq 12$  months had excellent 1- and 2-year OS rates of 100% and 75%. In addition, a trend for better OS was observed in patients with smaller primary tumors ( $\leq T2$ ). Our results are in agreement with a meta-analysis including 757 patients with oligometastatic NSCLC. After performing recursive partitioning analysis, the authors identified 3 risk groups regarding to N status and DMFS: low risk (N0 and DMFS  $\geq 2$  months), intermediate risk (N0 and DMFS  $\leq 2$ ) and high risk (N+ and DMFS  $\leq 2$  months). There was a significant 1- and 2-years OS difference among the groups 88.4% and 66.3% vs. 76.2% and 57.4% vs. 53.6% and 34.1%, respectively ( $p < 0.001$ ). Moreover, a higher T-stage predicted inferior OS in univariate analysis. However, T-stage could not be established as independent prognostic factor in a multivariate analysis (27). The evidence of other retrospective series support the data that shorter DMFS as well as synchronous metastases are associated with more aggressive tumor behavior and thereby decreased OS rates in patients with pulmonary metastases (28-30). The present findings are consistent with results from the study of Inoue et al. which demonstrated DMFS  $\geq 12$  to be a positive prognostic factor for OS among the patients with extracranial (lung, adrenal glands) and intracranial oligometastases (31). Cao et al. reported superior OS rates in patients with pulmonary metastases after mastectomy with DMFS  $\geq 18$  (32). In contrast to most published data, a recent retrospective study in a cohort of 206 patients with lung oligometastases identified synchronous metastasis as an independent prognostic factor for longer OS. (10) The possible explanation for the conflicting results named by the authors was a selection bias. ew prospective studies showed that patients even with initial stage IV NSCLC reach longer PFS or OS after ablative therapy for all active lesions and benefit from local therapy despite the advanced disease (33-36).

For the definition of oligometastatic disease, the number of metastases considerably varies between 1-5 lesions in 1-3 affected organs (37-39). Presence of multiple metastases is usually reported as one of the most important negative predictive factors for OS (8, 39-41). Although, a correlation between number of lesions and OS was not observed in the current study, our data demonstrated significantly longer PFS in the patient cohort with maximum 3 metastases (2-year PFS rates of 26.1 % vs. 0 %,  $p=0.002$ ). Similar findings were observed in a retrospective analysis of 66 patients with CRC where multiple lung lesions were associated with worse PFS (15). Furthermore, one surgical study of 615 patients with lung

metastases from CRC identified 3 metastases as a cut-off number for selection of operable patients (42). Nonetheless, other studies failed to demonstrate any relationship between number of metastases and survival outcomes (16) (43). The strict number of lesions alone might be an insufficient factor to predict survival outcomes since the metastases might vary significantly in size (44). Therefore, we assessed TTD and found a trend towards improvement in PFS for  $TTD \leq 5$  cm vs.  $TTD > 5$  cm (1-year PFS 40% vs. 14%,  $p=0.073$ ). Although our finding was not significant, TTD might be an important factor for discrimination of the patients with oligometastases. In a retrospective study on stage IV gastric cancer the metastatic tumor diameter  $\geq 55$  mm was found to be an adverse prognostic factor for OS after systemic therapy (45). Further studies are needed to examine the effect of TTD and number of metastases on outcome.

Masahiko et al. investigated the risk of rib fracture after SBRT (54–56 Gy in 9–7 fractions) for peripheral lung tumors. The 4-year probability of rib fracture was 47.7% when Dmax for the ribs was 54 Gy or more. In our cohort we did not observe any rib fractures. This might be explained by retrospective nature of the study and median follow-up that less than 4 years (46).

## Limitations

The major limitation of our study is its retrospective design with inhomogeneous primary tumor types. Different dose calculation algorithms were used. Treatment plan calculations with Ray-Tracing, Pencil Beam or Monte Carlo dose algorithms can produce large differences in dose for targets and organs at risk near lung tissue. A correction factor (e.g. 1.2) which should provide approximate equivalence between Ray-Tracing and Monte Carlo dose calculation algorithm was not used. Furthermore, multiple metastases in the same patient were treated with different fractionation regimens, so the assessment of prognostic value of SFRS vs. fSBRT for survival outcomes (OS, PFS, DMFS) was not possible. Nevertheless, our analysis provides valuable data on fractionation regimes and prognostic factors for OS and PFS treating lung metastases in oligometastatic patient cohort, irrespective of a relatively small sample size and dispersed follow up periods.

## Conclusions

We observed good LC and low toxicity rates after SFRS for small lung metastases. Long-term LC was achieved after short treatment schedules.  $KPS > 70\%$ , long DMFS and absence of locoregional lymph node metastases were found to be positive predictive factors for OS in patients with oligometastases after SBRT.

## Abbreviations

Biologically effective dose (BED), colorectal cancer (CRC), confidence interval (CI), clinical treatment volume (CTV), Cyberknife (CK), distant metastases-free survival (DMFS), equivalent dose in 2 Gy fractions (EQD2), fractionated stereotactic body radiotherapy (fSBRT), gross tumor volume (GTV), head and neck cancer (HNC), hazard ratio (HR), internal gross tumor volume (IGTV), local control (LC), lung metastases (LM), non-colorectal cancer (non-CRC), NSCLC (non-small-cell lung cancer), overall survival (OS), progression-free survival (PFS), planning treatment volume (PTV), renal cell carcinoma (RCC), single fraction radiosurgery (SFRS), stereotactic body radiotherapy (SBRT), total tumor diameter (TTD).

## **Declarations**

### **Ethics approval and consent to participate:**

Analysis of patient data was approved by the institutional medical ethics committee of the Charité - Universitätsmedizin Berlin (EA1/214/16). Because of retrospective nature of this study we did not obtain written nor verbal informed consents from the patients.

### **Consent for publication:**

Not applicable.

### **Availability of data and material:**

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### **Competing interests:**

The authors declare that they have no competing interests.

### **Funding:**

This study was supported by scholarship for Goda Kalinauskaite from Berliner Krebsgesellschaft, Ernst von Leyden-Stipendium.

### **Authors` contributions:**

GK acquired, analyzed and interpreted the patient data, conducted the statistical analysis, drafted the manuscript. IT contributed to data interpretation and manuscript writing. MK made substantial contributions to data acquisition. AK provided technical support, preparation of figures and critical review of the manuscript. AG and VB provided administrative support and critically revised the article. CS (Senger) and CS (Stromberger) participated equally in the design of the study, made substantial contributions to acquisition, analysis and interpretation of the data. All authors read and approved the final version of the manuscript.

## Acknowledgments:

Not applicable.

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## Table And Figure Legends

**Table 1** Dose constrains for organs at risk.

**Table 2** Patient and primary tumor characteristics.

**Table 3** Metastases and treatment characteristics.

**Table 4** Fractionation regimens.

**Table 5** Univariate and multivariate analysis of factors influencing OS.

**Table 5** Univariate analysis of factors influencing LC.

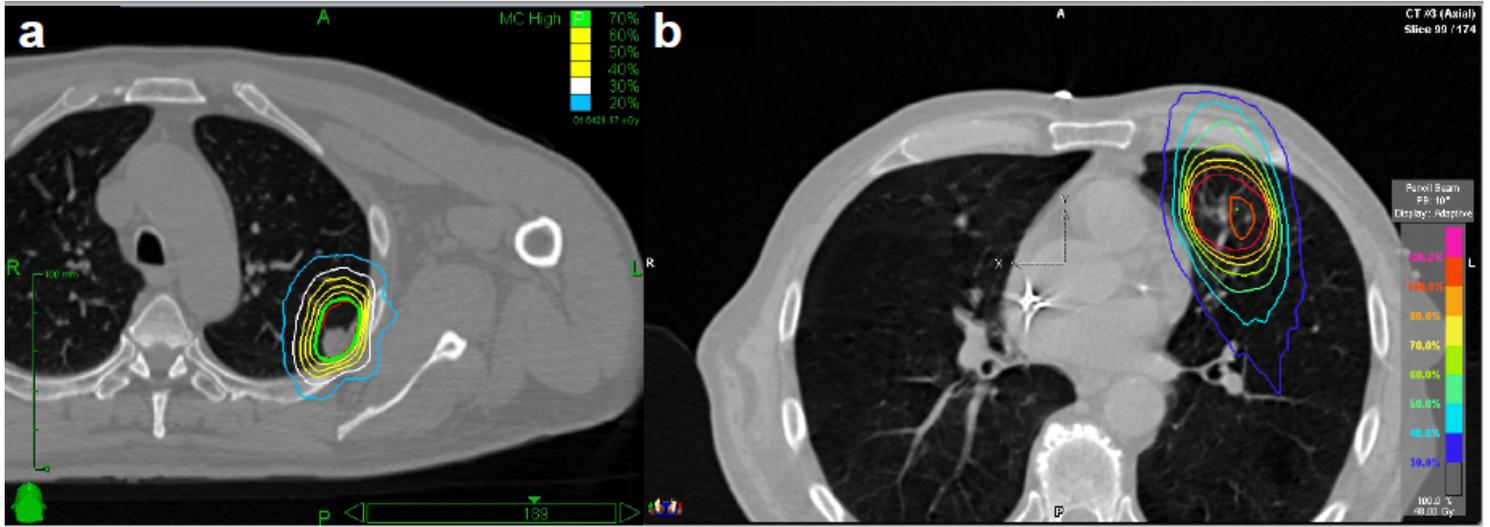
**Table 6** Univariate and multivariate analysis of factors influencing overall and progression-free survival.

**Table 7** Overall survival and local control rates after SFRS/fSBRT or pulmonary metastasectomy according to various studies.

**Figure 1** Radiotherapy treatment plan of (a) CyberKnife, (b) Novalis treatment system.

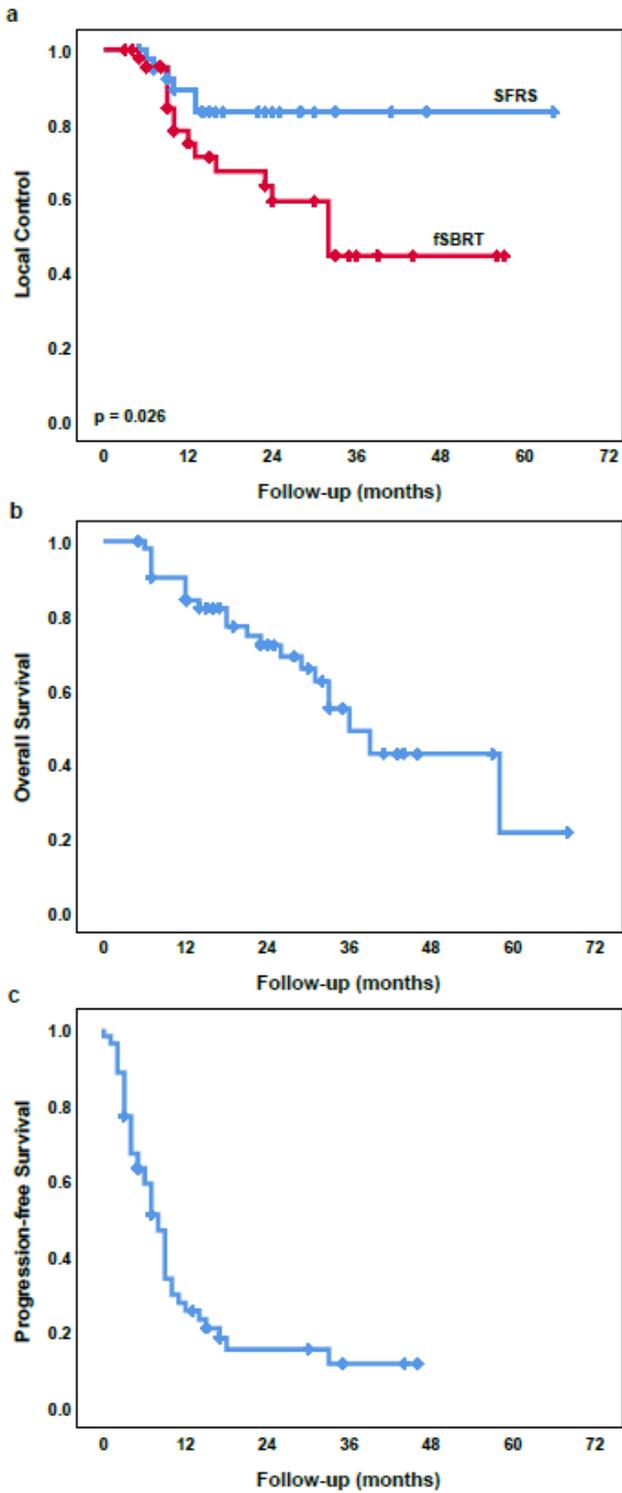
**Figure 2** Kaplan-Meier curves of (a) local control SFRS vs. fSBRT, (b) overall survival, (c) progression-free survival.

## Figures



**Figure 1**

Radiotherapy treatment plan of (a) CyberKnife, (b) Novalis treatment system.



**Figure 2**

Kaplan-Meier curves of (a) local control SFRS vs. fSBRT, (b) overall survival, (c) progression-free survival.

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