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Detection of second primary lung cancers on surveillance imaging following stereotactic ablative radiotherapy for non-small cell lung cancer

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Abstract

Development and detection of second primary lung cancer (SPLC) following stereotactic ablative radiotherapy (SABR) for lung cancer may differ from surgical patients. We analyze 134 patients treated with SABR followed with frequent surveillance imaging. Eighteen patients developed 21 SPLC at a median of 28.5 months, with good survival following definitive treatment of SPLC.

Introduction/Background: Second primary lung cancers (SPLC) are common following non-small cell lung cancer (NSCLC) treatment. Development of SPLC following stereotactic ablative radiation therapy (SABR) may differ as compared to surgical cohorts. We report incidence of and outcomes for SPLC detected by surveillance imaging in a cohort of patients treated with SABR.

Materials/Methods: Patients treated with SABR for node-negative NSCLC between February, 2007 to May, 2019 were retrospectively identified. Patient characteristics, frequency of surveillance imaging, development of SPLC, recurrence patterns, and survival were reviewed. Surveillance CT was performed Q3–4 month year 1, Q3–6 month year 2, Q6–12 month year 3–5, and Q12 month thereafter. Actuarial estimates of development of SPLC and overall survival (OS) were generated with competing risk analysis.

Results: We identified 134 patients treated with SABR with ≥6 months follow up. Eighteen (13.4%) developed a total of 21 SPLC at a median of 28.5 months (range 3.0–84.7 months) following SABR, 19 (90.5%) biopsy-proven. Twenty (95.2%) SPLC were detected by surveillance imaging. Three patients developed 2 metachronous SPLC. Three and 5 year SPLC estimates were 11.7% and 13.1%. Eighteen (85.7%) SPLC were treated with curative intent. Two and 3 year estimate of OS following detection of SPLC was 79.8% and 54.7%.

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Author Statement

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Conclusion: SPLC were more common in our cohort than other published studies. Outcomes following surveillance detected SPLC are similar to those of de novo early stage lung cancers. The high frequency of SPLC in our cohort suggests further studies to refine overall surveillance in very high-risk populations are needed.

Introduction

Non-small cell lung cancer (NSCLC) is a common and lethal malignancy, and patients with early-stage, node negative disease comprise approximately 16% of newly diagnosed NSCLC cases.[1] Surgical intervention remains the mainstay of treatment for fit patients with early-stage NSCLC. However, stereotactic ablative radiation therapy (SABR) has emerged in the past two decades as a definitive treatment option for patients with medically inoperable early-stage NSCLC following publication of several landmark prospective trials.[2–4] SABR relies on the delivery of ablative radiation doses over 1–5 fractions with steep dose gradients using precise tumor localization and motion management.

Second primary lung cancers (SPLC) are common following initial treatment of lung cancer, as the risk factors that predispose a patient to developing one lung cancer predispose the development of a surgical lung cancer management is well-described second cancer. While detection of SPLC following in the literature, [5,6] development of SPLC and relationship to surveillance imaging following SABR is less well-described. SABR is predominantly used in the medically inoperable population, who tend on average to be older, with greater comorbidities than the medically operable population. Thus, patterns and detection of SPLC may differ from that seen in the surgical population.

Timely detection of SPLC post SABR is important as it may allow opportunity for definitive management while localized and the possibility of increased survival for this patient cohort. The purpose of this study is to report incidence, timing, of and outcomes for SPLC detected in a cohort of patients treated with SABR for NSCLC followed by frequent surveillance chest CT. We hypothe-size that with regular surveillance, most SPLC will be detected at an early stage and treated with curative intent.

Methods and Materials

Patient Selection

Following institutional review board approval, we performed a retrospective review of all patients treated with SABR for node negative NSCLC at The University of California Davis Comprehensive Cancer Center between February, 2007 to May, 2019. Eligible patients were treated with SABR or hypofractionated radiation over 3–8 fractions for T1–4N0M0 NSCLC that was either inoperable or who refused surgery. Eligible patients must have received radiation treatment in the form of SABR or a SABR-like approach with up to 8 fractions with 50–60 Gy over 3–8 fractions, with minimum follow up period post- SABR of 6 months. Patients treated for synchronous primary and multifocal tumors were included. Patients' tumor and treatment characteristics, frequency and duration of surveillance chest CT, and development of SPLC, recurrence, and death were recorded.

Treatment

Patients were simulated with Vac-lok (CIVCO Medical Solutions, Orange City, IA) for immobilization in the supine position with arms above the head. Abdominal compression was used to limit diaphragmatic excursion to ≤1 cm as a surrogate for tumor motion, verified with fluoroscopy. Planning computed tomography (CT) scans were obtained with 2 mm slice thickness, and 10-phase four dimensional CT (4DCT) datasets were obtained at simulation. Gross tumor volume (GTV) was defined based on the planning CT scan with lung windowing. The maximum intensity projection or a review of all 10 phases from the 4DCT datasets were used to generate the internal target volume (ITV). A 5 mm margin was then added to the ITV to generate the planning target volume (PTV). Organs at risk were contoured based on cooperative group trial guidelines.[2] All patients were treated using 6 MV photon on Elekta-Synergy linear accelerator (Elekta AB, Stockholm, Sweden). Fluoroscopy and cone beam CT were obtained prior to each treatment for confirmation of tumor excursion and anatomy matching. The fractionation schedule was at the discretion of the treating radiation oncologist, and prescription doses range from 50–60 Gy over 3–8 fractions. Specific dose fractionation schedules used are included in Table 1.

Follow up and Imaging review

Surveillance CT was generally performed Q3–4 month year 1, Q3–6 month year 2, Q6–12 month year 3–5, and Q12 month thereafter to assess for treatment response and toxicity. Positron emission tomographic staging was performed for all patients with SPLC to assess for nodal or distant disease. Surveillance PET/CT was not routinely performed, but PET/CT was used to clarify equivocal CT findings, often in tandem with biopsy.

Recurrence within or at the margin of the PTV was classified as local tumor failure. Locoregional failures include any failure within the ipsilateral lung or regional nodes (ipsilateral hilar, ipsilateral supraclavicular, or mediastinal nodal). All other recurrences were classified as distant. Tumors suspected to represent SPLC were biopsied when feasible. When not feasible, new solitary lung tumors were reviewed in a multidisciplinary fashion for imaging characteristics and time-course suggestive of SPLC as opposed to a solitary tumor recurrence.

Statistical Analysis

Study endpoints included median age, smoking history, median time to SPLC following SABR, Actuarial estimates of development of SPLC, primary tumor control (PTC), locoregional control (LRC), freedom from distant metastases (FFDM), and overall survival (OS) were generated using competing risk analysis. To take into account competing risks for SPLC due to death and distant recurrence of index cancer, we implemented the cumulative incidence function to depict the cumulative incidence of recurrence of the index cancer versus SPLC versus death over time. Patients treated with curative intent for local or locoregional recurrences continued to undergo surveillance for new primaries, and thus these endpoints were not considered competing risks. All analyses were performed using Statview version 5.01 (SAS Institute Inc., Cary, NC) and R (www.R-project.org).

RESULTS

Patient Characteristics

We identified 134 pts treated with SABR for node-negative NSCLC with ≥6 months follow up who were eligible. The median follow-up for living patients was 40 months (range: 6–126 months) and for all patients was 38 months (range: 6–126 months). Seventy-five patients had biopsy-proven adenocarcinoma, 31 patients had squamous cell carcinoma, 7 patients had NSCLC not otherwise specified, and 21 patients were treated for a radiographically diagnosed lung cancer, based on multidisciplinary review of imaging showing CT and PET/CT characteristics consistent with lung cancer and growth over time. The median age at treatment was 75.1 years (range: 61.7–92.1), and median smoking history was 36.5 pack-year (PY) (range: 0–160 PY). Seventy-eight patients (58%) were female and 56 (41%) were male. Patient characteristics are shown in Table 1.

Survival, Recurrence Patterns, and Development of Second Primary Lung Cancers

Eighteen patients (13.4%) developed a total of 21 SPLC at a median of 25.9 months (range 3.0–84.7 months) following SABR, 18 (85%) of which were biopsy proven. Two (10%) were histologically consistent with small cell carcinoma. Three patients developed 2 separate metachronous SPLC following the initial course of SABR. The 3- and 5-year estimates of SPLC development were 11.7% and 13.1%, respectively (Figure 1). Nineteen of the 21 detected SPLC (90.5%) were early stage at detection and were treated with curative intent with SABR (n = 17) or microwave ablation (n = 1). One SPLC of small cell histology was metastatic at detection and elected for hospice, and one patient with poor performance status elected against any active treatment. One patient transferred care to another hospital at the time of SPLC detection and was lost to follow up prior to management of the SPLC. Three-year estimates of LC, LRC, and FFDM were 92.9%, 80.2%, and 86.6%, respectively (Figure 2 A–C). Two and 3 year estimates of OS following detection of SPLC were 79.8% and 54.7% respectively (Figure 3). Three year OS for the entire patient cohort was 76.3% (Figure 4). Characteristics of the patients developing SPLC are outlined in Table 2.

Role of Surveillance Imaging

The median time from SABR to first surveillance imaging was 3.0 months (range: 0.3–9.7 months), and the median number of scans performed in the first 12 months following SABR was 3 (range: 1–6). Surveillance metrics are shown in Table 3. Twenty (95.2%) of the identified SPLC were first detected on routine surveillance CT at a median of 28.5 months (range: 3–84.7 months) following completion of SABR and subsequently confirmed by PET/CT and/or biopsy. One SPLC (5%) was detected on a pre-operative chest x-ray 82 months post-SABR after discontinuing surveillance at over 4 years and 4 months post-SABR.

DISCUSSION

Although surgical resection with lobectomy and mediastinal lymph node sampling remains the standard of care treatment for medically operable, early stage NSCLC, SABR is considered the standard treatment for medically inoperable disease. [7–9] A substantial

body of literature addresses the development and outcomes of SPLC following surgical management of NSCLC. However, far fewer studies have evaluated SPLC development following SABR, or the potential implications for ongoing surveillance. Medically inoperable NSCLC patients typically have risk factors, such as advanced age, compromised pulmonary function, impaired cardiovascular fitness, more extensive smoking history, or poor performance status, which increase their operative risk. The baseline differences in the surgical and non-surgical population could all impact development and detection of SPLC.

Within the surgical literature, rates of development of SPLC among early stage NSCLC patients range from 4% to 15% as a crude rate and 1.4% to 6.0% per year, typically with ongoing risk of SPLC beyond 5 years. Table 4 highlights some of the largest series describing the detection of SPLC following surgery or radiation for early stage NSCLC.[5,6,10–15]

Far fewer papers assess development of SPLC following definitive radiation therapy. Jeremic et all conducted a review of patients treated with definitive radiation (non-SABR) for stage I-II NSCLC and identified a 1.4% per patient year rate of SPLC, with 14.2% at 10 years. The imaging modality used for surveillance was not indicated.[16] The only paper to our knowledge to assess development of SPLC following SABR, Spratt et al analyzed 366 patients treated with SABR. With a median follow up of 23 months, 5.2% of patients in their cohort developed a SPLC at a median of 16.5 months (6.5 to 71.1 months) and SPLC were more common among current smokers, [17] a lower rate than identified in our patient cohort. 32% of SPLC patients in their study developed SPLCs after 2 years, and the cumulative incidence of SPLC continued to rise up to 6 years from the end of SBRT. The median age in their cohort was 77 years (range, 50–95), and surveillance CT was performed every 3 months year 1–2 and every 6 months year 3–4, very similar to that identified in the current cohort.

Early detection of SPLC detection has also translated into improved OS in prior studies. Farrugia et al. demonstrated that SBRT to new primaries has been associated with improved OS in a matched pair analysis of 438 patients who underwent definitive SBRT for NSCLC. At a median follow-up of 24.8 months, the median time to SPLC was 36.8 months (19.5 to 78.8 months) and 24 patients required SBRT for a SPLC between 3 and 24 months from the prior treatment. Eighty-four had previously treated NSCLC and prior lung cancer ($P = .049$; HR = 0.71; 95% CI, 0.51–0.99) significantly correlated with OS.[18]

Discrepancies in rates of SPLC development between published series likely arise not only due to differences in baseline patient population, such as smoking history and age, but also due to varying methods of defining SPLC in contrast intrapulmonary metastases. The earliest system of classifying SPLC was that of Martini and Melamed, published in 1975, and included major histologic type, interval between metachronous tumors, and tumor location. [19] The American College of Chest Physicians (AACP) has published guidelines that incorporate multidisciplinary team review, radiologic, and cytologic/histologic features.[20] Our approach to identifying SPLC patients in the present study took this approach. Nonetheless, multi-disciplinary review includes a measure of subjectivity that may partially explain differences noted between published series as some

institutions may be more likely to classify isolated new lung tumors as recurrent disease rather than SPLC. Two and 3 year estimates of OS following detection of SPLC in our series, however, were comparable to those of many de novo early stage NSCLC series, at 79.8% and 54.7% respectively. These results suggest that misclassification of intra-thoracic metastases as SPLC was not likely a significant source of error. Additionally, many earlier series provide only crude rates of SPLC rather than actuarial or competing risks analysis and thus may underestimate risk of SPLC due to loss to follow up or loss to competing risks such as death or metastatic disease. Finally, we included patients treated initially for multifocal or synchronous primary tumors, which may have enriched the series for patients with a propensity to develop multiple lung cancers.

The current analysis has several limitations, including the modest cohort size and single institution, retrospective design. The inclusion of patients without biopsy-proven cancer introduces added uncertainty, and the use of frequent surveillance introduces the possibility of lead-time bias and may not be applicable to operable populations.

Our patient case series used relatively frequent surveillance CT, with chest CT typically performed every 3 months the first year and every 3–6 months year 2–3. This increased frequency may have contributed to the frequent detection of early new malignancies. The appropriate frequency for surveillance imaging following the definitive treatment of lung cancer remains poorly defined. Recent American Society of Clinical Oncology (ASCO) guidelines recom- mend CT chest every 6 months through year 3, to be followed by annual surveillance CT thereafter as a standard (16). Our use of more frequent surveillance arose from the challenges of following radiation-induced lung changes over time and differentiating these changes. However, in light of these recent ASCO guidelines we have moved toward offering surveillance every 6 months after a first 3 month CT if no concerning findings are noted.

CONCLUSIONS

In a node-negative NSCLC patient cohort treated with SABR, development of SPLC was relatively frequent, and outcomes following curative intent treatment of SPLC were similar to that of de novo lung cancers. The optimal strategy for identifying SPCL through surveillance remains unknown, but appears to be a major benefit of surveillance imaging.

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Disclosure

Muhtada Kamal Aldin: None. Leonel Kahn: None. Lihong Qi: None. Xiner Zhou: None. Megan Daly: Research Funding, EMD Serono, Genentech, Merck. Advisory Board: Boston Scientific (none related to current submission)

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Clinical Practice Points

- Second primary lung cancers are relatively frequent following treatment of NSCLC with SABR
- Outcomes following the detection of second primaries are excellent when detected at early stages and treated with curative intent
- Surveillance imaging plays a significant role in the detection of second primary lung cancers, and the optimal schedule, duration, and frequency remain incompletely defined

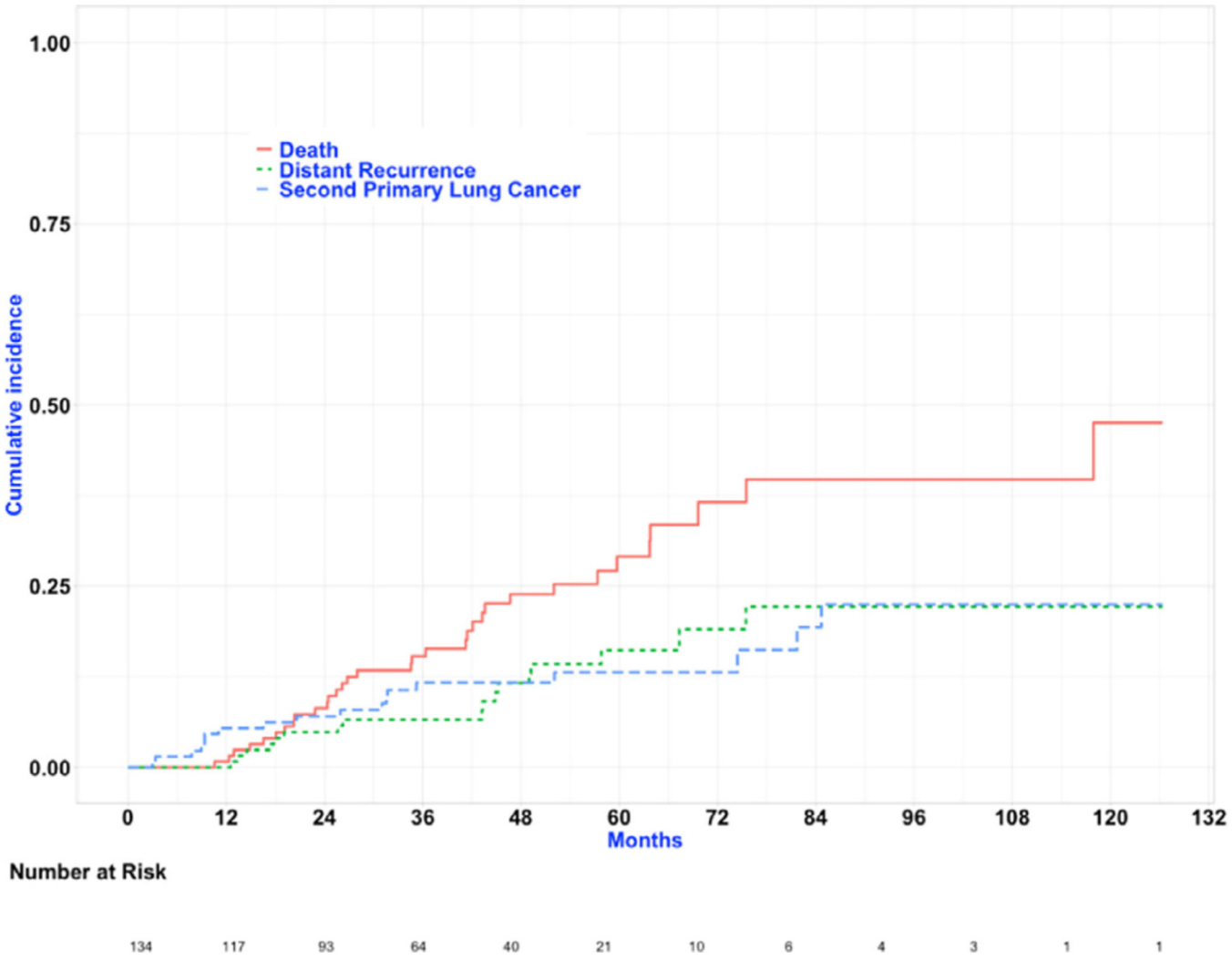

Figure 1.

Cumulative incidence functions for competing risks analysis for development of second primary lung cancer, distant recurrence, and death are shown above. The 3 and 5-year estimates were 11.7% and 13.1% respectively.

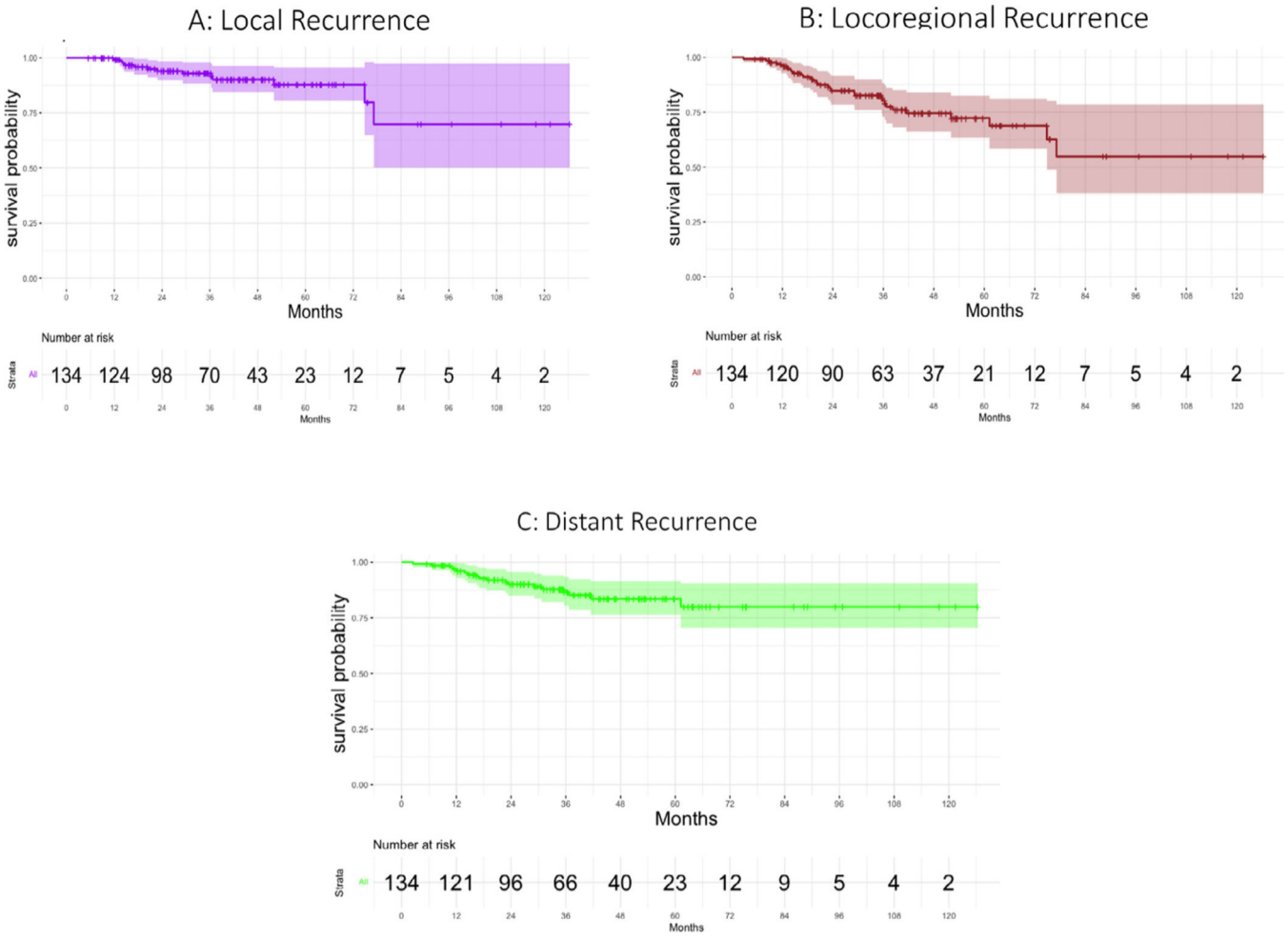

Figure 2.

Kaplan Meier estimates of freedom from (A) local, (B) locoregional, and (C) distant disease recurrence.

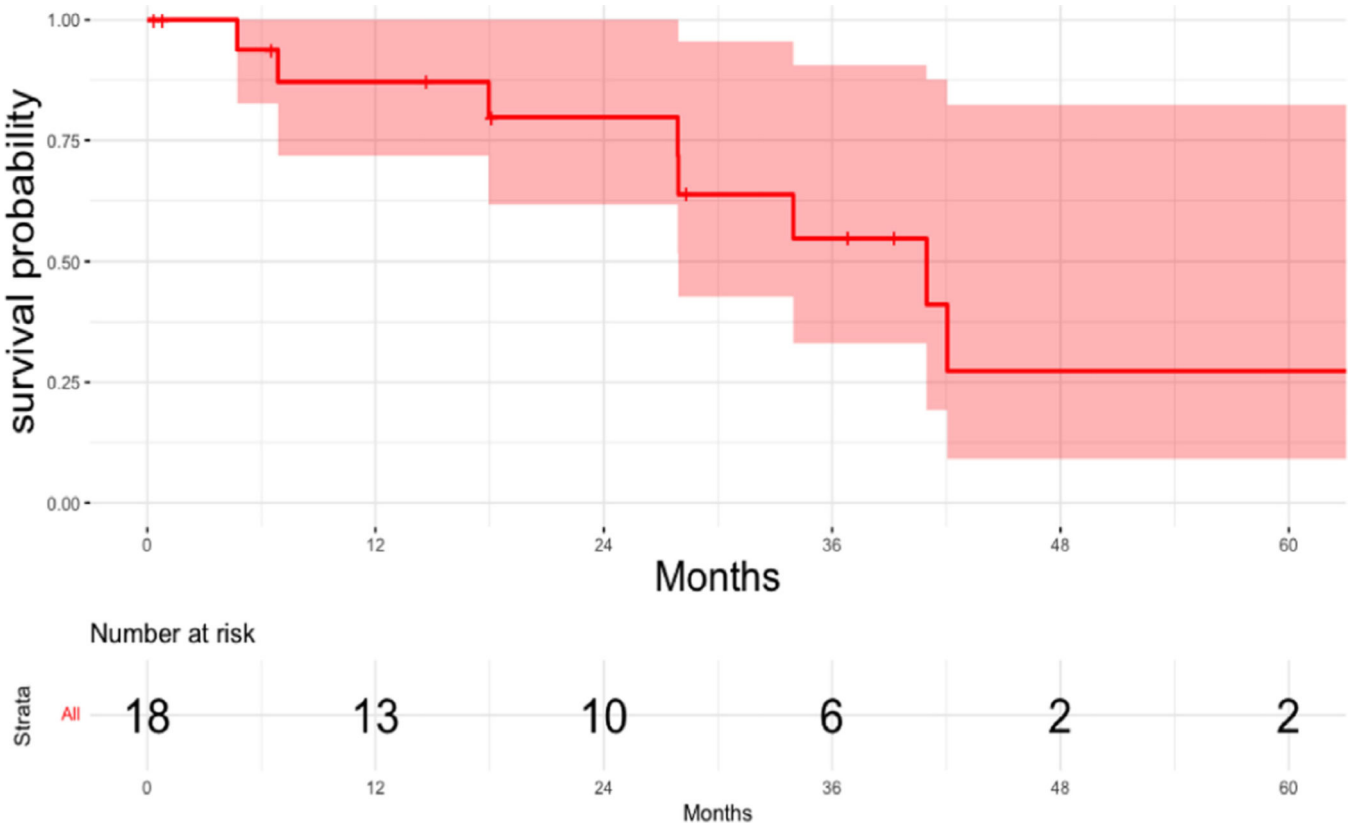

Figure 3.

Two and 3-year Kaplan Meier estimates of overall survival following detection of second primary lung cancer were 79.8% and 54.7% respectively.

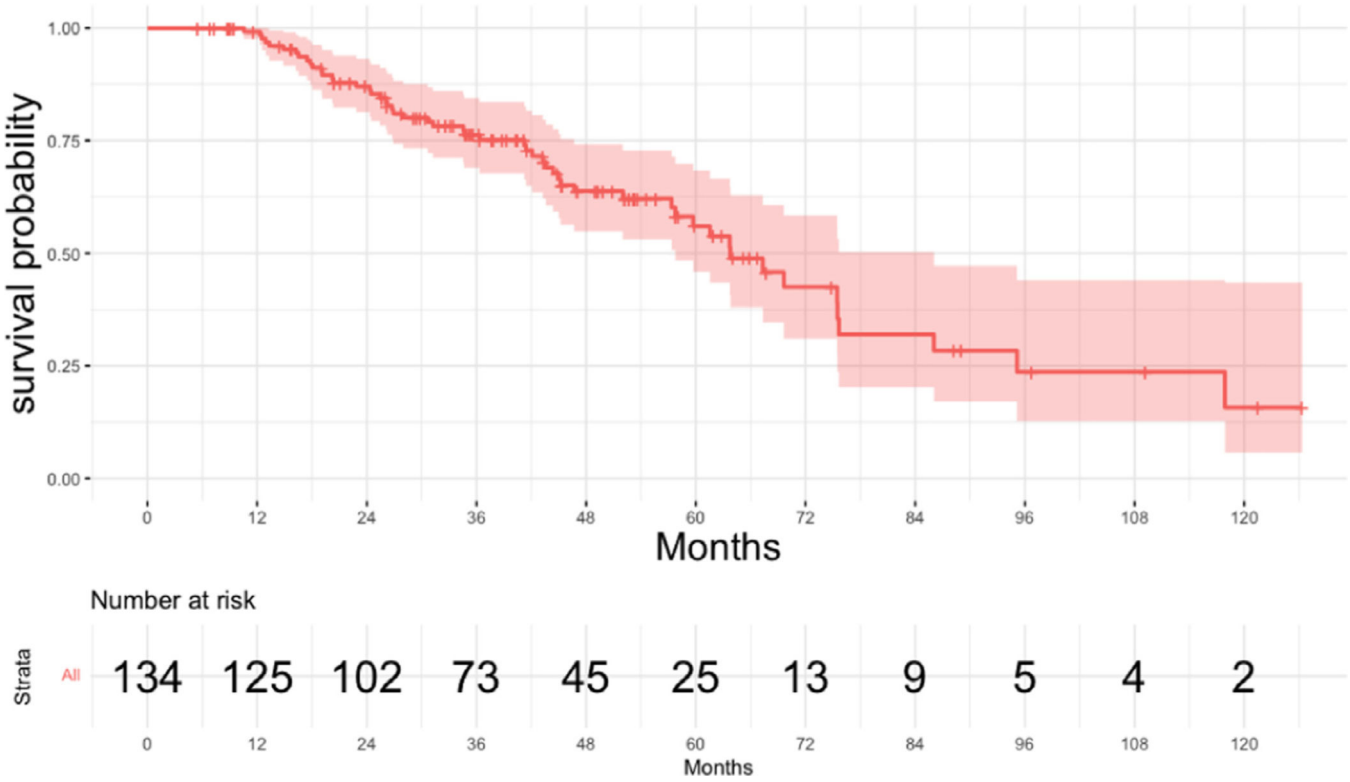

Figure 4.

Kaplan Meier estimate of overall survival for entire patient cohort is show above. Three year estimate of survival was 76.3%.

Table 1

Patient and Treatment Characteristics.

Age	**75.1 (range: 61.7–92.1)**	
Gender	Male	56 (41.8%)
	Female	78 (58.2%)
Smoking History (Pack-years)	36.5 (range: 0–160)	
Smoker status	Current	14 (10.4%)
	Former	106 (79.1%)
	Never	14 (10.4%)
Karnofsky Performance Status	90–100	34 (25.3%)
	80	40 (29.8%)
	70	26 (19.4%)
	≤60	34 (25.3%)
T Stage	1a	11 (8.2%)
	1b	61 (45.5%)
	1c	30 (22.4%)
	2a	8 (6.0%)
	2b	8 (6.0%)
	3	3 (2.2%)
	4	7 (5.2%)
	(Bilateral multifocal)	6 (4.5%)
Operability	Operable	27 (20.1%)
	Medically inoperable	101 (75.4%)
	Unknown	6 (4.5%)
Histology	Adenocarcinoma	75 (55.9%)
	Squamous Cell	31 (23.1%)
	NSCLC NOS	7 (5.2%)
	Unbiopsied	21 (15.6%)
Histology Focality of Initial Tumor	NSCLC NOS	7 (5.2%)
	Unbiopsied	21 (15.6%)
	Unifocal	116 (86.5%)
	Multifocal (2 or more tumors)	18 (13.4%)

Age	
75.1 (range: 61.7–92.1)	
Dose and Fractionation	
54–60 Gy in 3 fractions	19 (14.2%)
50 Gy in 4 fractions	54 (40.3%)
50–60 Gy in 5 fractions	45 (33.6%)
56–60 Gy in 8 fractions	3 (2.2%)

Abbreviations: T = Tumor; Gy = Gray.

Table 2

Patients with Second Primary Lung Cancers.

Patient	Histology of initial tumor	Smoking history (PY)	Location Initial Tumor	Time to SPLC (months)	Location SPLC	Histology of SPLC	Treatment of SPLC	OS after SPLC (months)	Current Status
1	Adenocarcinoma	50	RUL, LUL	20.6	RLL	unbiopsied	SABR	41.0	Deceased
				28.5	LUL	adenocarcinoma	SABR	33.1	
2	Squamous	30	LUL	3.3	RML	Squamous cell	SABR	27.9	Deceased
3	Adenocarcinoma	0	LUL	31.7	LUL	Adenocarcinoma	SABR	63.5	Deceased
				61.8	LLL	NSCLC NOS	SABR	33.3	
4	Unbiopsied	4	LUL	7.8	RUL	Unbiopsied	SABR	39.3	Alive
5	Squamous	60	RUL	74.4	RLL	Squamous	SABR	0.4	Alive
6	Adenocarcinoma	75	LUL	3.0	RUL	Adenocarcinoma	Microwave ablation	25.7	Deceased
7	NSCLC NOS	90	LUL	16.5	RUL	Squamous	SABR	27.9	Deceased
				32.0	RUL	Unbiopsied	SABR	12.4	
8	Adenocarcinoma	53	RLL	11.0	LUL	Adenocarcinoma	SABR	18.1	Alive
9	Unbiopsied-lagera	50	LUL	9.4	LLL	Squamous	SABR	6.9	Deceased
10	Adenocarcinoma	70	Lingula	25.9	disseminated	Small Cell	Hospice	4.7	Deceased
11	Adenocarcinoma	50	LUL	35.2	LLL	NSCLC NOS	SABR	14.7	Alive
12	Adenocarcinoma	100	RUL	52.1	RML	Squamous	SABR	34.0	Deceased
13	Squamous-stabile	72	RLL	9.4	LLL	Squamous	SABR	66.2	Deceased
14	Squamous	25	RUL	8.9	RML	Small cell	SABR	10.7	Deceased
15	Squamous	100	RUL	81.7	LUL	Squamous	No treatment	3.6	Lost to FU
16	Unbiopsied	30	LLL	31.5	LUL	Unbiopsied	SABR	33.9	Deceased
17	Adenocarcinoma	23	RLL	84.7	LLL	Adenocarcinoma	SABR	17.5	Alive
18	Adenocarcinoma	100	Lingula	31.8	Lingula	adenosquamous	Unknown	0.8	Lost to FU

Abbreviations: LLL = Left lower lobe; LUL = Left upper lobe; ML = Right middle lobe; NSCLC NOS = Non-small cell lung cancer not otherwise specified; PY = Pack-year; RUL = Right upper lobe; RLL = Right lower lobe; SABR = Stereotactic ablative radiotherapy; SPLC = Second primary lung cancer.

Table 3

Surveillance Imaging Frequency.

Metric [median (range)]	
Time to first scan	3.0 months (range: 0.3–9.7 months)
Number scans in months 1–12	3 (range: 1–6 scans)
Number scans in months 13–24	2 (range: 0–5)
Number scans in months 1–24	5 (range: 2–9)
Evaluable patients undergoing ≥3 scans months 1–12	90 (74%)
Evaluable patients undergoing ≥5 scans months 1–24	72 (74%)

Table 4

Prior studies Addressing Development of Second Primary Lung Cancers.

Study	Design	Patients	SPLC Rate	OS after SPLC	Surveillance
Wu et al 2020	SEER Database analysis	All patients treated with RT for lung cancer	N/A	Median OS 25 months	N/A
Mayne et al 2020	Single institution, retrospective	294 surgically treated patients with stage 1A NSCLC	15% crude rate	5-year OS 57.5%	CT chest, interval varied
Lou, 2013	Single institution, retrospective	1294	7% (3–6% per person year)	N/A	CT chest
Rice 2003	Single institution, retrospective	569	15% crude rate	Median OS 4.1 years	
Lamont 2002	Single institution, retrospective	124	15.3% (2.1% per patient per year)	N/A	CT chest annually
Boyle 2014	Single institution, retrospective	1484	5% at 3 years 8% at 5 years 16% at 8 years	N/A	
Aziz et al, 2002 11888775	Single institution, retrospective	892 surgically treated patients	5.7% crude rate	38% 5-year OS	N/A
Ha et al, 2014 25494009	Single institution, retrospective	1014	4.3% crude rate	31% 2-year OS Median OS 11.8 months	N/A
Jeremic 2001	Single institution, retrospective	194 patients treated with RT alone, stage I-II NSCLC	1.4% per patient year 6.0% at 5 years 14.2% at 10 years	30% 5-year OS	Modality not stated; Q2–3 months year 1–2, Q3–6 months year 3–4
Spratt	Single institution, retrospective	366 patients treated with SBRT for early stage NSCLC	5% crude rate 4.5% at 2 years	N/A	CT chest Q3 month year 1–2; Q6 month year 3–4
Current Study	Single institution, retrospective	134 patients treated with SABR for early stage NSCLC	11.7% 3-year estimate 13.1% 5-year estimate	2 year OS: 80% 3 year OS: 55%	CT chest Q3–4 month year 1, Q3–6 month year 2