

ORIGINAL ARTICLE



Stereotactic body radiotherapy for synchronous early stage non-small cell lung cancer

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ABSTRACT

Introduction: In patients with non-small cell lung cancer (NSCLC) who present with multiple pulmonary nodules, it is often difficult to distinguish metastatic disease from synchronous primary lung cancers (SPLC). We sought to evaluate clinical outcomes after stereotactic body radiotherapy (SBRT) alone to synchronous primary lesions.

Material and methods: Patients with synchronous AJCC 8th Edition Stage IA-IIA NSCLC and treated with stereotactic body radiation therapy (SBRT) to all lesions between 2009–2018 were reviewed. SPLC was defined as patients having received two courses of SBRT within 180 days for treatment of separate early stage tumors. In total, 36 patients with 73 lesions were included. Overall survival (OS), progression-free survival (PFS), cumulative incidence of local failure (LF), and regional/distant failure (R/DF) were estimated and compared with a control cohort of solitary early stage NSCLC patients.

Results: Median PFS was 38.8 months (95% CI 14.3-not reached [NR]); 3-year PFS rates were 50.6% (35.6–72.1). Median OS was 45.9 months (95% CI: 35.9-NR); 3-year OS was 63.0% (47.4–83.8). Three-year cumulative incidence of LF and R/DF was 6.6% (3.7–13.9) and 35.7% (19.3–52.1), respectively. Patients with SPLC were compared to a control group ($n=272$) of patients treated for a solitary early stage NSCLC. There was no statistically significant difference in PFS ($p=.91$) or OS ($p=.43$). Evaluation of the patterns of failure showed a trend for worse cumulative incidence of R/DF in SPLC patients as compared to solitary early stage NSCLC ($p=.06$).

Conclusion: SBRT alone to multiple lung tumors with SPLC results in comparable PFS, OS, and LF rates to a cohort of patients treated for solitary early stage NSCLC. Those with SPLC had non-significantly higher R/DF. Patients with SPLC should be followed closely for failure and possible salvage therapy.

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KEYWORDS

SBRT; synchronous primary lung cancer; NSCLC; lung cancer; radiation therapy; metachronous primary lung cancer

Introduction

Lung cancer is the leading cause of cancer mortality in the United States [1]. Patients who present with early stage non-small cell lung cancer (NSCLC) are treated definitively with localized therapy including surgery or radiation therapy. Surgical resection is currently the standard of care for medically operable patients. Large randomized evidence demonstrating equivalence of stereotactic body radiotherapy (SBRT) with surgery is lacking. However, for medically inoperable patients, or those who decline resection, SBRT is an established standard with high levels of local control [2]. Furthermore, SBRT is well tolerated with minimal toxicity (<4% grade 3 or higher) [3].

Much of the prospective data for SBRT in early stage NSCLC includes only patients with a solitary parenchymal nodule at presentation [2,4,5]. Approximately 0.5% of patients may present with multiple synchronous primary lung cancers (SPLC) [6]. Classifying a patient as having two separate primaries versus metastatic disease is challenging and requires multidisciplinary review. Advancements in

imaging and pathologic sampling techniques have improved the diagnostic accuracy for this condition.

Historically, survival in patients with synchronous primary lung cancer has been relatively poor with a reported five-year survival rate of 44% [7] and has been primarily managed with resection when possible [7,8]. Involvement of multiple lobes may increase operative risk, particularly if complicated by baseline comorbidities [9,10].

Recently, SBRT is increasingly being utilized in the clinical scenario of SPLC as well as metachronous primary lung cancers (metachronous defined as tumors in the lung presenting >180 days apart as opposed to synchronous presenting <180 days). Many of the available studies examining the optimal management strategies for this situation have included more than one treatment modality (surgery, SBRT, radiofrequency ablation, or other interventional techniques) [11–15]. The current study reports on the clinical outcomes and experience of using SBRT alone for patients presenting with SPLC. We also used a contemporaneous cohort of 273

patients with solitary early stage NSCLC managed with SBRT to compare clinical outcomes.

Material and methods

Patient selection and treatment

In this IRB-approved study, patients treated with SBRT to all lesions of primary synchronous early stage NSCLC between 2009 and 2018 were reviewed. Study data were collected and managed using REDCap electronic data capture tools hosted by the Wake Forest Clinical and Translational Science Institute [16]. Patients without any follow-up or those with prior lung cancer were excluded. For the purposes of this study, SPLC's were defined as patients who received two courses of SBRT within 180 days of each other for solitary primary nodules [8,11,15]. Patients treated for synchronous disease were identified by query of the electronic medical record and the departmental radiation therapy care management software (MOSAIQ®, Elekta, AB) for lung SBRT delivered to two or more sites within 180 days of each other. All patients underwent multidisciplinary thoracic oncology evaluation staging work up with computed tomography (CT) and/or [¹⁸F] fluorodeoxyglucose (FDG) positron emission tomography (PET) prior to treatment. Brain magnetic resonance imaging (MRI) was also obtained at the discretion of the treating clinician. Referral for biopsy was considered in all patients with a newly diagnosed lung nodule concerning for putative NSCLC (i.e. with serial growth on subsequent CT imaging or increased FDG avidity). Endobronchial ultrasound (EBUS) was also considered when imaging revealed suspicious hilar or mediastinal lymph nodes. The study cohort of patients with synchronous primary NSCLC was compared to a control group ($n = 272$) of patients treated with SBRT for a new diagnosis of a solitary early stage NSCLC lesion. Patients treated at the same institution were reviewed and corresponding patient and tumor factors were abstracted.

Patient simulation included custom vacuum cushion immobilization with abdominal compression to restrict respiratory motion. An internal gross tumor volume (iGTV) was contoured by co-registering the maximum intensity projection and four-dimensional CT (4D-CT) images without intravenous contrast. The planning target volume (PTV) was generated by an isotropic expansion of 5 mm from the iGTV [17]. Central tumors were defined as tumors within 2 cm of the proximal bronchial tree. At our institution, after the completed multidisciplinary workup, patients are ideally treated with SBRT regimens BED >100 simultaneously. In cases where normal tissue tolerance is a concern, patient safety or other logistic factors required, SBRT regimens with lower BED are utilized and rarely, the treatments are performed sequentially. SBRT is routinely prescribed using a variety of techniques including 8–11 three-dimensional beams, intensity-modulated radiotherapy or volumetric modulated arc therapy. Planning goals include 95% of the PTV to receive the prescription dose with a goal heterogeneity of 130–140% and high-dose conformity indexes in accordance with RTOG protocol guidelines. Organ at risk constraints have been reported previously [18]. Treatments were delivered using 6-MV photons from gantry-based linear

accelerators. Daily image guidance was used prior to each treatment utilizing cone-beam CT image guidance.

Outcomes and follow-up

Patients were followed with routine CT imaging of the chest and physician visits according to institution guidelines of every 3 months for the first three years and every 6 months until an annual visit after 5 years. Outcome measures were calculated from the date of the first fraction (of the first course, for SPLC patients) of SBRT. Progression-free survival (PFS) was defined as time from SBRT start to disease recurrence (local, regional, or distant), last clinical follow-up or death, whichever occurred first. Overall survival (OS) was defined as time to death from any cause or last clinical follow-up. Local failure (LF) was defined as progression within the planning target volume (PTV), lobar failure was defined as progression within the PTV or the treated lobe, regional/distant failure (R/DF) as progression within the hilar or mediastinal nodal regions, distant metastasis, or both, and new primary was defined as new metachronous pulmonary nodule treated with definitive intent and no other therapies to address possible metastatic disease after thorough multidisciplinary review. Patients with multiple nodules or involved pleural effusion were considered to have a distant failure. Time to local failure or regional/distant failure was calculated as the time from the date of SBRT start to failure, death (competing risk event), or last follow-up (right censor). Toxicity, including rate and severity of pneumonitis were graded per the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 based upon review of the medical record.

Statistical analysis

Data were summarized using count (frequency) and median (interquartile range [IQR] or range) for categorical and continuous variables, respectively. Variables were compared between groups using the Chi-square or Fisher's exact test where appropriate for categorical variables and the Kruskal–Wallis test for continuous variables. Time-to-event outcomes were calculated from the first day of the first course of SBRT. OS and PFS were estimated using the Kaplan–Meier method and compared between groups using the log-rank test. Local failure and regional/distant failure were estimated using competing risk methodology (death without failure as the competing risk) and compared using Gray's test [19]. Follow-up duration was estimated using the reverse Kaplan–Meier method [20]. Cases with missing data for a given variable were excluded from the specific analysis. Statistical analyses were performed using R version 3.6 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Tumor and patient characteristics

A total of 79 lesions treated in 39 patients were identified. Two patients without any follow-up and one who had both

Table 1. Patient and tumor characteristics of patients with solitary and synchronous primary NSCLC treated with SBRT.

Patient Characteristics	Synchronous Primary (n = 36)	Solitary Primary (n = 272)	Overall (n = 308)	p
Age (median [IQR])	73 [67, 77]	71 [65, 79]	72 [65, 78]	.84
Gender (%)				
Female	22 (61.1)	94 (34.6)	116 (37.7)	<.01
Male	14 (38.9)	178 (65.4)	192 (62.3)	
BMI (median [IQR])	25.00 [22.15, 27.60]	25.27 [22.20, 30.58]	25.23 [22.20, 30.50]	.6
ECOG (%)				
0	1 (2.9)	18 (6.6)	19 (6.2)	.64
1	21 (61.8)	132 (48.5)	153 (50.0)	
2	10 (29.4)	96 (35.3)	106 (34.6)	
3	2 (5.9)	25 (9.2)	27 (8.8)	
4	0 (0.0)	1 (0.4)	1 (0.3)	
Smoking status (%)				
Never	2 (5.9)	10 (3.7)	12 (3.9)	.3
Current	15 (44.1)	89 (32.7)	104 (34.0)	
Former	17 (50.0)	173 (63.6)	190 (62.1)	
Pulmonary function test (%)				
No	12 (35.3)	141 (51.8)	153 (50.0)	.1
Yes	22 (64.7)	131 (48.2)	153 (50.0)	
Supplemental oxygen (%)				
No	29 (85.3)	220 (81.2)	249 (81.6)	.73
Yes	5 (14.7)	51 (18.8)	56 (18.4)	
PET/CT (%)				
No	0 (0.0)	15 (5.5)	15 (4.9)	.31
Yes	35 (100.0)	257 (94.5)	292 (95.1)	
MRI brain (%)				
No	17 (48.6)	209 (76.8)	226 (73.6)	<.01
Yes	18 (51.4)	63 (23.2)	81 (26.4)	
Biopsy (%)				
No	4 (11.1)	77 (28.3)	81 (26.3)	.05
Yes	32 (88.9)	195 (71.7)	227 (73.7)	
Tumor Characteristics	Synchronous Primary (n = 73)	Solitary Primary (n = 272)	Overall (n = 345)	p
Central lesion (%)				
No	60 (82.2)	238 (87.5)	298 (86.4)	.33
Yes	13 (17.8)	34 (12.5)	47 (13.6)	
Peripheral lesion (%)				
No	22 (30.1)	70 (25.7)	92 (26.7)	.54
Yes	51 (69.9)	202 (74.3)	253 (73.3)	
Lesion biopsied (%)				
No	34 (46.6)	77 (28.3)	111 (32.2)	<.01
Yes	39 (53.4)	195 (71.7)	234 (67.8)	
Histology of biopsied lesion (%)				
Adenocarcinoma	20 (51.3)	85 (43.8)	105 (45.1)	.49
Squamous cell carcinoma	16 (41.0)	80 (41.2)	96 (41.2)	
Adenosquamous	1 (2.6)	1 (0.5)	2 (0.9)	
Large cell	0 (0.0)	3 (1.5)	3 (1.3)	
NSCLC NOS	2 (5.1)	22 (11.3)	24 (10.3)	
Other	0 (0.0)	3 (1.5)	3 (1.3)	
T stage (AJCC 8 th ed.) (%) ^a				
T1a	16 (21.9)	23 (8.5)	39 (11.3)	.01
T1b	35 (47.9)	123 (45.2)	158 (45.8)	
T1c	18 (24.7)	92 (33.8)	110 (31.9)	
T2a	3 (4.1)	26 (9.6)	29 (8.4)	
T2b	1 (1.4)	8 (2.9)	9 (2.6)	
Stage (AJCC 8 th ed.) (%) ^a				
IA	69 (94.5)	238 (87.5)	307 (89.0)	.23
IB	3 (4.1)	26 (9.6)	29 (8.4)	
IIA	1 (1.4)	8 (2.9)	9 (2.6)	
Tumor size (median [range])	1.50 [0.6, 4.2]	1.95 [0.7, 5.0]	1.90 [0.6, 5.0]	<.01
Dose (median [range])	50.0 [50.0, 60.0]	50.0 [34.0, 54.0]	50.0 [34.0, 60.0]	.74
BED ₁₀ (median [range])	100.0 [75.0, 151.20]	100.0 [75.0, 151.2]	100.0 [75.0, 151.2]	.39

ECOG: Eastern Cooperative Oncology Group performance status; EBUS: endobronchial ultrasound; BED: biologically effective dose.

^aLesions were individually staged using T-stage based on size as each individual lesion was defined as a primary rather than a satellite nodule (T3/4).

Patients with missing data for the particular variable of interest are excluded.

lesions treated with 40 Gy in 5 fractions were excluded and the remaining 73 lesions treated in 36 patients were analyzed. Baseline characteristics are summarized in Table 1. The majority of patients were female and baseline ECOG performance status was 0–1 in 65% and 2–3 in 35%. Most patients were current (44%) or former (50%) smokers, and were staged with PET/CT imaging (100%). Pathologic confirmation

of NSCLC *via* biopsy of at least one lesion was obtained in 32 of 36 patients (89%). Both lesions were biopsied in 7 of the 32 patients (22%). For these 7 patients, 2 patients had tumors with discordant histology and 5 had concordant histology. In the cases where the lesion was not biopsied and in patients without any pathologic confirmation of cancer, multidisciplinary discussion utilizing imaging findings and

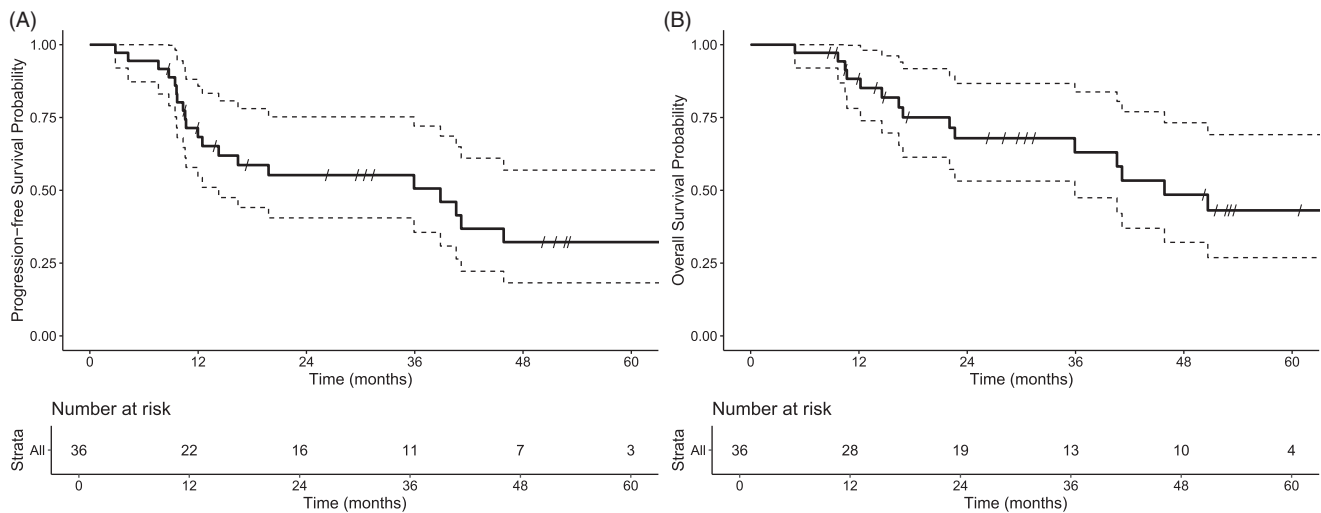


Figure 1. Progression-free survival (A) and overall survival (B) for patients treated with SBRT to synchronous early-stage NSCLC.

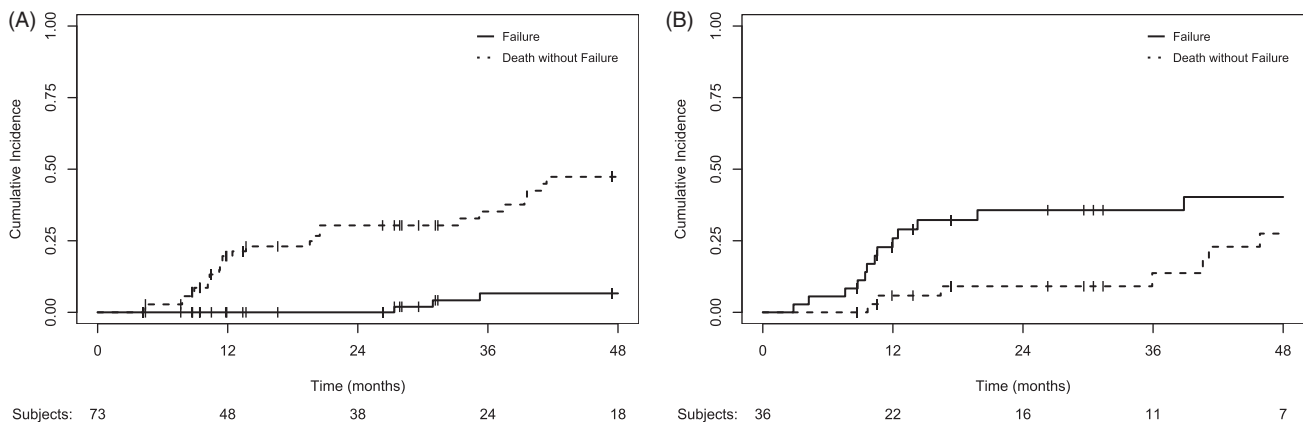


Figure 2. Cumulative incidence of local failure (A) and regional/distant failure (B) with death as a competing risk for patients treated with SBRT to synchronous early-stage NSCLC. Solid line: failure; Dashed line: death without failure.

clinical suspicion established a diagnosis. EBUS evaluation of the mediastinum was performed in 5 patients (16%). MRI of the brain was obtained in 51.4%. Supplemental oxygen was in use at baseline in 14.7% of patients. All patients had at least 2 lesions treated, with one patient having 3 lesions. Both treated lesions were diagnosed at the initial consultation in 35 of 36 (97%) patients. Nineteen (53%) patients started treatment with SBRT to each lesion starting on the same day and 32 (89%) patients had treatment to all lesions within 30 days. Chemotherapy was used following the delivery of SBRT in only 1 patient.

In total, 39 tumors were pathologically-proven NSCLC: 20 adenocarcinoma, 16 squamous cell carcinoma, 1 adenosquamous carcinoma and 2 NSCLC not otherwise specified. The tumors were located in the same lung in 17 patients (47.2%). Most tumors ($n=61$) were treated with 50Gy in 5 fractions with other dose/fraction schedules including 50Gy/10 fractions ($n=7$), 54Gy/3 fractions ($n=3$), and 60Gy/8 fractions ($n=2$).

Survival and disease recurrence

Median follow-up was 51.5 months (95% CI: 29.6-not reached [NR]). Median PFS was 38.8 months (95% CI 14.3-NR).

Estimated 1- and 3-year PFS rates (95% CI) were 68.3% (54.4–85.8) and 50.6% (35.6–72.1), respectively (Figure 1(A)). Median OS was 45.9 months (95% CI: 35.9-NR) (Figure 1(B)). Kaplan–Meier estimates of OS at 1- and 3-years (95% CI) were 88.3% (78.1–99.8) and 63.0% (47.4–83.8), respectively.

Cumulative incidence rates (95% CI) of LF and combined R/DF at 1- and 3-years were as follows: LF, 0% (0–0) and 6.6% (3.7–13.9); R/DF, 25.9% (11.3–40.5) and 35.7% (19.3–52.1) (Figure 2). The competing risk of death without local failure at 3-years was 35.2% (Figure 2(A)), while the corresponding 3-year competing risk of death without regional/distant failure was 13.7% (Figure 2(B)). In total, 13 of 36 patients experienced disease recurrence (patients could experience more than 1 event): 3 patients experienced a local failure (12 patients experienced alternate definition of local/lobar failure), 5 patients experienced regional failure and 12 patients had distant metastasis. A single patient that did not exhibit distant failure but had an isolated regional failure at 10 months was salvaged with chemoradiation to the mediastinum. The patient is alive at last follow up 53 months from start of initial SBRT. The most common site of first failure was distant only ($n=8$), followed by regional only ($n=3$), regional plus distant ($n=2$).

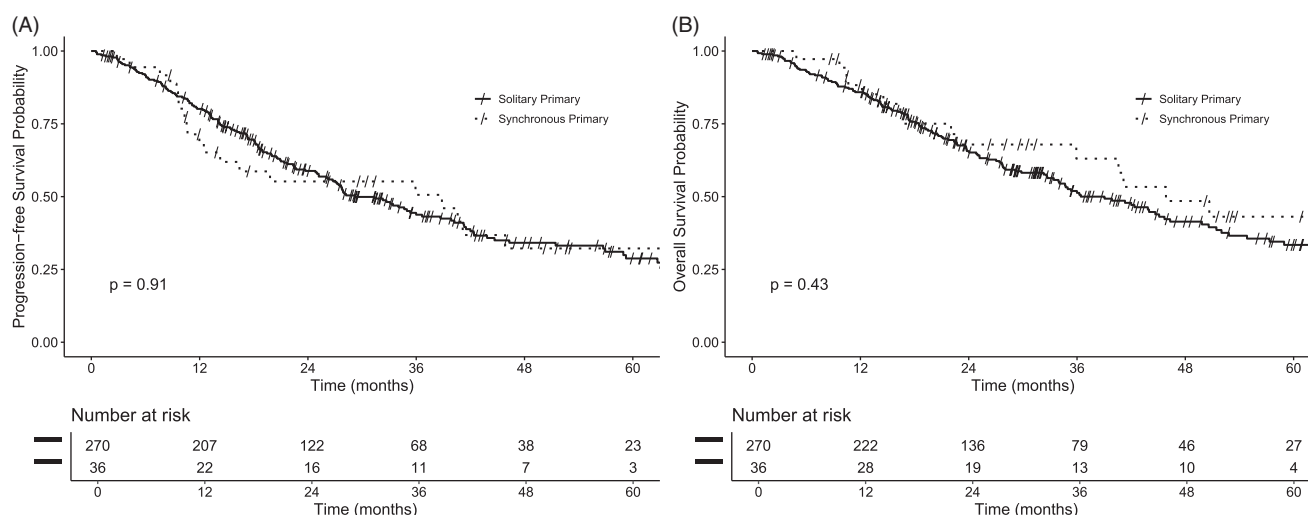


Figure 3. Progression-free survival (A) and overall survival (B) after SBRT to a solitary early stage NSCLC versus synchronous primary NSCLC.

Additional new primary NSCLC was diagnosed in 8 patients at a median time from initial SBRT of 17.1 months (95% CI: 6.1–64.8). Median OS in patients with new primary NSCLC was not significantly different from those without a new primary NSCLC (median OS 66.7 months v. 45.9 months, log-rank $p = .34$).

Synchronous primary NSCLC versus single early stage NSCLC

The study cohort of 36 patients with synchronous primary NSCLC was compared to a control cohort of 273 patients with a solitary early stage NSCLC treated with SBRT. Patients with SPLC were significantly more likely to be female and to have undergone biopsy (of at least 1 lesion) and were less likely to have received MR brain initial staging. The remainder of patient-specific factors were not significantly different between groups (Table 1). Tumor-specific factors that differed between groups included biopsy of each individual lesion and tumor size. The remainder of tumor-related factors including central/peripheral location, histology, overall stage, size, prescription dose and prescription BED₁₀ were not significantly different between groups (Table 1).

The median follow-up for the solitary early stage NSCLC control group was 41.8 months (95% CI: 36.8–48.0) and did not differ from that of SPLC ($p = .65$). The median PFS was 29.2 months (95% CI: 26.7–38.7) for the solitary NSCLC group; 1-year PFS was 80.1% and 3-year PFS was 43.8%. There was no significant difference between groups with regard to PFS (log-rank $p = .91$) (Figure 3(A)). Median OS for solitary NSCLC group was 36.4 months (95% CI: 33.4–46.3); 1- and 3-year OS rates were 85.9% and 51.3%, respectively (Figure 3(B)). There was no significant survival difference between the solitary NSCLC and SPLC patients ($p = .43$). There was no significant difference between LF ($p = .18$) and patients with SPLC exhibited worse combined R/DF compared to solitary NSCLC patients, though this did not reach statistical significance ($p = .06$). One- and 3-year cumulative incidence of R/DF for solitary NSCLC was 8.0% (4.7–11.3) and 18.0% (13.0–22.9). Grade 2 or greater pneumonitis occurred in 1 patient (2.8%)

with SPLC and 3 patients (1.1%) with solitary NSCLC ($p = .4$). There was no grade 4 or 5 pneumonitis in either group.

Discussion

The optimal treatment of patients with SPLC remains controversial. Pathologic assessment of one or more lesions is not always practical or safe, and these situations are often difficult to distinguish from an oligometastatic state. The current study evaluates disease control and survival outcomes after SBRT was delivered as definitive treatment to all SPLC lesions, which is somewhat unique amongst the sparse literature reporting on SPLC management [11,14,15,21]. Only one patient in our study had systemic therapy following their definitive therapy and was treated with single agent weekly taxotere. After no progression after 16 weeks of taxotere, systemic therapy was stopped and the patient did not have progression until a lobar recurrence 3 years later.

In the current study, SPLC was defined as patients with multiple lesions treated with SBRT within 180 days of each other. This definition was pre-specified *ab initio* to be consistent with other studies examining patients with multiple NSCLC primaries treated in a 6-month time frame [8,11,15]. There remains some variation in the time frame which defines SPLC as reported in the literature [14]. Due to the very definition of SPLC, analyses of treatment outcomes may be subject to immortal time bias, with those patients surviving long enough to have multiple SPLC lesions treated exhibiting variable survival rates compared to those with solitary primary lung cancers or those who do not survive to develop a ‘second primary’ lung cancer. The risk of confounding in this study is low, given that the majority of our patients (32 of 36, 89%) had all synchronous lesions treated within the same month. The small population size of patients treated outside of this 1-month window limits our power to evaluate for potential differences in outcomes based on time to new primary NSCLC. To our knowledge, there is no clear consensus regarding the optimal time-frame in which a patient should be diagnosed with synchronous versus meta-

A high index of suspicion for regional or distant disease is critical in the work up for presumed SPLC as one of the lesions may represent oligometastatic disease. Ideally, patients with suspected SPLC would have all lesions biopsied in order to provide evidence of different pathologic entities. However, patients with lung cancer often have multiple comorbidities and poor lung functional reserve making biopsy of all lesions imprudent and may not affect outcomes after SBRT anyway [22]. There have been multiple other studies that have showed similar results, suggesting that empiric SBRT is a reasonable approach when clinical history and imaging are suggestive of early stage lung cancer in a pulmonary nodule [23].

The standard work-up should include PET/CT imaging and, if a lesion is larger or central in location, an MRI of the brain to rule out metastatic disease [24]. Consideration of an EBUS is important to comprehensively assess the mediastinum, particularly if baseline imaging reveals any suspicious lymphadenopathy [25]. Only 14% of our patients with SPLC underwent an EBUS which was completed as routine work up or after imaging revealed suspect lymph nodes in 1 patient. Of the 5 patients that had an EBUS procedure completed, only 1 patient eventually did have regional/distant failure which occurred at 10 months following SBRT treatment. Although combined regional/distant failure was the dominant pattern of failure, only 3 patients experienced regional failure alone as the site of first failure. The role of a staging EBUS in this cohort is unclear, but we advocate its consideration in medically fit patients with SPLC eligible for SBRT to all nodules.

SBRT has been shown to provide excellent local control of early stage solitary NSCLC lesions as shown in multiple large randomized trials [2,4,5]. Our study of patients with SPLC similarly demonstrated that SBRT offers excellent local control with a cumulative incidence of local failure at 3 years of 6.6%. An alternate definition of local disease control, lobar failure, occurred in 12 of 36 (33%) patients. This is consistent with other reported studies examining SBRT for patients with SPLC which included lobar failure as the definition for local control [11,12,14,15,21]. The rate of lobar failure appears to be high in the cohort of patients with two synchronous primaries. It is difficult to conclusively state that this is a reflection of possible metastatic disease or elevated due to reporting patient lobar failures in these patients which have two lobes involved at presentation and two independent lobes with risks for future lobar failures. Long term results of RTOG 0236 demonstrated a 5-year primary and involved lobe failure after SBRT at 20% in patients that only have one lobe involved [26].

Ten patients (28%) were found to develop an additional new primary NSCLC after SBRT for SPLC and were subsequently treated with localized therapy including SBRT and radiofrequency ablation. We distinguished patients with new primaries for this cohort of patients with SPLC as separate entities than patients that have a truly metastatic disease process present. Rationale for this was based on the fact that these patients were treated with a local definitive therapy option for the new lung nodule and not with systemic

therapy. Only 1 patient had a biopsy of the new primary and the rest were treated empirically. Two of the patients with new primaries went on to have an eventual metastatic disease process. The patients that developed a new primary had similar outcomes to those patients that did not, suggesting that salvage therapies (including repeat SBRT) are effective in treating subsequent, metachronous lung primary tumors after treatment of SPLC which has already been reported in multiple studies [11–14,27]. In the studies which specifically compared patients with metachronous NSCLC and SPLC there are conflicting conclusions in terms of survival outcomes. In two studies it was found that patients with metachronous NSCLC had improved PFS and OS compared to patients with SPLC [11,13]. In contrast, another study found patients treated with synchronous SBRT had similar OS and freedom from progression compared to patients treated for single lesion NSCLC [14].

With regard to patterns of failure in this cohort, we observed non-significantly increased rates of combined R/DF in patients with SPLC compared to those with solitary tumors. Patients with SPLC historically were not offered definitive local therapy due to concern for high rates of regional and distant failure which may make any definitive local therapy futile. On the contrary, our study showed that these patients have similar PFS and OS as our cohort with solitary early stage NSCLC patients treated with SBRT. Despite a numerically higher cumulative incidence of combined R/DF, we believe that a 3-year rate of 35% is reasonable in this population which would have otherwise started systemic therapy after being classified as having metastatic disease at initial presentation. In that case, the most common site of progression after first-line systemic therapy is within areas of initial disease at presentation [28]. Therefore, these patients may indeed benefit from definitive local therapy.

The increased regional/distant failures may be reflective of subclinical/microscopic metastatic disease at the time of treatment despite a negative work-up. If some of the patients in our cohort truly had metastatic disease, they may have still benefited from the local definitive therapy that they received, similar to studies examining SBRT for treatment of oligometastatic disease [29–31]. However, given the higher estimated probability of regional and/or distant failure in SPLC, close imaging follow-up and a high suspicion for disease recurrence is warranted. Additionally, these patients may benefit from consolidation systemic therapy, similar to locally advanced NSCLC [32]. Consolidative systemic therapy for early stage NSCLC is currently being investigated in the Pacific-4 trial which is comparing durvalumab vs placebo following SBRT (NCT03833154).

The primary limitations of this investigation are its retrospective nature and its limited sample size. Therefore, it is prone to patient selection bias with differences in surgical operability as well as loss of patient follow-up due to frequent death and comorbid illnesses in this population of patients with lung cancer. As a relatively rare entity, a limited number of patients with SPLC were available in the comparison to the cohort of patients who were treated for solitary

early stage NSCLC with SBRT. This limits our statistical power to detect differences in survival outcomes. Additionally, several treatment planning systems and SBRT techniques were used in treatment of patients over the time frame included in this study. Many of these represent unavoidable limitations which are common among retrospective studies. Despite these limitations, this study offers valuable insight into an uncommon clinical scenario of treating multiple synchronous primary NSCLC lesions with SBRT.

Conclusion

Treatment of multiple lung tumors in patients with SPLC with SBRT alone results in comparable PFS, OS, and LF compared to patients with solitary early stage NSCLC tumors managed with SBRT. Patients with SPLC (versus those with solitary NSCLC) may be at an increased risk of regional and/or distant failure and should be followed closely in surveillance.

Disclosure statement

The views expressed in this article are those of the authors and do not reflect the official policy or position of the Department of the Army, Department of Defense, or the U.S. Government.

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