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ORIGINAL ARTICLE

Can dosimetry affect local control and survival in patients with early-stage lung cancer treated with Stereotactic Ablative Radiotherapy (SABR)? An analysis of the UK's largest cohort of lung SABR patients

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ABSTRACT

Purpose/objectives: A recent study has shown that tight conformity of lung Stereotactic Ablative Radiotherapy (SABR) plans might worsen loco-regional control and can predict distant metastases. The study aims to report overall survival (OS), progression-free survival (PFS), local recurrence free survival (LRFS), and dosimetry of early-stage lung cancer patients treated with SABR and to try to explore any dosimetric predictor of outcomes.

Material and methods: Patients treated in our institute (May 2009–August 2018) were included. Electronic medical records were reviewed for baseline characteristics, treatment details, and outcomes. Dosimetric data were extracted from Xio and Monaco software. Patients were treated according to the United Kingdom (UK) SABR consortium guidelines. Kaplan–Meier's analysis with log-rank test was used for survival analysis. The univariate and multivariable Cox regression model was used for correlating dosimetric variables and outcomes.

Results: We treated 1266 patients with median age of 75 years and 47.4% were male. Median follow up was 56 months. Median OS was 36 months with 1, 2, and 5 years OS of 84.2%, 64.5%, and 31.5%, respectively. Median for PFS and LRFS was not reached. One, 2, and 5 years PFS were 87.4%, 78.4%, and 72.5%, respectively. One, 2, and 5 years LRFS were 98.2%, 95.1%, and 92.5%, respectively. Planning target volume (PTV), dose to 99% volume of PTV (D99), and R50 (volume receiving the 50% dose/volume (PTV)) were significantly associated with OS. PTV, mean lung dose (MLD), V20 (volume of lung minus gross tumour volume (GTV) receiving 20 Gy), V12.5 (volume of lung minus GTV receiving 12.5 Gy), and dose fractionation were significantly associated with PFS. Nothing was associated with LRFS on univariate analysis. R100 of >1.1 was associated with better OS, PFS, and LRFS compared to R100 ≤ 1.1.

Conclusion: SABR achieves good clinical outcomes in patients with early-stage lung cancer; even in elderly patients with multiple comorbidities. In the largest UK early lung cancer cohort treated with SABR, we found that dosimetry correlates with clinical outcomes. Further validation of these results is needed to guide future optimisation of SABR delivery.

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KEYWORDS
Stereotactic Ablative Radiotherapy; lung cancer; dosimetry; conformity; early-stage

Introduction

Stereotactic Ablative Radiotherapy (SABR) is an established treatment for early-stage non-small cell lung cancer (NSCLC) patients [1–3]. It is well tolerated with low rates of toxicity and achieves local tumour control in more than 90% of patients [4]. Even because SABR is offered to elderly patients with a poor physiological reserve and/or multiple comorbidities compared to surgical cohorts, SABR has shown comparable local control, overall survival (OS), disease-free survival, and cancer-specific survival [5–7]. Although combined analysis of ROSEL and STARS trial data suggest superior OS with SABR (3 years OS 95% vs. 79%), the intention to treat analysis was limited by small sample size and short follow up [8]. On the contrary, a recent propensity match study using The Surveillance, Epidemiology, and End Results (SEER) program data has shown better cancer-specific survival with surgery compared to SABR for stage IB disease; the results of this retrospective cohort study were potentially affected by confounding variables [9]. Overall survival of SABR patients has been correlated with biologically effective dose (BED) [10]. A recent study has shown that tight conformity of radiotherapy plans, i.e., reducing the radiation dose outside the target volume might worsen loco-regional control and can predict the development of more distant metastases [11]. Although treatment toxicity has been correlated with SABR dosimetry [12–15], there is a lack of robust data correlating SABR dosimetry with local control and survival. The study aims to report OS, progression-free survival (PFS), local recurrence free survival (LRFS), and dosimetry of UK's largest

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cohort of early-stage lung cancer patients treated with SABR. We also investigate the relationship between SABR dosimetry and the outcomes.

Material and methods

Settings

Patients treated for stage I/II lung cancer at a single UK radiotherapy center were included in this study. Patients were treated between May 2009 and August 2018. Electronic medical records were reviewed for baseline characteristics, treatment details, and patients outcomes. Dosimetric data were extracted from Xio and Monaco software (Elekta AB, Stockholm, Sweden).

Study population

To be considered for SABR, patients:

- Had a multidisciplinary team agreed on the diagnosis of lung cancer. This was histologically proven and/or based on the presence of a metabolically active lung lesion on a positron emission tomography (PET) scan and/or based on a growing lesion on serial computed tomography imaging.
- Had a T1–T2 (<5 cm) N0M0 tumour.
- Were unsuitable for surgery due to comorbidity, technical inoperability, or patient choice.
- Had a peripheral tumour: defined as >2 cm in all directions from the proximal bronchial tree.

We have restaged the tumours according to AJCC 8th edition TNM staging for the reporting purpose. Any patient with synchronous primary lung cancer or ≥2 lung nodules treated with SBRT, were excluded from the analysis. The Charlson comorbidity score was recorded retrospectively for all patients.

Treatment

Patients were treated according to the UK SABR consortium guidelines [16]. Patients were treated with 54 Gy in three fractions, 55 Gy in five fractions, 60 Gy in eight fractions, or 50 Gy in eight fractions depending on tumour location. The details of patient selection, radiotherapy planning technique, treatment delivery technique and follow up protocol have been published previously [17]. For the planning target volume (PTV), plan conformity was assessed using three indices, R100-((volume receiving the 100% dose/volume (PTV)), R50 ((volume receiving the 50% dose/volume (PTV)), and D2cm (maximum dose to any point 2 cm from the edge of the PTV). Maximum, minimum, and mean dose to PTV, i.e., DPTV max, DPTV min, and DPTV mean has been recorded. We also recorded dose received by 95% volume of PTV (D95) and 99% volume of PTV (D99). We also recorded mean lung dose (MLD), V20 (volume of total lung minus gross tumour volume (GTV) getting 20 Gy), and V12.5 (volume of lung minus GTV getting 12.5 Gy).

Follow up

Patients have first followed up 6 weeks post completion of SBRT, then three monthly for the first year, then 4 monthly in the second year, and then 6 monthly. At each visiting patient usually had a chest-X-ray PA view done. Response assessment CT scan of the chest was done 4–6 months post-treatment. Then, a CT scan of the chest was done yearly once or earlier if clinically indicated. Local recurrence was defined as a failure within or adjacent to the PTV. Nodal failure was defined as disease recurrence within intrathoracic, hilar, mediastinal, or supraclavicular lymph nodes. Distant relapse was defined as the development of metastases at all other sites. All patients with suspected recurrence has been discussed in our MDT. We have taken into account serial CT scan, PET-CT scan, and biopsies when done; before confirming any recurrence.

The second primary tumours were defined using all available radiologic and pathological information according to a modified version of the criteria of Martini *et al*. [18,19]. We defined second malignancy as a new pulmonary malignancy occurring in a different lobe or lung than the first tumour with no intervening involved lymph nodes and no evidence of any distant metastases, different histology or subtype, and/or different molecular characteristics. However, we did not mandate a minimum interval of 2 years between the first and second primary malignancies. We also accepted the second primary tumours in the same lobe of the lung when they were of different histology or outside the previous radiation field [19].

Statistical analysis

OS was defined as the date of diagnosis until the date of death. Progression-free survival was defined as the end of treatment date to the development of any recurrence. The LRFS was defined as the last treatment date until the development of local relapse. Patients were censored at last follow up if no other event had occurred. Overall survival, PFS, and LRFS probabilities were estimated using Kaplan–Meier's survival analysis. The difference in survival probabilities (OS, PFS, and LRFS) between varies stratified subgroups, e.g., R100, dose-fractionation, R50, PTV, etc.; has been analysed using log rank test. A univariate and multivariable Cox regression model was used to explore the correlation between the dosimetric variables and outcomes (OS, PFS, and LRFS), using IBM SPSS statistics version 21 software (Armonk, NY). Proportional hazards assumption was assessed by computing time dependent covariate and analysing ominous tests of model coefficients. The continuous dosimetric variables were stratified into subgroups by dividing them above and below the median. Those subgroups were also analysed with univariate and multivariable analysis as mentioned before. All statistical analyses were two-sided at a significance level of 5%.

Results

Results for 1266 patients with stage I/II NSCLC lung cancer were available for analysis. The baseline clinical characteristics of the treated patient have been summarised in Table 1. The median age for patients in the whole cohort was 75 years (range 38–97 years). Fifty-three percent of patients were female. The median follow up was 56 months. Histopathological confirmation was available for 31.8% of patients and all were non-small cell lung carcinoma; other patients were treated based on a radiological diagnosis. Specific histologies were as follows: squamous cell carcinoma (148 patients), adenocarcinoma (220 patients), adenosquamous cell carcinoma (two patients), NSCLC – not otherwise specified (19 patients), and large cell carcinoma (13 patients). More than 99% of patients had PET-CT scans. We have used Herder risk model for PET-CT scan, in our MDT to decide the risk of malignancy and need of treatment [20]. The median Charlson comorbidity index was 6 (range 2–11). The median tumour size was 20 mm (range 4–63 mm). In our series, only four patients were more than 5 cm in size (T3). We have discussed these patients in our MDT meeting. Although these tumours were larger than 5 cm, considering the tumour location, patient's fitness, acceptable plan parameters; we decided to go ahead with SABR for these patients. We could only retrieve FEV1 data for 1000 patients and DLCO data for 854 patients. Median FEV1 and DLCO were 1.3 L and 52%, respectively.

Table 1. Baseline clinical characteristics.

Variable	Category	Number	%
Age	Median 75 years		
	Range 38–97 years		
Sex	Male	600	47.4
	Female	666	52.6
PET-CT	Yes	1260	99.5
	No	6	0.5
Smoking history	Never smoker	46	3.6
	Ex-smoker	583	46.1
	Current smoker	335	26.5
	Not recorded	302	23.9
Smoking pack years	≤10	8	0.6
	11–20	21	1.7
	21–40	80	6.3
	>40	262	20.7
	Not recorded	895	70.7
Eastern Co-Operative Oncology Group (ECOG) Performance status	ECOG 0	52	4.1
	ECOG 1	422	33.3
	ECOG 2	551	43.5
	ECOG 3	205	16.2
	Unknown	36	2.8
Confirmation of diagnosis	Histopathology	402	31.8
	Imaging	864	68.2
Tumour location	Lower lobe	360	28.4
	Other lobe	906	71.6
T stage	T1a	97	7.7
	T1b	574	45.3
	T1c	378	29.9
	T2a	179	14.1
	T2b	34	2.7
	T3	4	0.3
Dose fractionation	54Gy in 3 fractions	199	15.7
	55Gy in 5 fractions	822	64.9
	60Gy in 8 fractions	213	16.8
	50Gy in 8 fractions	32	2.5

Median OS was 36 months. Overall survival at 1, 2, 3, 4, and 5 years was 84.2%, 64.5%, 50%, 39.3%, and 31.5%, respectively (Figure 1). The median PFS was not reached. 1, 2, 3, 4, and 5 years PFS were 87.4%, 78.4%, 74.2%, 72.9%, and 72.5%, respectively (Figure 1). Median for local control was not reached. Local control at 1, 2, 3, 4, and 5 years was 98.2%, 95.1%, 93.3%, 92.9%, and 92.5%, respectively (Figure 1).

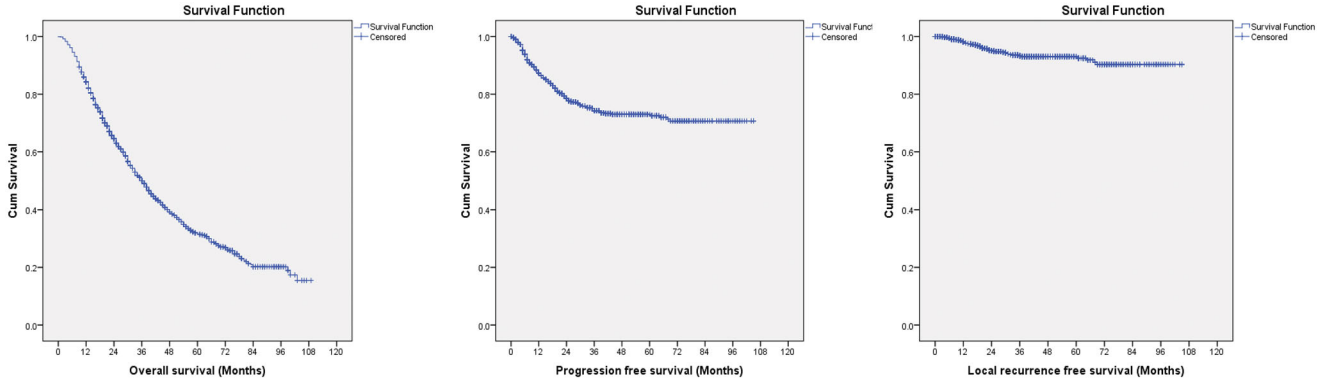
Fifty-eight (4.7%) patients developed local recurrence (29 local only, 16 local and nodal, seven local and distant, six primaries, nodal and distant recurrence). One hundred and two (8.1%) patients developed nodal recurrence (16 local and nodal, 49 isolated nodal, 31 nodal and distant, six primary, nodal, and distant). One hundred and sixty (12.6%) patients developed distant recurrence (116 distant recurrences without local or nodal recurrence, 31 nodal and distant, seven primary and distant, six primaries nodal and distant). Second primary lung malignancy was seen in 2.4% patients and 0.3% developed second extra thoracic malignancy (Figure 2).

Dosimetric data are summarised in Table 2. The median PTV was 30.3 cm^3 (range 5.5–213.4 cm^3). The PTV was found to be lower in patients treated with three fractions (median 17.9 cm^3, range 5.8–83.4 cm^3) compared to five fractions (median 32.9 cm^3, range 5.5–213.4 cm^3, p value = .000) and eight fractions (median 36.1 cm^3, range 7.2–188.2 cm^3, p value = .000).

Median values of R100, R50, and D2cm were 1.1 (range 0.68–3.19), 5.6 (range 2.2–15.6), 32.8 Gy (range 9.3–56.3 Gy), respectively. In our study, only 0.9% of patients had R100 of >1.4 (exceeding the minor deviation) and 9.5% had R100 of >1.2. In plans where the R100 > 1.4, the median PTV volume was 9.7 cm^3 (range 5.5–33.3 cm^3); this probably reflects that conformality is lost for small volumes when using 5 mm MLCs. The median PTV of patients with R100 > 1.2 was 15.7 cm^3 (range 5.5–113.7 cm^3) which was lower than the overall cohort was. The median MLD, V20, and V12.5 was 3.9 Gy (range 0.58–10.46 Gy), 5% (range 0.96–19.27%), and 9.3% (range 1.3–28.6%), respectively.

Univariate Cox proportional hazard analysis correlating dosimetric variables with OS, PFS, and LRFS has been summarised in Table 3. On univariate Cox regression analysis, PTV (HR 1.006, 95%CI 1.003–1.008) (Figure 3), D99 (HR-0.966, 95%CI 0.939–0.994), and R50 (HR 0.951, 95%CI 0.908–0.995) were significantly associated with OS. On multivariable Cox regression analysis PTV (HR 1.011, 95%CI 1.006–1.015) and DPTV min (HR 1.058, 95%CI 1.003–1.115) were significantly associated with OS (Supplementary Table 1). D99 of >53 Gy (median OS 39 vs. 33 months, p value .042) and R100 of >1.1 (median OS 39 vs. 33 months, p value .049) was significantly associated with improved OS (Figure 4) on Kaplan–Meier's survival analysis (Supplementary Table 2) but not on multivariable Cox regression analysis (Supplementary Table 3).

PTV (HR 1.009, 95%CI 1.006–1.013) (Figure 3), MLD (HR 1.098, 95%CI 1.018–1.185), V20 (HR 1.064, 95%CI 1.021–1.109), V12.5 (HR 1.032, 95%CI 1.005–1.060), and dose fractionation (HR for five fraction regimen 1.538, 95%CI 1.025–2.308, HR for eight fraction regimen 1.837, 95%CI



Interval start time (Months)	0	12	24	36	48	60
Number entering interval	1266	1064	680	436	282	183
Number exposed to risk	1253	989	627	402	259	161

Interval start time (Months)	0	12	24	36	48	60
Number entering interval	1266	903	561	347	235	156
Number exposed to risk	1152	771	467	295	195	125

Interval start time (Months)	0	12	24	36	48	60
Number entering interval	1266	970	602	375	255	170
Number exposed to risk	1126	799	493	316	212	136

Figure 1. Kaplan–Meier's survival curve showing OS, PFS, and LRFS of overall cohort.

Table 2. Dosimetric characteristics.

	Mean	Median	Range	IQR
PTV volume (cm^3)	37.89	30.30	5.51–213.41	30.06
PTV volume (cm^3)				
3 fractions	31.7	17.9	5.8–83.4	14.9
5 fractions	39.3	32.9	5.5–213.4	29.6
8 fractions	46.2	36.1	7.2–188.2	41.1
D95% (Gy)	55.4	55.05	31.9–62	0.3
D99% (Gy)	53.24	53.17	25.2–59.6	1.23
R100 (volume (100%)/volume (PTV))	1.11	1.10	0.68–3.19	0.08
R50 (volume (50%)/volume (PTV))	5.89	5.6	2.2–15.58	2.07
Maximum dose to >2 cm of PTV (Gy)	33.18	32.8	9.3–56.35	5.97
Mean lung dose (Gy)	4.17	3.93	0.58–10.46	1.99
V20 (%)	5.69	5.07	0.96–19.27	3.44
V12.5 (%)	10.07	9.3	1.31–28.61	5.42
Maximum dose to PTV (Gy)-DPTV max	70.62	69.45	60.90–90.05	4.40
Minimum dose to PTV(Gy)-DPTV min	49.35	49.95	15.9–60.96	3.35
Mean dose to PTV (Gy)-DPTV mean	61.72	61.08	32.4–71.81	3.12

1.161–2.909) were significantly associated with PFS on univariate analysis. On multivariable analysis, PTV (HR 1.01, 95%CI 1.003–1.017) and dose fractionation (HR for eight fraction regimen 1.725, 95%CI 1.029–2.890) were significantly associated with PFS (Figure 5; Supplementary Table 1). Sixty Gray in eight fractions regimen was better (HR 0.495, 95%CI 0.246–0.996) compared to 50 Gy in eight fractions regimen in terms of PFS (mean PFS 69.8 vs. 23.6 months, p value .043) but not for OS or LRFS. PTV $\leq$30 cm^3 (mean PFS 83.9 vs. 76.2, p value .002), R100 $>$ 1.1 (mean PFS 84.6 vs. 75.8 months, p value .001) (Figure 4), R50 $>$ 6 (mean survival 77.1 vs. 73.8 months, p value .004), and MLD $\leq$4 Gy (mean survival 81.9 vs. 77.3 months, p value .041) were associated with improved PFS on univariate Kaplan–Meier's survival analysis (Supplementary Table 2). On multivariable Cox regression analysis only R100 (HR for R100 $\leq$ 1.1–1.39, 95%CI 1.049–1.842) and dose fractionation (HR for eight-fraction regimen 2.015, 95%CI 1.056–3.848) were statistically significant (Supplementary Table 3). None of the dosimetric parameters were found to be associated with LRFS on univariate analysis but on multivariable analysis, dose fractionation was found to be associated with LRFS (HR for eight-fraction regimen 3.526, 95%CI 1.058–11.749). R100 of $>$1.1 was associated with better LRFS (mean LRFS 100.2 vs. 95.9 months, p value .029) on univariate Kaplan–Meier's survival analysis (Figure 4; Supplementary Table 2) but no variable was found to be significant on multivariable Cox regression analysis (Supplementary Table 3).

In a subset analysis, we tried to explore the association of D95, D99, PTV max dose (DPTV max), DPTV min, and PTV mean dose (DPTV mean) with the outcomes for three different dose fractionation.

On subset analysis of three fraction regimen, D95 (HR 0.824, 95%CI 0.692–0.983) and D99 (HR 0.867, 95%CI 0.753–0.998) were significantly associated with OS on univariate analysis. On multivariable analysis, D95 (HR 9.996, 95%CI 1.115–86.492) was significantly associated with PFS.

On subset analysis of five fraction regimen, D95 (HR 1.555, 95%CI 1.142–2.117), D99 (HR 0.743, 95%CI 0.599–0.922), and DPTV mean (HR 0.799, 95%CI 0.710–0.899) were significantly associated with OS on multivariable analysis. D95 (HR 1.256, 95%CI 1.051–1.500) was significantly associated with PFS on univariate analysis.

On subset analysis of eight-fraction regimen, DPTV min (HR 0.948, 95%CI 0.915–0.982) was significantly associated with PFS on univariate analysis. On multivariable analysis, D95 (HR 1.749, 95%CI 1.067–2.865) and D99 (HR 0.551, 95%CI 0.351–0.865) were significantly associated with PFS. D95 (HR 0.911, 95%CI 0.833–0.996) and D99 (HR 0.918, 95%CI 0.846–0.995) were significantly associated with LRFS on univariate analysis but on multivariable analysis, no dosimetric parameter showed significant association with LRFS.

Discussion

In this article, we report on the association between treatment outcomes and dosimetric parameters within the largest cohort of patients with early-stage lung cancer treated with SABR in the UK. Our key results include (1) increasing PTV volume can significantly worsen the outcomes. (2) R100 of

Table 3. Univariate Cox proportional hazard analysis correlating dosimetric variables with outcomes.

Variables	Overall survival HR (95%CI)	Progression-free survival HR (95%CI)	Local recurrence free survival HR (95%CI)
PTV volume (cm^3)	1.01 (1.00–1.01)	1.01 (1.01–1.01)	1.00 (0.99–1.01)
Dose to 95% volume of PTV	0.97 (0.94–1.00)	1.00 (0.95–1.06)	0.94 (0.85–1.05)
Dose to 99% volume of PTV	0.97 (0.94–0.99)	0.98 (0.93–1.03)	0.95 (0.86–1.05)
R100	0.47 (0.21–1.07)	0.85 (0.25–2.89)	0.10 (0.00–4.20)
R50	0.95 (0.91–0.99)	0.87 (0.80–0.94)	0.89 (0.75–1.06)
D2cm	1.01 (1.00–1.03)	1.02 (1.00–1.05)	1.00 (0.94–1.05)
Mean lung dose (Gy)	1.01 (0.97–1.06)	1.10 (1.02–1.18)	1.09 (0.93–1.28)
V20 (%)	1.01 (0.98–1.03)	1.06 (1.02–1.11)	1.03 (0.94–1.13)
V12.5 (%)	1.01 (0.99–1.02)	1.03 (1.00–1.06)	1.03 (0.97–1.09)
DPTV max	1.00 (0.98–1.01)	1.00 (0.97–1.02)	0.97 (0.91–1.03)
DPTV min	0.98 (0.96–1.00)	0.97 (0.94–1.00)	0.99 (0.92–1.06)
DPTV mean	0.99 (0.97–1.01)	1.02 (0.98–1.06)	0.96 (0.88–1.04)
Dose fractionation			
3 fraction	1	1	1
5 fraction	0.99 (0.81–1.20)	1.54 (1.02–2.31)	2.63 (0.94–7.33)
8 fraction	1.00 (0.78–1.28)	1.84 (1.16–2.91)	2.75 (0.88–8.52)
Dose fractionation			
60 Gy in 8#	1	1	1
50 Gy in 8#	1.08 (0.58–2.01)	0.49 (0.25–1.00)	1.04 (0.13–8.32)

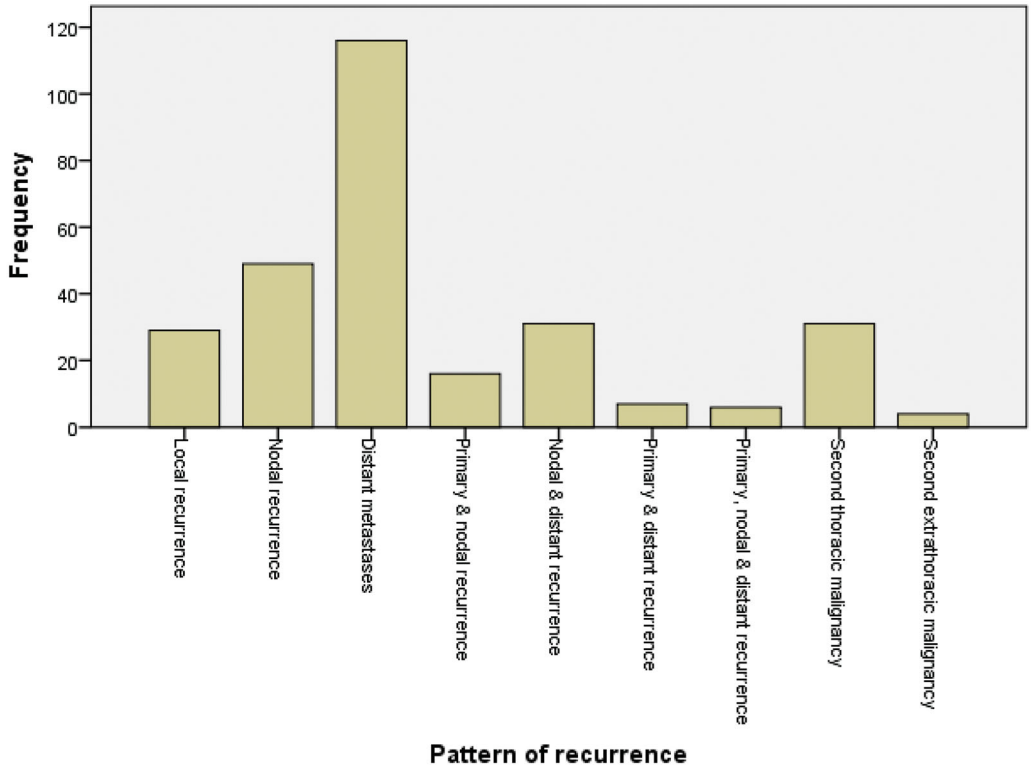


Figure 2. Pattern of recurrence of overall cohort.

>1.1 resulted in better outcomes, indicating that tight conformality with steep dose gradient may worsen outcomes. (3) Greater R50 improved OS and PFS. (4) PFS is better with three-fraction regimen compared to 5 or 8 fraction regimen.

Spratt et al. [19] reported recurrence patterns in a series of 366 early-stage lung cancer patients treated with SABR; 2-year cumulative incidence for local, nodal, distant failures, and second primary malignancy was 12.2%, 16.1%,15.5%, and 5%, respectively. Senthi *et al.* [21] reviewed 676 patients with 2-year local, regional, and distant recurrence rates of 4.9%, 7.8%, and 14.7%, respectively. Corresponding 5-year rates were 10.5%, 12.7%, and 19.9%), respectively. Second primary lung cancer (SPLC) reported developing in 6% of patients. In our series, local (4.7%), nodal (8.1%), and distant recurrences (12.7%) were slightly lower with only 2.4% of patients developing SPLC. Prospective and retrospective studies have shown excellent 2- or 3-year LC rates ranging from 80 to 100% [22–24]. Updated results of the Radiation Therapy Oncology Group (RTOG) 0236 trial has shown 5 year LC of 93%, 5 years OS 40%, and median OS of 4 years, in three-fraction SBRT regimen [4,25]. In a recent retrospective study by Schonewolf *et al.* 2 years and 5 year LC rates of

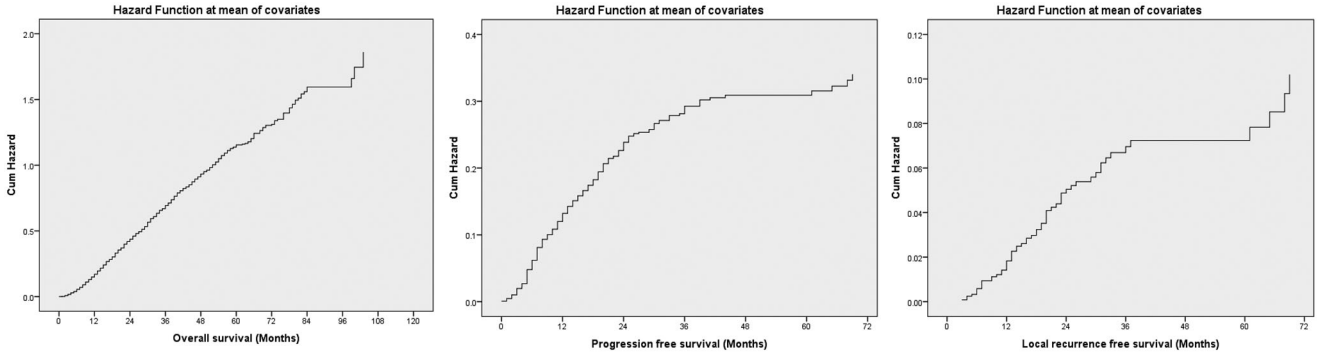
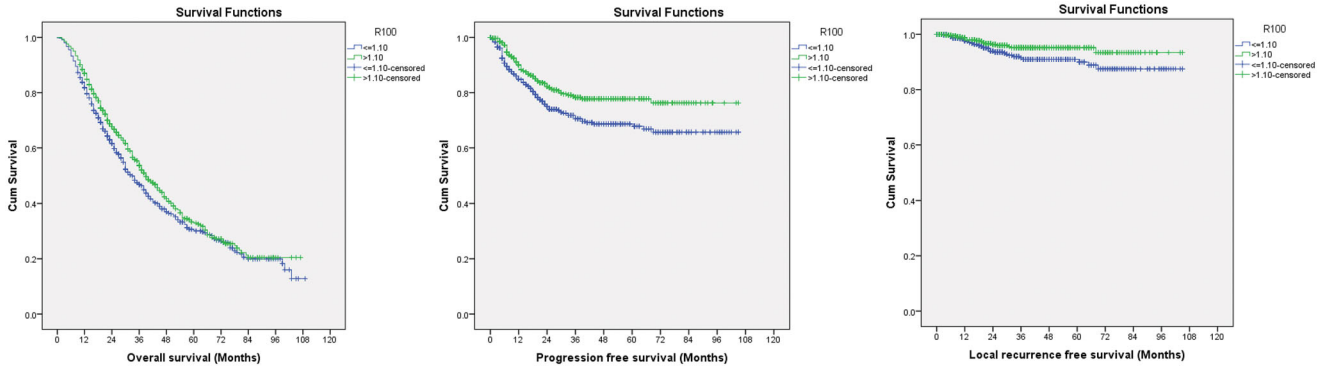


Figure 3. Hazard function showing correlation of PTV volume with OS, PFS, and LRFS.

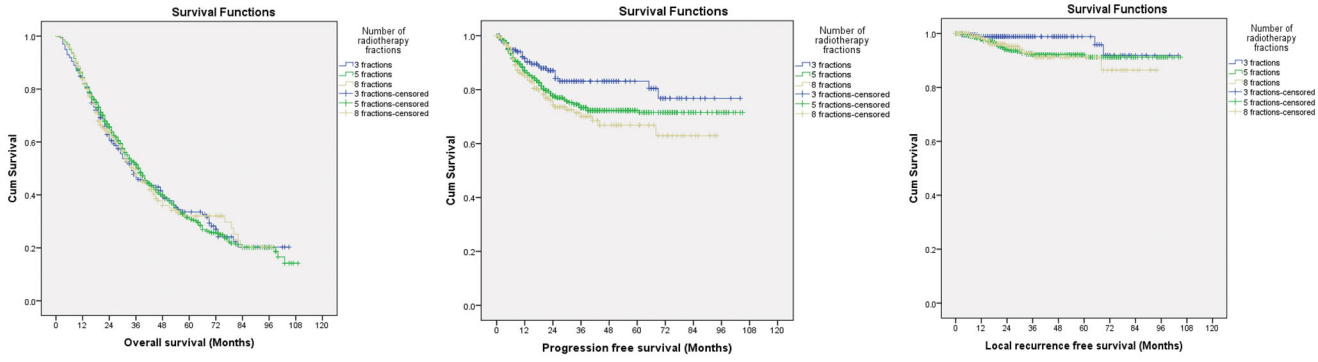


Interval start time (Months)		0	12	24	36	48	60
Number exposed to risk	R100≤1.1	662	512	319.5	201	138	86
	R100>1.1	591	477	308	200	120	74

Interval start time (Months)		0	12	24	36	48	60
Number exposed to risk	R100≤1.1	607	393	230	149	103	67
	R100>1.1	545	378	237	146	92	58

Interval start time (Months)		0	12	24	36	48	60
Number exposed to risk	R100≤1.1	587	408	245	162	115	75
	R100>1.1	539	391	247	154	97	60

Figure 4. Kaplan–Meier's survival curve showing correlation between R100 with OS, PFS, and LRFS.



Interval start time (Months)		0	12	24	36	48	60
Number exposed to risk	3-fraction	196	154	100	68	51	32
	5-fraction	816	648	418	268	170	105
	8-fraction	241	186	109	66	38	23

Interval start time (Months)		0	12	24	36	48	60
Number exposed to risk	3-fraction	179	121	77	53	38	24
	5-fraction	754	515	313	196	127	81
	8-fraction	219	134	76	46	30	20

Interval start time (Months)		0	12	24	36	48	60
Number exposed to risk	3-fraction	176	124	81	58	42	26
	5-fraction	736	530	326	208	137	87
	8-fraction	214	145	85	49	32	22

Figure 5. Kaplan–Meier's survival curves showing OS, PFS, and LRFS for three different dose-fractionation.

95.6% and 93.7% were reported [26]. In our cohort, 2 year and 5 year LC rates were 95.1% and 92.5%, which is consistent with published literature. A meta-analysis of 19 studies reporting PFS has shown 1, 3, and 5 years PFS of 87.1%, 65.8%, and 65.8% in stage I lung cancer patients treated with SBRT [7]. Although 1 year PFS was similar (87.4%), 3 and 5 years PFS rates were longer (74.2% and 72.5%, respectively) in our cohort. Three-year OS rates for medically inoperable early-stage lung cancer as reported in the most series range from 40% to 80% [4,27–31], but cancer recurrence rates are low, suggesting that patients died of non-cancer-related comorbidities. In our study, the median OS was 36 months with a 3-year OS rate of 50%, which is in concordance with published literature.

The mean PTV of patients treated in the RTOG 0236 trial was 45 cm^3 (range 10.7–117 cm^3) [32]. In a series reported by Shrimali et al. median PTV was 30.8 (range 5.5–84.7 cm^3) [33]. In our cohort, median PTV volume was 30.3 cm^3 (range from 5.5 to 213.4 cm^3). Noticeably, PTV volume was smaller in patients treated with three fractions compared to five or eight fractions. This reflects the risk-adapted dose-fractionation decision process in the UK, which is dependent on tumour size and position [16]. We found that PTV volume was an independent predictor of OS and PFS.

The conformality of the lung SBRT plan has been evaluated in the RTOG 0236 [32] and 0618 protocols [34], where plan acceptability was defined as a conformity index <1.2. Dose conformity levels from the ROSEL study [35] have been useful in evaluating lung SABR plan quality by giving 'tolerance' and 'minor deviation' values for the R100%, R50%, and D2cm metrics. This has been adopted UK SABR consortium guidelines [16]. In our study, only 0.9% of patients had R100 of >1.4 (exceeding the minor deviation) and 9.5% had R100 of >1.2. The mean V20 reported in RTOG 0236 trail after heterogeneity correction was 5.9% (range 2.5–14.1%) [32]. In our study, the mean V20 was 5.7% (range 0.96–19.27%).

A retrospective review has shown that tumours of less than 2 cm have local control rates independent of the SABR dose. For tumour sizes greater than 2 cm, higher local control rates were seen at 5-year follow-up, with 60 Gy in four fractions (BED = 150 Gy10) as compared with 48 Gy in four fractions (BED=106 Gy10) (76.2% vs. 60.6%) [36]. Larger tumour size is associated with a high risk of recurrence and worse survival in patients treated with SABR [19]. In our study, an eight-fraction regimen was inferior in terms of PFS compared to five fractions and three fractions. The eight-fraction schedule was also found to be inferior to the three-fraction regimen in terms of LRFS, but not to five-fractions. There was no difference in OS between the three-dose fractionation schedules.

Surgical series have reported microscopic disease extension in the region of 8–26 mm in NSCLC patients [37–40]. It is assumed that high dose penumbra is sufficient to treat microscopic disease extension when treating with SABR techniques [33]. It is possible that as SABR treatment plans become increasingly conformal, with steeper dose gradients, tumour control will be compromised. There are few studies, which assess the effects of lung SABR dosimetry on clinical outcome [11]. Diamant et al. explored the correlation between radiation dose close to PTV with loco-regional recurrence and distant metastases in 217 patients. They showed a tight conformality of radiotherapy plans with a mean dose of $\leq$20.8 Gy delivered to a 3 cm rind around the PTV resulted in a higher rate of distant metastases (2-year distant metastases rate 60% vs. 5%). They suggested caution for radiotherapy plans with steep dose gradients and raised the question about the need for secondary margins in the region of 2 cm around PTV with a lower prescription dose (around 21 Gy) to take into account microscopic disease extension and to reduce the risk of distant metastases [11].

In our study, R100 >1.1 was associated with better OS, PFS, and LRFS. This probably indicate that tightly conformal plans are probably not able to sterilise all microscopic disease leading to more recurrence. A larger R50 resulted in better OS and PFS but does not seem to have any correlation with local control. There was not any correlation with D2cm and outcomes probably indicating the fact that dose to >2 cm distance from PTV, where the risk of microscopic disease extension is quite small, does not affect the outcomes as long as OAR doses are within the acceptable limit. Higher D99 has been shown to improve OS in the overall group and subset analysis; it also is shown to be associated with better LC and PFS for an eight-fraction regimen. We found that higher MLD, V20, and V12.5 was associated with worse PFS.

Being, a retrospective cohort the study has its limitation. The other drawback is that we have not been able to evaluate the impact of the subsequent line of treatment on the survival outcome. In our previous treatment planning system (TPS), Xio used a superposition algorithm while present TPS, Monaco uses Monte-Carlo. The dose differences between these two algorithms have not been evaluated in this study. Whether SABR done in different time period have affected the outcomes or not; has not been evaluated in our study. We have not included any clinical variable, e.g., age, sex, performance status, smoking, stage in our multivariable analysis as the correlation of clinical variables with the outcomes will be published in our separate publication.

In conclusion, SABR achieves good clinical outcomes in patients with early-stage NSCLC; many patients treated with this technique are elderly and have significant medical comorbidities. In the largest UK early lung cancer cohort treated with SABR, we found that dosimetric data are associated with clinical outcomes. Tight conformality of SABR plans might worsen outcomes. Further validation of these results is needed to guide future optimisation of SABR delivery.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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