Repeat Stereotactic Body Radiation Therapy (SBRT) for Salvage of Isolated Local Recurrence after Definitive Lung SBRT

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Abstract

Purpose: Optimal management of isolated local recurrences after stereotactic body radiation therapy (SBRT) for early non-small cell lung cancer (NSCLC) is unknown and literature describing repeat SBRT for in-field recurrences after initial SBRT are sparse. We investigate the safety and efficacy of salvage SBRT for isolated local failures after initial SBRT for NSCLC.

Methods/Materials: Patients receiving SBRT for isolated local recurrence after initial SBRT for early NSCLC were identified using a prospective registry. Both courses were 3–5 fractions with a biologically effective dose (BED10) of 100Gy. Local failure was defined as within 1 cm of the initial planning target volume (PTV) or an overlap of the 25% isodose lines of the first and second treatments. Failures >1 cm beyond the PTV and without 25% overlap, or with additional recurrence sites were excluded. Kaplan-Meier analysis was used to estimate survival.

Results: A total 21 patients receiving salvage SBRT from 2008 to 2017 were identified. Median interval from initial SBRT to salvage SBRT was 23 months (7–52). Six patients (29%) had central tumors. Median follow-up time from salvage SBRT was 24 months (3–60). Median overall survival after salvage was 39 months. After reirradiation, two-year primary tumor control was 81%, regional nodal control was 89%, distant control was 75% and overall survival was 68%. Grade 2 pneumonitis occurred in 2 patients (10%) and grade 2 chest wall toxicity in 4 patients (19%). No grade 3+ toxicity was observed.

Conclusions: Salvage SBRT for isolated local failures after initial SBRT appears safe, with low treatment-related toxicity and encouraging rates of tumor control.

Keywords

lung cancer; stereotactic body radiation therapy; local failure; reirradiation; salvage

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Introduction

Stereotactic body radiotherapy (SBRT) is an established treatment option in the management of patients with early-stage non-small cell lung cancer (NSCLC). Prospective studies have demonstrated that SBRT achieves high rates of local tumor control (1–3). Compared to conventionally-fractionated radiotherapy (CFRT) for early stage NSCLC, SBRT is associated with equivalent tumor control, shortened treatment times, and decreased toxicity, with larger retrospective studies even suggesting a survival benefit (4–7). Although development of distant metastases is the predominant pattern of failure after treatment with SBRT, primary tumor and local recurrences are still observed in approximately 10–15 % of patients (8–10). However, salvage options for isolated post-radiation local failures are limited, with surgery or retreatment with radiotherapy as potential modalities.

While salvage surgical resection after previous thoracic irradiation has shown encouraging results, most patients experiencing post-radiation local relapse are not operative candidates (11–13). Therefore, reirradiation may be the only viable salvage option for many patients. Retreatment with CFRT has been reported for locoregional failures, with generally-poor outcomes (14, 15). Although salvage SBRT after initial CFRT has been described in select small series of heterogeneous patient groups ranging from early stage to locally-advanced and metastatic, few data exist to guide us on the role of reirradiation with SBRT for isolated recurrences after initial SBRT for early-stage NSCLC (16–19). Importantly, questions regarding the safety and efficacy in this setting are still largely unanswered as the few studies attempting to answer this question often include treatment of new lesions outside the initial high-dose field, which confounds the rates of both toxicity and control. The purpose of our study is to determine the tumor control and tolerability of repeat SBRT as salvage for isolated local recurrences within the high-dose volume of initial SBRT for early-stage NSCLC.

Materials and Methods

An institutional review board-approved, prospectively-maintained database was used to review patients with early-stage NSCLC initially treated with definitive SBRT who experienced isolated local recurrences salvaged with repeat SBRT. All patients opted in for inclusion. Both SBRT courses for all patients were 3–5 fractions with a biologically effective dose (BED10) of 100 Gy. We included only patients with isolated recurrences within the high-dose region of their initial SBRT treatment, including the Radiation Therapy Oncology Group (RTOG) 0236 definition of primary tumor failure encompassing lesions within 1 cm of the original planning target volume (PTV), and/or new primaries with SBRT treatment having overlap of at least the 25% prescription isodose line with the initial SBRT treatment. Patients with involved lobar failures that were further than 1 cm from the original PTV and did not have 25% isodose line overlap were excluded from the current study. This was done due to concerns of misrepresenting both tumor control and toxicity outcomes if patients with less overlap of the two SBRT treatments were included given that lobar failures may often be far from the original lesion despite being in the same anatomic lobe.

Patients were evaluated by a multidisciplinary team, with pretreatment evaluation including history and physical examination as well as pulmonary function testing in most patients. Medical inoperability was determined by a cardiothoracic surgeon and/or pulmonologist. At both time of initial diagnosis and salvage, patients were staged clinically with computerized tomography (CT) of the chest, positron emission tomography (PET), and/or mediastinal staging with endobronchial ultrasound (EBUS) or mediastinoscopy as indicated. Candidacy for reirradiation with repeat definitive SBRT was determined by the treating radiation oncologist after assessment of medical comorbidities, tumor location and prior organ at-risk (OAR) doses, as well as individual patient goals of care.

We have described our institutional SBRT technique in a previous manuscript (20). Abdominal compression was utilized to minimize the range of tumor motion. Daily cone beam CT was used to confirm patient setup and target verification. Delivery types included both coplanar and noncoplanar 3-dimensional conformal (3DCRT), intensity-modulated radiation therapy (IMRT), and volumetric modulated arc therapy (VMAT). For 3DCRT, prescription was typically to the 75% to 85% isodose line so that 95% of the prescribed dose covers the PTV. Plan optimization for IMRT/VMAT treatments was set to recapitulate coverage and hotspots similar to the 3DCRT plans. No specific universal dosimetric constraints were used for reirradiation, we took particular care to ensure cumulative doses to high-risk OARs, such as the spinal cord 2 Gy equivalent dose (EQD2) not exceeding 50 Gy. No specific chest wall constraints were used in initial or salvage SBRT planning with the exception of attempting to avoid hotspots within the chest wall. Cumulative EQD2 doses to high-risk OARs were calculated by voxel-based dose accumulation.

Patients were followed with serial CT scans at 6 weeks' post-treatment, then every 3 months for 2 years, followed by every 6 months for 3 additional years. Follow up was calculated from time of salvage SBRT treatment until death or last follow-up. Primary tumor failure was defined as radiographic evidence of local enlargement of the treated primary tumor. Hilar and mediastinal nodal recurrences were considered regional failures. New lung cancers developing 5 years or greater from salvage were considered new primaries. Metachronous primary lung cancers were defined if they fulfilled one of the following criteria per the 2013 American College of Chest Physicians (ACCP) guidelines: tumor of a different histology, a tumor of the same histology but in a different lobe than the initial primary and no evidence of nodal involvement or systemic metastases, or a tumor of the same histology but temporally separated with at least a 4-year interval between cancers and no evidence of systemic metastases (21). Toxicity was graded per the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. The Kaplan-Meier method was used to estimate local control and survival probabilities. Significance was considered at $p < 0.05$ and all significance levels were 2-sided. IBM® SPSS® Statistics, version 23 was used for all statistical analyses.

Results

Out of 1,209 patients in our institutional lung SBRT database, 844 patients had early stage NSCLC. Of these, 803 received an initial SBRT course with BED >100 Gy. Isolated local recurrence occurred in 44 of 803 patients, with 25 patients receiving SBRT reirradiation.

Four patients receiving SBRT with BED <100 Gy were excluded. Therefore, we identified 21 patients receiving salvage SBRT at our institution between 2008 and 2017 who met the aforementioned inclusion and exclusion criteria. Patient, tumor, and treatment-related characteristics are summarized in Table 1. The remaining 19 patients with isolated local recurrences who did not receive repeat SBRT either died of intercurrent disease prior to retreatment (6 patients), were reirradiated with conventionally-fractionated RT due to periesophageal location (6 patients), received systemic therapy alone (5 patients), or declined reirradiation (2 patients). Compared to the 21 patients receiving salvage SBRT with BED >100 Gy, the 23 remaining patients with local failures had statistically similar baseline characteristics except for a larger tumor diameter at recurrence (Supplementary Table 1).Median interval between initial definitive SBRT for early-stage NSCLC and salvage SBRT for isolated local failure was 23 months (7 – 53 months). Median age at salvage was 75 (59 – 89). No patients received out-of-field RT or previous chemotherapy prior to salvage. Reirradiation prescription dose was 50 Gy in 5 fractions (biological effective dose, $BED_{10} = 100$ Gy) for 12 patients and 54 Gy in 3 fractions ($BED_{10} = 151$ Gy) for 9 patients. Figure 1 shows a representative salvage SBRT plan. There were 6 patients with central tumors per RTOG 0813 criteria, with the remaining 15 patients having peripheral tumors. All 6 central tumors were within 2cm of but not directly abutting or invading the main bronchi or other mediastinal structures. No patients had tumors adjacent to the proximal bronchial tree. After salvage SBRT, no patients received adjuvant chemotherapy. Pre-treatment pulmonary function tests were obtained in 14 patients (66%). The median FEV1 was 1.5 L and 53% (range, 0.6 – 2.9 L and 29 – 109%, respectively), and median DLCO was 44% (range, 35 – 59%).

Cumulative dosimetric data was also obtained. Equivalent dose in 2-Gy fractions (EQD2) was calculated via voxel-based dose accumulation based on the point maximum doses (D_{max}) to adjust for variation in dose-fractionation schemes. An α/β ratio of 10 was used for tumor calculations, 3 for non-neural tissue calculations, and 2 for spinal cord and brachial plexus calculations. The median cumulative tumor EQD2/10 D_{max} was 168.3 Gy (97.3 – 266.6), median cumulative lung EQD2/3 D_{max} was 286.1 Gy (137.0 – 469.6), median cumulative cord EQD2/2 D_{max} was 12.2 Gy (3.0 – 21.1), median cumulative esophagus EQD2/3 D_{max} was 18.7 Gy (4.9 – 37.2), median cumulative heart EQD2/3 D_{max} was 21.8 Gy (0.5 – 109.6), median cumulative brachial plexus EQD2/2 D_{max} was 10.8 Gy (0.7 – 63.1), median cumulative lung – internal target volume (ITV) receiving 20 Gy (V20) was 12.0% (6.4 – 16.5), and median cumulative lung – ITV EQD2/3 mean dose was 5.5 Gy (3.0 – 9.0).

Median follow-up after retreatment with SBRT was 24 months (3 – 60 months). The median post-salvage overall survival was 39 months (95% confidence interval [CI], 27 – 52 months). The estimated post-salvage 2-year primary tumor control was 81% (95% CI, 60 – 100%), involved lobar control was 81% (95% CI, 60 – 100%), regional nodal control was 89% (95% CI, 71 – 100%), distant control was 75% (95% CI, 57 – 100%), and overall survival was 68% (95% CI, 51 – 96%) for patients (Figure 2). The patterns of failure among study patients is shown in Table 2, with distant failure being the most common sites of treatment failure. There were zero isolated local recurrences after salvage SBRT. However, there were two patients who failed locally and also had either a nodal or distant failure concomitantly.

Four patients developed biopsy-proven metachronous lung primaries after salvage at a median time of 19.5 months post-SBRT. Of these, 3 were new early-stage NSCLC, 1 in a separate lobe of the ipsilateral lung and 2 in the contralateral lung, while 1 was limited-stage small cell lung cancer in the contralateral lung.

Treatment-related adverse events were relatively low, with zero grade 3+ toxicity observed in this series. Two patients developed symptomatic grade 2 radiation pneumonitis, managed with steroids. Grade 3+ pneumonitis was not observed in this cohort. Chest wall toxicity developed in four patients, two of which were rib fractures, which was all managed conservatively with over-the-counter medication. Non-pneumonitis pulmonary toxicity, esophagitis or significant skin toxicity was not observed. Only 3 patients had post-treatment pulmonary function testing, however, with minimal changes observed in these patients compared to baseline.

Discussion

Herein, we report our institutional experience of salvage SBRT for isolated local relapse after initial SBRT for early stage NSCLC. We achieved promising local and distant control rates after salvage, as well as favorable survival in this medically-inoperable population with significant comorbidities. Importantly, we observed acceptably low rates of pneumonitis and chest wall toxicity at extended follow-up. We observed no esophagitis or bronchial tree toxicity in centrally-located tumors. However, no patients in our series had "ultra-central" tumors, defined as directly abutting or invading the proximal bronchial tree (22). This is particularly encouraging given the highly-selected cohort of patients with local recurrence within the high-dose volume of an initial SBRT course with a BED_{10} of at least 100Gy.

Despite high rates of local control in patients receiving of commonly-employed regimens of BED_{10} of 100 Gy or greater, local recurrence after definitive SBRT is not uncommon, with actuarial rates of up to 20% in large series with long-term follow-up (23, 24). Therefore, delineating the optimal salvage options for these patients is of utmost importance. However, options for salvage in patients experiencing local failures after initial SBRT are both limited and poorly-characterized. Several reports have published high rates of tumor control with acceptably low toxicity after salvage lobectomy for local recurrences after being treated with upfront SBRT, with isolated reports of fistula formation being the primary life-threatening adverse event and 3-year survival greater than 70% (11–13, 25). Even with these encouraging results, salvage surgical resection is a safe option in only a select subset of favorable patients initially treated for SBRT. Even in initially operable patients treated with upfront SBRT, only approximately 20% of patients with a local recurrence undergo salvage lung resection (11, 25). Therefore, for the majority of patients, radiotherapy remains the only definitive salvage option in this setting.

Conventionally-fractionated reirradiation with either photon or proton therapy has been previously reported after initial conventional RT, for recurrent locally-advanced or oligometastatic NSCLC, with acceptable local control rates but relatively high rates of pneumonitis (14, 26–28). Interstitial brachytherapy with iodine-125 seeds for intrathoracic recurrences after conventional RT have also been reported, although in a small group of

heterogeneous patients with both primary lung tumors and pulmonary metastases (29). A more recent series describing intensity-modulated proton therapy (IMPT) for thoracic reirradiation to a median 66 cobalt-Gy equivalent in 33 fractions demonstrate durable local control with no grade 4 or 5 toxicity and low levels of pneumonitis compared to previous reports, suggesting this may be a promising option for locally advanced intrathoracic recurrences at centers with access to IMPT (30).

SBRT for thoracic reirradiation has been previously described, almost exclusively in the setting of previous conventionally-fractionated RT for a heterogeneous group of early stage to metastatic lung cancer, with a wide range of local control and survival as well as toxicity likely owing to a wide range of initial and retreatment doses, broad patient inclusion, and systemic therapy use (16, 31–33). However, our understanding of the role of SBRT after initial SBRT is even less well-defined. The few studies evaluating this frequently include patients with metastatic disease, often use regimens greater than 5 fractions with BED_{10} less than 100Gy, are intermixed with conventionally-fractionated regimens, and are usually in the situation of treating out-of-field intrathoracic failures (34–37). Even in more carefully-controlled studies including marginal or intralobar failures, new same-lobe lesions may be far away from the initial high-dose volume and can therefore underrepresent toxicity risk and overestimate control rates (19). Still, these provide important preliminary work in understanding feasibility and outcomes for repeat SBRT in a wide array of therapeutic settings. To our knowledge, the series by Hearn and colleagues and two cases reported by Nishimura *et al* are the only previous studies reporting outcomes of SBRT for salvage of isolated local recurrence after initial SBRT with both courses' BED_{10} 100 Gy for early stage NSCLC (18, 38). In 10 patients with a median follow-up of 13.8 months, 2 patients developed distant failure and 4 had local failure, with no grade 3–5 toxicity observed. Our results in 21 patients are comparable to Hearn *et al* in terms of control and safety, although distant metastases were still the predominant pattern of failure in our series with extended follow-up, akin to patterns in the upfront SBRT setting for early NSCLC (8, 9).

One of the primary concerns of thoracic reirradiation has been of potentially life-threatening treatment-related toxicity, particularly in centrally-located tumors. Fatal bleeding in central tumors and a case of gastric perforation in peripheral lower lobe tumors have previously been reported (34, 39). We report zero grade 3+ toxicity, including zero bronchial tree toxicity or esophagitis in the 6 patients with centrally-located tumors. High rates of symptomatic pneumonitis have been reported after thoracic reirradiation, particularly with the use of conventionally-fractionated radiation therapy, with the volume receiving 5 Gy (V5) and 20 Gy (V20), both predicting for pneumonitis (31, 40). Accordingly, out-of-field failures are associated with higher rates of pneumonitis than in-field recurrences, which may well be due to the increased low-dose volume of lung parenchyma and may at least partially explain why we observed relatively low rates of pneumonitis. Chest wall toxicity was the most common adverse event in our study. In the upfront SBRT setting, the volume of irradiated chest wall, maximum dose to the chest wall, and prescription dose and fractionation all predict for chest wall toxicity, although no similar predictors currently exist after reirradiation (41–43). While we aim to avoid hotspots in the chest wall during the planning process, specific chest wall constraints are not routinely used in our treatment planning process, which may influence the rates observed in the current series.

Although the strengths of our study include the relatively large number of patients and strict inclusion criteria, there are considerable limitations. At least 25% isodose overlap was required to minimize confounding of toxicity and efficacy by lesions without high-dose overlap at time of reirradiation. However, there can still be considerable distance between the two PTVs while maintaining at least 25% isodose overlap, although this distance may be much less than if a same lobe or same lung criterion was used. Furthermore, our encouraging outcomes may be influenced by selection bias, since not all local failures after initial SBRT received reirradiation. Given the retrospective design, grade 1–2 toxicity may be under-reported, further influenced by the fact that adverse events were physician-reported, as patient-reported quality of life outcomes could more accurately assess treatment effects. Although pre-treatment PFTs were obtained on most patients, only 3 patients had post-SBRT testing performed, so the true effect on pulmonary function after repeat SBRT is unknown. Although our follow-up of 24 months is longer than most comparable reirradiation series in this high-risk cohort, late adverse events may be inadequately captured. Accordingly, estimates of tumor control may be significantly affected with a longer study duration. Furthermore, we have evolved our institutional SBRT techniques over the study period, and although most study patients were treated with noncoplanar 3DCRT, VMAT is being increasingly utilized in our clinic for lung SBRT. Despite these limitations, reirradiation with SBRT appears to be a safe and effective salvage option for isolated local failures after initial SBRT.

For patients with early-stage NSCLC treated with definitive SBRT experiencing isolated local failure, reirradiation with definitive-dose SBRT appears to be feasible and well-tolerated. For medically-inoperable patients with local relapse in early-stage NSCLC, repeat SBRT should be considered as a potential salvage option and warrants further investigation, although caution should be taken, particularly with centrally-located tumors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding:

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Highlights:

- Local recurrences occur in 10–15% of early stage NSCLC after definitive SBRT

- Salvage SBRT safety and efficacy for local recurrence after initial SBRT is unknown

- Median overall survival after salvage SBRT was 39 months in 21 patients

- Primary tumor and distant control at 2 years were 81% and 75% after salvage

- We observed no grade 3+ AEs, with grade 1–2 pneumonitis in 10% and CW pain in 19%
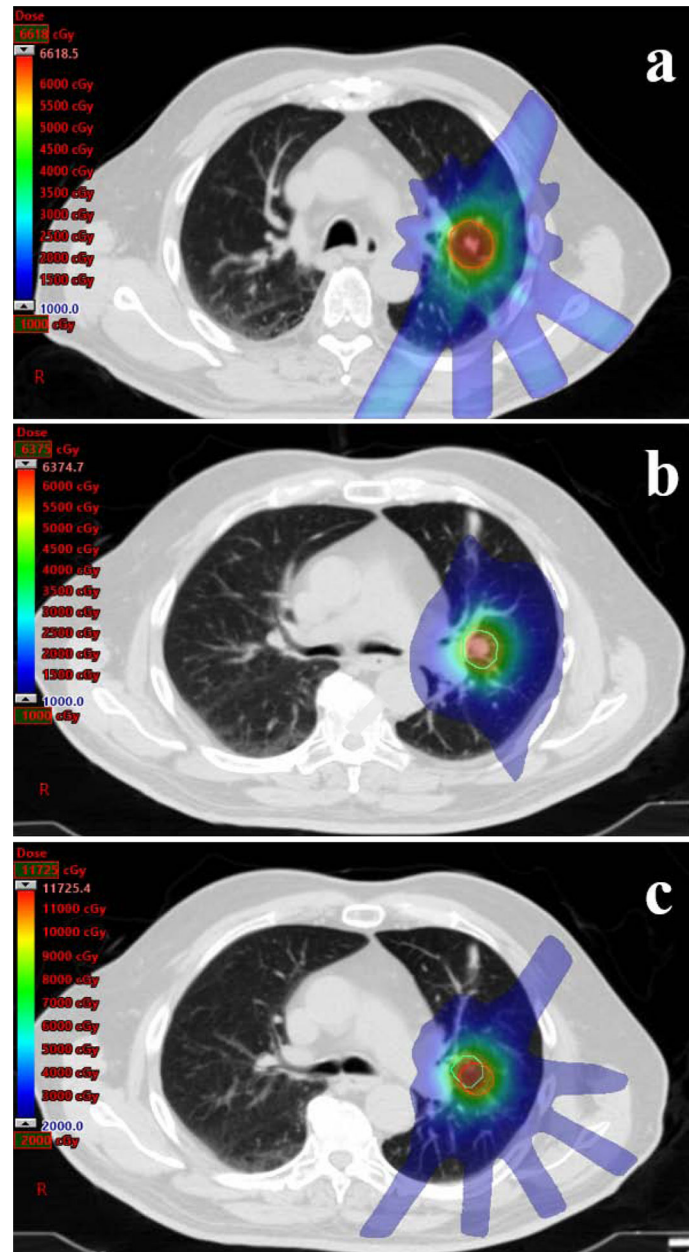
Figure 1.
Prescription isodose distributions for a patient treated with salvage SBRT to 50Gy in 5 fractions for an isolated local recurrence after initial SBRT to 54Gy in 3 fractions. The planning target volume (PTV) of the initial plan (a) is indicated by the red line. The PTV of the salvage plan (b) is indicated by the green line. The composite plan (c) with both PTVs is displayed, with a maximum cumulative point dose of 117 Gy.
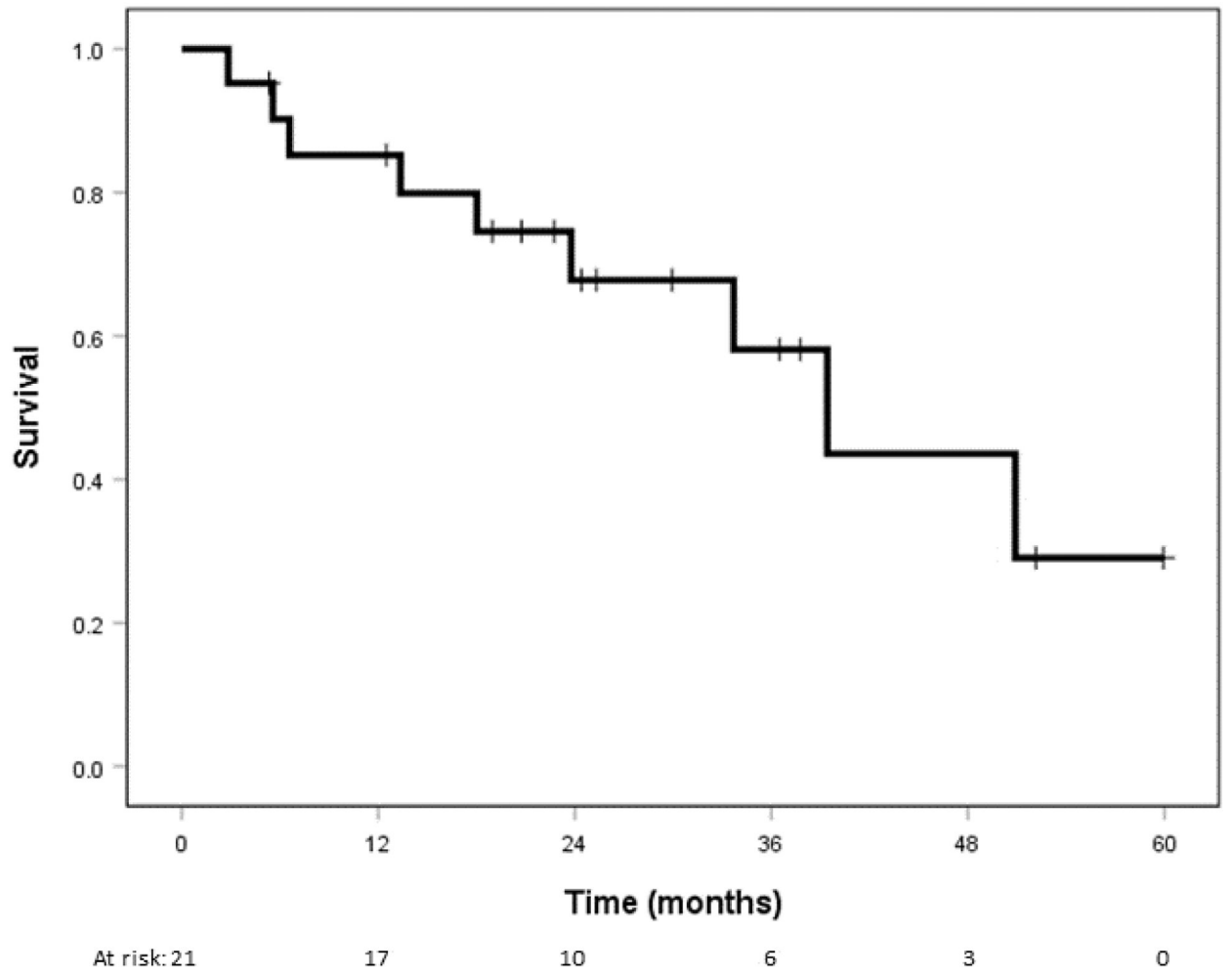
Figure 2.
Kaplan-Meier curve for overall survival.

Table 1.

Patient- and treatment-related characteristics (n=21)

Characteristic	Value (% or range)
Age at salvage (years), median	75 (59 – 89)
Sex	
Male	13 (62%)
Female	8 (38%)
BMI, median	26 (18 – 37)
Smoking status	
Never	1 (5%)
Former	9 (43%)
Current	11 (52%)
Smoking pack-years, median	55 (27 – 110)
Age-adjusted CCI, median	6 (2 – 11)
KPS, median	80 (60 – 100)
Histology	
Squamous cell carcinoma	7 (33%)
Adenocarcinoma	5 (24%)
NSCL NOS	3 (14%)
Biopsy unable to be obtained	6 (29%)
Initial tumor diameter (cm), median	2.0 (0.9 – 3.6)
Tumor diameter at salvage (cm), median	1.4 (1 – 2.5)
Initial PET SUV, median	5.4 (1 – 17)
PET SUV at salvage, median	6.2 (2.3 – 22)
Central location	6 (29%)
Mediastinal staging	
PET alone	19 (90%)
EBUS	1 (5%)
Mediastinoscopy	1 (5%)
Initial dose and fractionation	
50 Gy in 5 fractions	7 (33%)
54 Gy in 3 fractions	14 (67%)
Salvage dose and fractionation	
50 Gy in 5 fractions	12 (57%)
54 Gy in 3 fractions	9 (43%)

BMI, body mass index; CCI, Charlson comorbidity index; KPS, Karnofsky performance status, NSCLC NOS, non-small cell lung cancer not otherwise specific; PET, positron emission tomography; SUV, standardized uptake value; EBUS, endobronchial ultrasound

Table 2.

Patterns of failure after salvage SBRT among study patients (n=21)

Failure type	Number	Time to event, median (range)
Local	2	22.4 months (21.3 – 23.5)
Local only	0	
Local and nodal	1	
Local and distant	1	
Nodal	1	23.5 months
Nodal and local	1	
Distant	4	12.2 months (1.5 – 21.4)
Distant only	3	
Distant and local	1	
Metachronous lung	4	19.5 months (12.0 – 59.3)