ORIGINAL ARTICLE

Can reducing planning safety margins broaden the inclusion criteria for lung stereotactic ablative body radiotherapy?

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Abstract

Introduction: Stereotactic ablative body radiotherapy (SABR) is currently indicated for inoperable, early-stage non-small cell lung carcinoma (NSCLC). Advancements in image-guidance technology continue to improve treatment precision and enable reductions in planning safety margins. We investigated the dosimetric benefits of margin reduction, its potential to extend SABR to more NSCLC patients and the factors influencing plan acceptability. **Methods:** This retrospective analysis included 61 patients (stage IA–IIIA) treated with conventional radiotherapy. Patients were ineligible for SABR due to tumour size or proximity to organs at risk (OAR). Using Pinnacle auto-planning, three SABR plans were generated for each patient: a regular planning target volume margin plan, a reduced margin plan (gross tumour volume GTV+3 mm) and a non-margin plan. Targets were planned to 48Gy/4 or 50Gy/5 fractions depending on location. Plans were compared in terms of target coverage, OAR doses and dosimetric acceptability based on local guidelines. Predictors of acceptability were investigated using logistic regression analysis. **Results:** Compared to regular margin plans, both reduced margin and non-margin plans resulted in significant reductions to almost all dose constraints. Dose conformity was significantly worse in non-margin plans ($P < 0.05$) and strongly correlated with targets' surface area/volume ratio ($R^2 = 0.9$, $P < 0.05$). 26% of reduced margin plans were acceptable, compared to 54% of non-margin plans. GTV overlap with OARs significantly affected plan acceptability (OR 0.008, 95% CI 0.001–0.073). **Conclusion:** Margin reduction significantly reduced OAR doses enabling acceptable plans to be achieved for patients previously excluded from SABR. Indications for lung SABR may broaden as treatment accuracy continues to improve; further work is needed to identify patients most likely to benefit.

Introduction

For patients with early-stage non-small cell lung cancer (NSCLC) which is inoperable, stereotactic ablative body radiotherapy (SABR) is the current standard of care, offering excellent local control rates ≥85%[1,2] and competing with the outcomes of surgical interventions.[3] SABR relies on state-of-the-art image-guided radiation therapy (IGRT) and motion management techniques to deliver highly conformal ablative doses in a limited

number of fractions.[1] In population studies, the introduction of SABR has led to improving overall survival and reducing the number of patients left untreated.[4]

However, patients diagnosed with early-stage NSCLC represent only about 20% of new lung cancer cases, limiting the number of patients who can benefit from lung SABR.[5] Up to 40% of NSCLC patients are diagnosed with locally advanced (non-metastatic) disease.[6] For those with inoperable disease, improvements in overall survival with concurrent chemoradiation have been modest over the last 10–15 years.[7] The use of immune checkpoint inhibitors after chemoradiation has recently been shown to significantly improve survival.[8] Nevertheless, a major challenge in managing this patient cohort is the associated comorbidities and poor respiratory function that preclude a significant proportion of patients from undergoing guideline-recommended treatments.[9]

The limited curative options available to those unfit for conventional radiotherapy have prompted early investigations into the potential role of SABR in more advanced tumours. This includes exploring SABR for lesions invading the chest wall,[10] or as a boost following chemoradiation for stage III disease.[11] Others have reported on the safety and effectiveness of SABR on larger tumours including T3-4N0M0[12] and stage II disease.[13] In a U.S. nation-wide analysis, higher biologically effective doses were associated with improved survival in stage II (node-negative) disease treated with SABR.[14] Finally, a planning study has demonstrated the feasibility of using protracted SABR fractionations for patients with N2/N3 locally advanced NSCLC.[15]

A major challenge in using SABR on larger tumours is limiting the dose to healthy organs to minimise the risk of severe toxicity.[14] IGRT technologies continue to undergo tremendous advancements, improving the accuracy of treatment delivery, permitting significant margin reductions and enabling safe escalation of dose to cancerous tissue without exceeding healthy tissue tolerances.[16,17] Most recent is the incorporation of magnetic resonance imaging (MRI) into the radiotherapy workflow and the development of linear accelerators with fully integrated MRI capabilities.[16] Though still in its infancy, this technology promises to transform radiotherapy treatments and substantially reduce the safety margins required. In the context of lung SABR, a phase I trial showed MRI guidance (with tumour tracking) allowed margins reduction down to 3–5 mm around the gross tumour volumes, as opposed to the conventional 5 mm around the internal target volume.[18,19] This is expected to allow delivering higher biologically effective doses to more central lesions[20] and potentially broaden the indications for lung SABR.[17]

This study aims to simulate the dosimetric benefits of reducing planning safety margins for lung SABR treatments. Identification of the factors influencing the likelihood of achieving acceptable plans for such lesions is also a goal. This has been undertaken with a particular interest in the potential to broaden the criteria for lung SABR treatments to include patients with larger, more advanced lesions.

Methods and Materials

This retrospective analysis included all NSCLC patients (stage IA–IIIA) treated with conventionally fractionated radiotherapy between 2014 and 2019 at our local centre. The study has been reviewed and approved by the Human Research Ethics Committee at the South Western Sydney Local Health District. All patients were deemed ineligible for SABR due to tumour size and/or proximity to organs at risk. Patients underwent free-breathing 4DCT scans with 2 mm slice thickness. The internal target volume (ITV) approach was used to account for motion, encompassing the gross tumour volume (GTV) on the inhalation, exhalation and maximum intensity projection (MIP) scans. The planning target volume (PTV) was created by adding an isotropic margin of 5 mm to the ITV.

Three lung SABR plans were generated for each patient, a conventional margin plan treating the PTV, a reduced margin plan targeting the GTV+3 mm margin and a third non-margin plan targeting only the GTV. Reduced and non-margin plans were based on the GTV at the end of exhalation, as real-time tumour tracking during treatment is assumed. Following the RTOG-0813 guidelines, central lesions were planned to a dose of 50 Gy in 5 fractions while peripheral ones were planned to 48 Gy in 4 fractions. The planning technique was 6 MV volumetric modulated arc therapy (VMAT) with two dynamic arcs of 200 degrees. The adaptive convolution dose calculation algorithm was used with a dose grid resolution of 2mm. Plans were normalised to achieve total dose (TD) coverage to 99% of the target volume.

All plans were generated using Pinnacle Auto-planning.[3] Plans were then reviewed and manually optimised (if needed) by a single dosimetrist. Optimisation was performed by increasing the 'weighting' of any unmet optimisation goals or OAR dose constraints in consecutive steps of 5 points. Target volume coverage was prioritised during optimisation, and attempts to reduce OAR doses were made until target coverage was compromised. Final plans for each patient were separately analysed and compared considering target coverage, OAR doses, conformity of the 100% isodose line (CI100%) and

homogeneity index (HI). Plans were also compared in terms of the number of violations to dose constraints. Plans were deemed acceptable if they met our local guidelines for target coverage and OAR constraints (Appendix 1), which align with (if not stricter) than RTOG-0813 guidelines.[21]

A repeated measure, one-way ANOVA was used to test for significance (followed up by Tukey's test for pairwise comparisons). To examine the effects of margin reduction on plan quality, we investigated the relationship between target volume and both conformity and homogeneity of the dose in all three plans. Similarly, we investigated the relationship between dose conformity and a number of targets' (GTV, GTV+3 mm and PTV) radiomics shape features, including surface area/volume ratio, sphericity, elongation and flatness.

Finally, multivariable logistic regression was used as a means of identifying the main factors influencing the likelihood of achieving acceptable plans. Investigated variables included tumour centrality, stage, volume (as a continuous variable) and overlap with any surrounding OARs (as a dichotomous variable). Univariate analysis was performed to determine the odds ratio and significance of each factor; colinearity between factors was tested using Spearman's correlation test. All statistical analysis was performed using IBM SPSS Statistics Software (version 23.0.0), with the exception of the figures in (Appendices 4 and 5), which were generated using Python, version 3.6.5 (Python Software Foundation).

Results

A total of 61 patients (183 VMAT plans) were included in the final analysis. Table 1 provides a summary of patients' characteristics and the SABR dose prescriptions used. Significant differences in target volume were found among the three plans (Table 2); the PTV had a median volume of 198.1 mL (IQR: 123.8–424.7) compared to 75.5 mL (IQR: 37.0–157.6) for the GTV+3 mm and 39.5 mL (IQR: 18.2–85.3) GTV ($P < 0.05$). On average, PTV volume was a factor of 2.4 larger than GTV+3 mm and 3.7 times larger than GTV volume. T1 lesions had a mean volume of 13.4 mL ($\pm$12.8) compared to 57.0 mL ($\pm$62.7) and 177.4 mL ($\pm$163.3) in T2 and T3 lesions, respectively ($P < 0.05$).

Target volume coverage

All plans achieved adequate target coverage; Figure 1 provides illustrations of the dose distributions achieved for two representative patients: (a) and (b). The maximum dose was significantly higher in margin plans

Table 1. Characteristics of the patients included in the study ($N = 61$).

Gender	
Male	34
Female	27
Histology	
Adenocarcinoma	28
Squamous cell	27
Large cell	1
Unknown	5
Laterality	
Left lung	37
Right lung	24
Lobe	
Upper	36
Middle	5
Lower	20
Stage (TNM)	
IA	
T1a N0 M0	7
T1b N0 M0	10
IB	
T2a N0 M0	13
IIA	
T2 N0 M0	3
T2b N0 M0	7
IIB	
T3 N0 M0	11
IIIA	
T3b N1 M0	10
SABR dose planned	
50 Gy/5F	52
48 Gy/4F	9

with a mean of 70.8 Gy (95% CI: 70.1–71.5) compared to both reduced and non-margin plans at 69.1 Gy (95% CI: 68.7–69.5) and 69.2 Gy (95% CI: 68.7–69.7), respectively (Table 2). The D5% and D2% were significantly lower in reduced margin plans compared to both other plans (all $P < 0.05$). Mean dose–volume histograms (DVHs) for the three plan scenarios are shown in Figure 2.

Regarding plan quality, mean CI100% was lowest in margin plans at 1.1 (95% CI: 1.1–1.1), followed by reduced margin at 1.3 (95% CI: 1.3–1.4) then non-margin plans at 1.6 (95% CI: 1.5–1.7) ($P < 0.05$). Of the 61 non-margin plans, 24 had a CI100% of higher than 1.5; these patients tended to have smaller GTV volumes with 85% <25 ml and 66% <15 ml. Margin plans had significantly higher HI scores compared to both reduced and non-margin plans ($P < 0.05$). The effect of target volume on CI100% and HI scores is shown in Appendix 2. For CI100%, a power function relationship was significant for reduced margin and non-margin plans (R^2 of 0.5 and 0.8, respectively ($P < 0.05$). For HI, a linear correlation offered the best fit with R^2 values of 0.6

Table 2. Comparing *Margin, Reduced margin* and *Non-margin* plans in terms of dose-volume metrics to their respective target volume.

	Margin		Reduced margin		Non-margin		
	Mean (±SD)	95% CI	Mean (±SD)	95% CI	Mean (±SD)	95% CI	*P*-value
Volume (mL)	316.3 ± 290.6	241.9–390.7	132.8 ± 164.7	90.6–175.0	86.3 ± 122.9	54.8–117.8	<0.001
Maximum dose (Gy)	70.8 ± 2.7	70.1–71.5	69.1 ± 1.6	68.7–69.5	69.2 ± 1.9	68.7–69.7	<0.001
Minimum dose (Gy)	34.6 ± 9.4	32.2–37.0	40.3 ± 8.9	38.0–42.6	42.6 ± 7.3	40.7–44.5	<0.001
Mean dose (Gy)	59.3 ± 1.2	59.0–59.6	59.5 ± 1.3	59.2–59.8	60.7 ± 1.4	60.4–61.1	<0.001
$D_{98\%}$ (Gy)	49.2 ± 2.4	48.6–49.8	50.8 ± 2.3	50.2–51.4	52.1 ± 2.3	51.5–52.7	<0.001
$D_{95\%}$ (Gy)	51.5 ± 1.5	51.1–51.9	52.8 ± 1.7	52.4–53.2	53.9 ± 1.8	53.4–54.4	<0.001
$D_{50\%}$ (Gy)	59.7 ± 1.2	59.4–60.0	60.1 ± 1.3	59.8–60.4	61.2 ± 1.3	60.7–61.5	<0.001
$D_{5\%}$ (Gy)	66.1 ± 1.7	65.7–66.5	64.9 ± 1.7	64.5–65.3	66.1 ± 1.7	65.7–66.6	<0.001
$D_{2\%}$ (Gy)	67.3 ± 1.7	66.9–67.7	65.9 ± 1.7	65.5–66.3	66.9 ± 1.6	66.6–67.4	<0.001
CI 100%	1.1 ± 0.1	1.1–1.1	1.3 ± 0.2	1.3–1.4	1.6 ± 0.4	1.5–1.7	<0.001
CI 50%	4.0 ± 0.9	3.8–4.2	5.4 ± 1.8	4.9–5.9	7.7 ± 4.9	6.5–8.9	<0.001
HI	1.4 ± 0.1	1.4–1.4	1.4 ± 0.0	1.4–1.4	1.4 ± 0.0	1.4–1.4	<0.001
D_{2cm} (%)	0.8 ± 0.1	−1.2–2.8	0.7 ± 0.1	−1.1–2.5	0.6 ± 0.1	−1.1–2.3	<0.001

CI, *n*% conformity index of the *n*% isodose line; D_{2cm}, maximum dose 2 cm away from target as % of total dose; $D_{n\%}$, dose received by at least *n*% of target volume; GTV, gross tumour volume; HI, homogeneity index; PTV, planning target volume.

and 0.3 for margin and non-margin plans, respectively ($P < 0.05$).

Regarding targets' radiomics shape features, there was a strong linear correlation between CI100% and surface area/volume ratio (Appendix 3(a)). This relationship was strongest in non-margin plans ($R^2 = 0.9$, $P < 0.05$) followed by reduced margin ($R^2 = 0.6$, $P < 0.05$) then conventional margin plans ($R^2 = 0.1$, $P < 0.05$). No significant correlation was found between CI100% and targets' sphericity (Appendix 3(b)). Appendix 4 summarises cross-correlations among all radiomics features investigated along with CI100% and HI.

Dose–volumetric parameters of OARs

Table 3 compares the three plans in terms of doses to OARs. Compared to margin plans, reduced margin plans achieved significantly lower doses to all OARs except for brachial plexus, trachea and the spinal cord. Doses to the bronchial tree$_y$, heart, trachea, oesophagus, great vessels and ribs decreased by at least 50%. Similarly, non-margin plans had significantly lower doses to almost all OARs, with at least 70% reduction in doses to the heart, trachea, oesophagus, ribs, great vessels and skin. Figure 2 compares the three plans in terms of mean DVH for each organ.

Plan acceptability

Plans were also compared in terms of acceptability, defined as meeting all local requirements for target coverage and OAR dose constraints (Fig. 3). Of the 61 plans with conventional margins, only one was deemed acceptable while remaining plans had at least two violations. Of the 61 reduced margin plans, 16 were considered acceptable (26%), 11 of which were stage IA, three stage IB, one IIA and one IIB. Also of note, out of 21 patients with T3 lesions, only one had an acceptable plan after margin reduction. With zero margins, 33 patients were deemed acceptable (54%), of which, 15 had stage IA tumours, while 12, five and one patient had stage IB, IIA and IIB, respectively.

With regard to the factors influencing plan acceptability, a summary of univariate (i.e. unadjusted) analysis for each factor is provided in Table 4. GTV overlap with at least one OAR had a major effect with an odds ratio of 0.008 (95% CI: 0.001–0.073, $P < 0.001$). Only 18.2% of those with GTV overlap had acceptable plans, compared to 81.8% of those with no overlap achieving acceptable plans. GTV and PTV volumes were also significant predictors, although these two factors are highly correlated (Spearman correlation of 0.9) (Appendix 5). Every unit increase in GTV volume was associated with a 4.4% decrease in the odds of achieving an acceptable plan. Some tumour stages showed significance, although the relatively small number of patients in each group makes it difficult to interpret their predictive importance. Tumour centrality did not show significant predictive value.
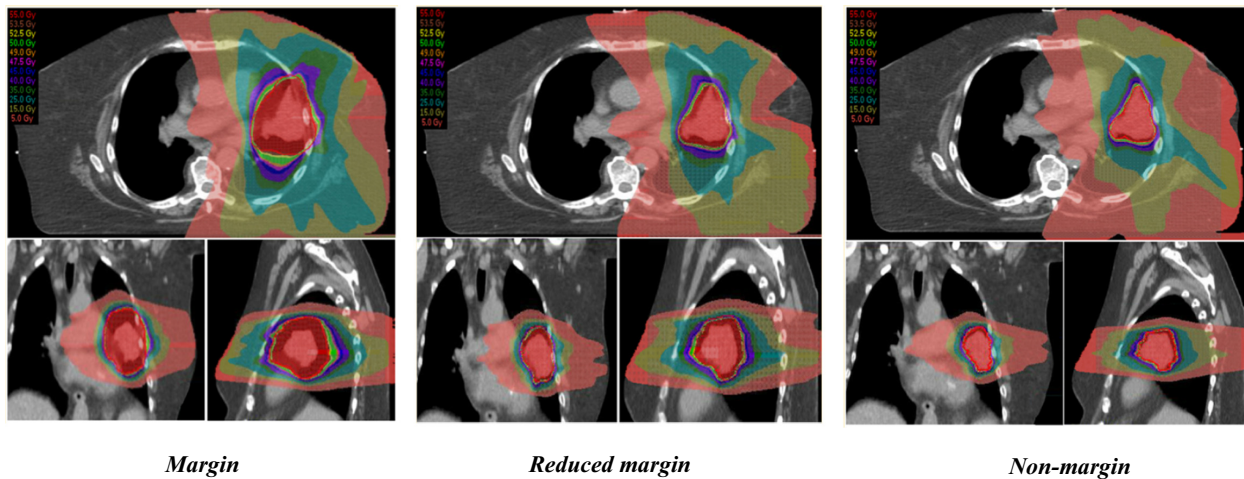
Discussion

The dosimetric gains associated with margin reduction have been investigated in lung SABR treatment plans. Reducing margins to 3mm around the GTV and removing the need for ITV by using tumour tracking

Patient (a)

Margin   Reduced margin   Non-margin

Patient (b)

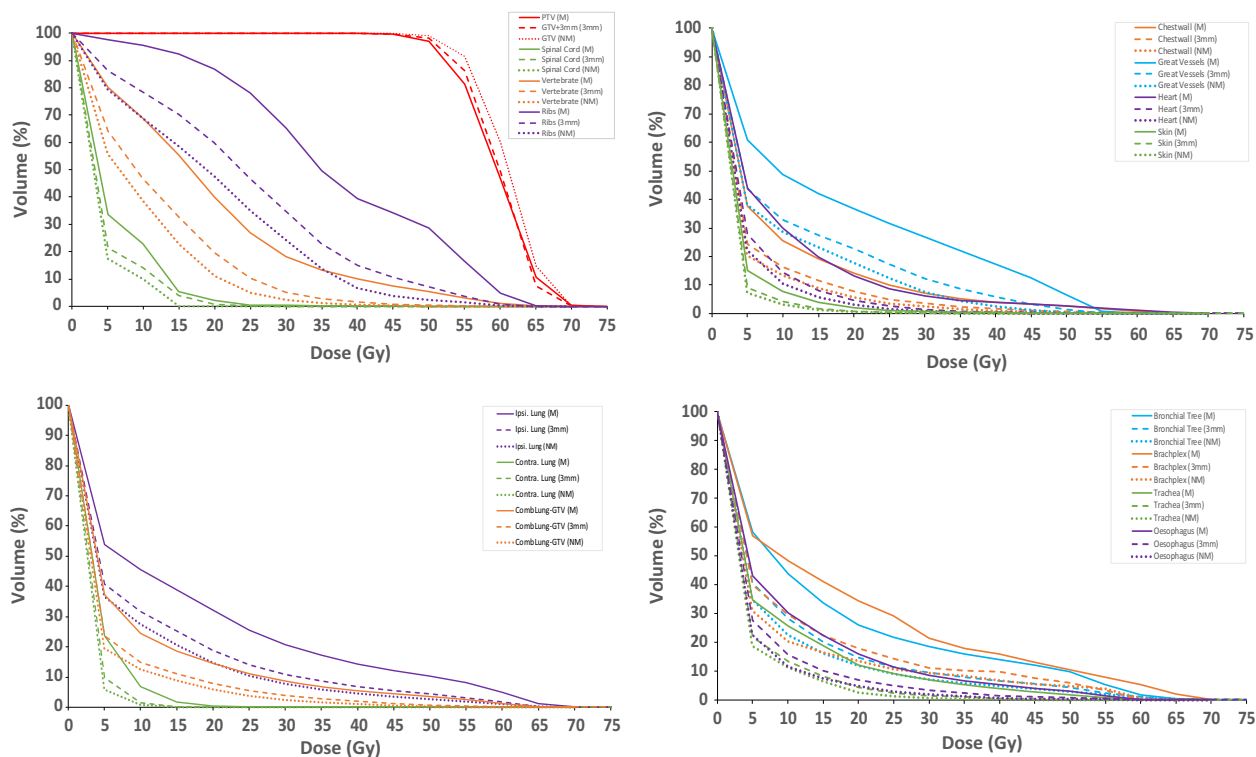Margin   Reduced margin   Non-margin
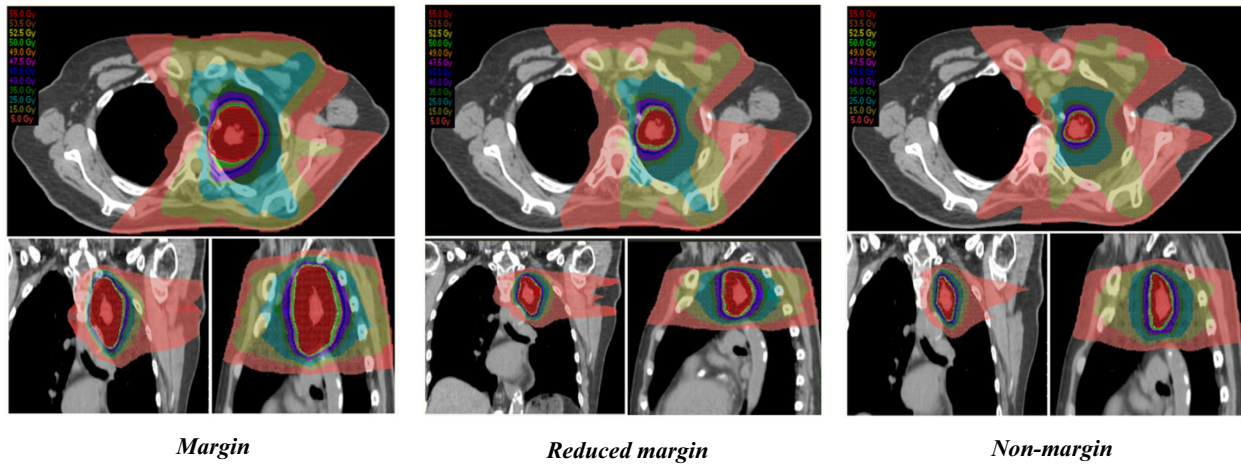
Figure 1. Illustrations of the dose distribution achieved in *Margin*, *Reduced margin* and *Non-margin* plans for two representative patients (a) and (b).

resulted in approximately a 2.4-fold reduction in target volume, along with significant decreases to almost all organ-specific dose constraints (Table 2).

Previous studies have similarly investigated the potential benefits of margin reduction. However, to our knowledge, this is the first investigation done in the context of more advanced tumours. Wojcieszynski et al., used a sample of 10 early-stage NSCLC to compare VMAT SABR plans, with conventional margins, against MRI-based (GTV+3 mm) plans based on the Tri-Cobalt-60 machine.[22] Although both techniques achieved clinically acceptable plans, no significant reductions in doses to OARs were found. This study was limited by the small sample size and the increased geometric penumbra associated with Cobalt-60 source beams.[22] More recently,

Park et al. compared intensity-modulated radiotherapy (IMRT) plans with reduced margins against conventional VMAT plans in 22 early-stage NSCLC patients.[23] In this study, margin reduction resulted in significantly lower doses to the bronchus, ribs, ipsilateral lung and whole body mean dose. Conversely, reduced margin plans had higher doses to the skin, spinal cord and the contralateral lung, attributed to the different characteristics between IMRT and VMAT delivery techniques.[23]

Including patients who had previously been excluded enabled assessing the potential for margin reduction to increase the indications for SABR to include more NSCLC patients. Based on our findings, reducing planning margin to 3mm around the GTV and assuming tumour tracking led to acceptable plans being achieved in 25% of patients

Figure 2. Comparing *Margin* (M) *(Solid line)*, *Reducedmargin* (3 mm) *(Dashed line)* and *Non-margin* (NM) plans *(Dotted line)* in terms of mean dose-volume histograms for targets and organs at risk. GTV, gross tumour volume; PTV planning target volume.

previously excluded from SABR. The majority of these patients had stage T1-2a tumours, suggesting that benefits were limited to small lesions in close proximity to critical OARs. More protracted dose schedules could be considered for patients with larger tumours. Additionally, we explored the potential gains of treating with zero margins, which increased the proportion of acceptable plans to 54%. Of course, this is a more hypothetical scenario aiming to further explore the relationship/trend between margin reduction and dosimetric benefits, and to reveal what could be considered as the utmost limit of what is achievable in hypothetically perfect conditions with anatomical targeting.

Planning with zero margins resulted in significantly worse conformity scores compared to both margin and reduced margin plans. The majority of these plans had very small target volumes (<15 mL), which is consistent with previous findings indicating dose conformity to be influenced by target volume.[24] Interestingly, however, even PTV, GTV+3mm and GTV targets of very similar volumes still had considerably different conformity scores (Appendix 2(a)), suggesting that volume may not be the only contributing factor. This difference was also observed in the automatically generated plans (prior to

any manual optimisation), which increased the likelihood that it was not merely a result of random variations or intra-planner uncertainty.

It has been suggested that targets of complex shapes may be associated with difficulty achieving good conformity, especially in the context of thorax treatments as the low density of lung tissue causes loss of intermediate dose conformity.[24] Our analysis supports this notion by revealing a strong positive correlation between conformity and surface area/volume ratio (Appendix 3(a)); a metric commonly used to describe the complexity of 3D shapes. Simply expanding the target volume to add margins resulted in smoothing out the shape and reducing the surface area/volume ratio. Sphericity is another shape feature that describes the roundness of a particular shape relative to a sphere (1 indicates a perfect sphere). Although no clear relationship could be found between dose conformity and this metric (Appendix 3(b)). Other features correlating with dose conformity included maximum 2D diameter slice and least axis length, though these features were also highly correlated with surface area/volume ratio (Appendix 4).

Despite being a potentially curable disease, many patients with advanced tumours do not receive guideline-

Table 3. Comparing *Margin*, *Reduced margin*, and *Non-margin* plans in terms of organ-specific dose–volumetric parameters

Organ at risk	Parameter	Margin Mean ± SD	Margin 95% CI	Reduced margin Mean ± SD	Reduced margin 95% CI	Non-margin Mean ± SD	Non-margin 95% CI	P-value
Bronchial tree	Max (Gy)	42.9 ± 22.6	37.1–48.7	32.7 ± 23.7	26.6–38.8	29.8 ± 24.7	23.5–36.1	<0.05
	$V_{18\ Gy}$ (mL)	7.5 ± 9.9	5.0–10.0	4.3 ± 6.8	2.6–6.0	3.5 ± 5.7	2.0–5.0	<0.05
	$V_{35\ Gy}$ (mL)	4.2 ± 6.7	2.5–5.9	2.0 ± 3.9	1.0–3.0	1.5 ± 3.0	0.7–2.3	<0.05
Lungs-GTV	Max (Gy)	68.9 ± 4.8	67.7–70.1	64.2 ± 5.7	62.7–65.7	60.5 ± 6.2	58.9–62.1	<0.01
	Mean (Gy)	8.7 ± 3.8	7.7–9.7	5.1 ± 2.7	4.4–5.8	4.1 ± 2.2	3.5–4.7	<0.01
	$V_{5\ Gy}$ (mL)	1440.0 ± 885.4	1213.2–1666.8	921.6 ± 680.2	747.4–1095.8	764.6 ± 561.1	620.1–909.1	<0.01
	$V_{10\ Gy}$ (mL)	939.8 ± 569.7	793.7–1085.7	577.4 ± 401.2	474.6–680.2	488.7 ± 346.1	400.1–577.4	<0.01
	$V_{12.5\ Gy}$ (mL)	808.9 ± 482.1	685.4–932.4	490.9 ± 353.6	400.3–581.5	405.5 ± 305.8	327.2–483.8	<0.01
	$V_{20\ Gy}$ (mL)	553.3 ± 347.5	464.3–642.3	301.5 ± 248.6	237.8–365.2	223.4 ± 199.5	172.3–274.5	<0.01
	D_{1000cc} (Gy)	9.2 ± 7.9	7.2–11.2	4.9 ± 5.2	3.6–6.2	3.8 ± 4.2	2.7–4.9	<0.01
	D_{1500cc} (Gy)	5.3 ± 5.0	4.0–6.6	2.8 ± 3.2	2.0–3.6	2.1 ± 2.5	1.5–2.7	<0.01
Heart	Max (Gy)	40.1 ± 26.1	33.4–46.8	30.8 ± 24.7	24.5–37.1	27.3 ± 23.2	21.4–33.2	<0.05
	$V_{32\ Gy}$ (mL)	26.3 ± 38.9	16.3–36.3	8.5 ± 19.9	3.4–13.6	4.4 ± 11.8	1.4–7.4	<0.01
Brachial plexus	Max (Gy)	37.1 ± 23.4	23.0–51.2	26.5 ± 21.7	13.4–39.6	21.5 ± 18.9	10.0–33.0	0.178
	$V_{30\ Gy}$ (mL)	2.1 ± 3.5	0.0–4.2	1.1 ± 3.3	−0.9–3.1	0.9 ± 3.2	−1.0–2.8	0.656
Trachea	Max (Gy	23.7 ± 21.1	17.0–30.5	16.3 ± 17.4	10.7–21.9	13.8 ± 16.1	8.6–19.0	0.047
	$V_{18\ Gy}$ (mL)	3.5 ± 6.5	1.4–5.6	1.5 ± 3.6	0.3–2.7	1.0 ± 2.6	0.2–1.8	<0.05
	$V_{35\ Gy}$ (mL)	1.3 ± 3.4	0.2–2.4	0.2 ± 0.8	−0.05–0.5	0.1 ± 0.3	0.0–0.2	<0.05
Oesophagus	Max (Gy)	34.7 ± 19.9	29.5–39.9	25.2 ± 18.9	20.3–30.1	21.1 ± 17.2	16.6–25.6	<0.05
	$V_{18.8\ Gy}$ (mL)	5.4 ± 7.1	3.6–7.2	2.5 ± 5.3	1.1–3.9	1.8 ± 4.1	0.7–2.9	<0.05
	$V_{27.5\ Gy}$ (mL)	3.3 ± 5.8	1.8–4.8	1.4 ± 3.7	0.4–2.4	0.8 ± 2.7	0.1–1.5	<0.05
Chest wall	Max (Gy)	58.9 ± 12.9	55.5–62.4	51.7 ± 14.5	47.8–55.6	46.9 ± 14.9	42.9–50.9	<0.01
	$V_{30\ Gy}$ (mL)	79.4 ± 69.1	60.9–97.9	39.8 ± 53.9	25.4–54.2	27.2 ± 43.9	15.4–39.0	<0.01
Spinal cord	Max (Gy)	15.9 ± 8.6	13.7–18.1	12.4 ± 7.9	10.4–14.4	9.5 ± 7.3	7.6–11.4	<0.05
	$V_{13.5\ Gy}$ (mL)	2.5 ± 5.0	1.2–3.8	1.8 ± 4.8	0.6–3.0	0.2 ± 0.4	0.1–0.3	<0.05
	$V_{22.5\ Gy}$ (mL)	0.3 ± 1.2	−0.02–0.6	0.1 ± 0.2	0.04–0.20	0.0 ± 0.0	0.0–0.0	0.1145
Vertebrate	Max (Gy)	58.2 ± 11.4	52.1–64.3	45.4 ± 13.4	38.2–52.6	37.7 ± 14.5	30.0–45.4	<0.05
Ribs	Max (Gy)	56.7 ± 10.7	55.0–58.5	46.9 ± 15.6	44.3–49.5	39.6 ± 14.8	37.2–42.0	<0.01
	$V_{40\ Gy}$ (mL)	4.4 ± 4.0	3.7–5.1	1.8 ± 3.0	1.3–2.3	0.8 ± 1.9	0.5–1.1	<0.01
Great vessels	Max (Gy)	41.9 ± 19.2	36.9–46.7	32.4 ± 21.1	27.0–37.9	27.6 ± 20.0	22.4–32.8	<0.05
	$V_{35\ Gy}$ (mL)	7.1 ± 11.7	4.1–10.1	2.2 ± 6.0	0.64–3.76	1.2 ± 4.4	0.1–2.4	<0.05
	$V_{47\ Gy}$ (mL)	3.03 ± 6.83	1.3–4.8	0.7 ± 2.6	0.04–1.4	0.3 ± 1.7	−0.1–0.7	<0.05
Whole body	Mean (Gy)	6.4 ± 3.7	5.4–7.4	4.4 ± 3.0	3.6–5.2	3.3 ± 2.5	2.7–3.9	<0.01
	$V_{50\%}$ (mL)	1075.1 ± 749.9	881.4–1268.8	534.4 ± 518.9	400.3–668.5	391.1 ± 428.7	280.4–501.7	<0.01
Skin	Max (Gy)	36.5 ± 15.5	32.5–40.5	28.4 ± 11.6	25.4–31.4	25.5 ± 11.0	22.7–28.3	<0.01
	$V_{24\ Gy}$ (mL)	18.6 ± 31.4	10.6–26.7	6.5 ± 15.8	2.5–10.6	4.1 ± 11.4	1.2–7.0	<0.05
	$V_{30\ Gy}$ (mL)	10.5 ± 22.6	4.7–16.3	3.4 ± 10.2	0.8–6.0	2.1 ± 6.7	0.3–3.9	<0.05

[1]Max maximum dose, GTV, gross tumour volume; V_{nGy}, volume receiving a dose of n Gy; D_{ncc}, dose received by a volume of n cc; $V_{50\%}$, volume receiving 50% of prescription dose.

recommended treatment. In some cohorts, approximately 40% of patients do not receive curative intent treatments,[9,25] while 17% receive no treatment at all.[26] Associated respiratory comorbidities are among the most common reasons for precluding treatment.[9,27] Age is also a significant factor with up to 79% of patients over the age of 76 not receiving curative intent treatments, even though elderly patients experience similar benefits from curative treatments compared to their younger counterparts.[25,27] This could be attributed, at least partly, to the logistics associated with attending six weeks daily treatments and patients' ability to tolerate the treatment.[28] In the context of early-stage disease, SABR allowed for a curative treatment option to be conveniently delivered over 4 or 5 outpatient visits, which had a particularly significant impact in elderly patients, reducing the number of those left untreated and improving the overall population-based survival rates.[4]

This work joins efforts investigating the feasibility of extending SABR as a treatment option to more NSCLC patients. More specifically, the role of margin reduction in minimising doses to surrounding OARs. Additionally, we investigated factors influencing the probability of achieving acceptable plans, which could be used as an

Conventional margins (PTV)

Reduced margin (GTV+3mm)

Non-margin (GTV)
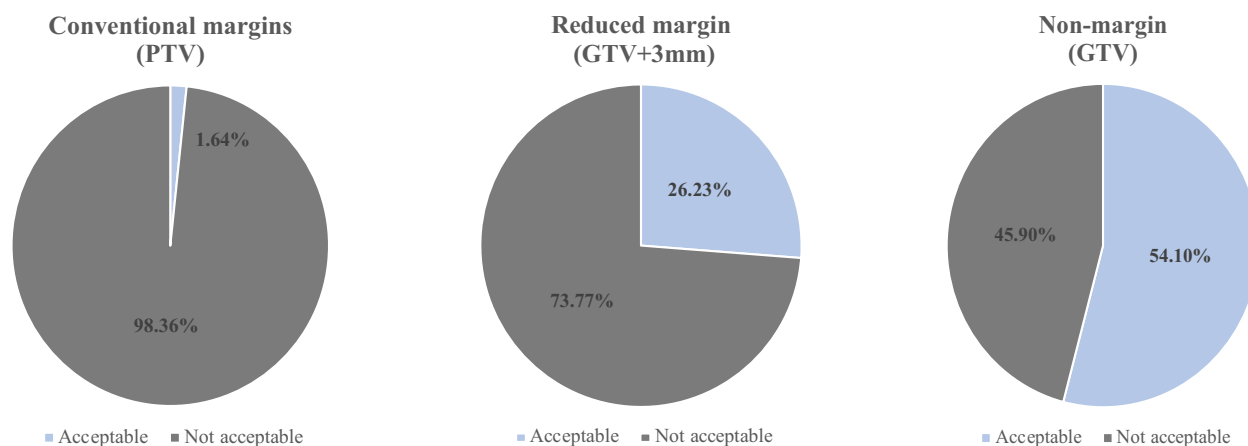
Figure 3. The proportion of acceptable and not acceptable plans, from a total of 61 plans, for each of the three planning margin scenarios. GTV, gross tumour volume; PTV, planning target volume.

Table 4. Summary of univariate (unadjusted) analysis of odds ratio for each predictor of plan acceptability

Predictor	Acceptable ($n = 33$)	Not acceptable ($n = 28$)	Odds ratio (95% CI)	align="left">P-value
Overlap	6	27	0.008 (0.001–0.073)	<0.001
Mean GTV volume (SD)	24.6 (20.0)	159.1 (151.5)	0.956 (0.930–0.983)	0.002
Mean PTV volume (SD)	155.7 (97.8)	505.6 (328.1)	0.989 (0.983–0.995)	<0.001
Central	26	25	0.286 (0.054–1.507)	0.140
Stage				
IA	15	2	10.833 (2.20–53.29)	0.003
IIA	5	5	0.82 (0.21–3.19)	0.776
IB	12	1	15.43 (1.86–128.31)	0.011
IIB	1	10	0.056 (0.007–0.476)	0.008
IIIA	0	10	0	0.999

CI, confidence interval; GTV, gross tumour volume; PTV, planning target volume.

early step towards identifying patients most likely to benefit from MRI-guided treatments. We identified GTV volume and direct overlap with OARs as major factors in determining the probability of achieving an acceptable plan, although our analysis was limited by the small sample size and further work is needed to develop robust models able to predict the potential benefits to patients without the need to generate full treatment plans.

Future predictive models may also benefit from incorporating more precise measures of distances between target volume and surrounding organs. Knowledge-based planning (KBP) fundamentally relies on the same concept of applying regression analysis on a library of retrospective plans to identify correlations between targets' geometric location and doses to OARs. This paradigm has recently been used to predict patients' eligibility for liver SABR treatments[29] and to identify head-and-neck cancer patients most likely to benefit from proton therapy.[30] Another future direction is employing

tumour control and normal tissue complication probability models to estimate the clinical benefits of margin reductions.

Limitations of this study include the retrospective nature of the analysis and the potential biases associated with it. We did not account for the effects of the magnetic field on dose distribution, although this was shown to be small and unlikely to affect plan acceptability.[31] We also did not explore milder dose fractionations, which may have increased the number of acceptable plans, but the main focus was to simulate the effect of margin reductions enabled by real-time imaging and tracking technologies. Finally, we did not explore the practical considerations (e.g. motion management) of margin reduction. While the choice of using a reduced margin of GTV+3 mm was based on the smallest margin used clinically, it must be remembered that large-scale studies of local control and progression-free survival are still awaited to confirm the safety of such reductions in planning margins.

Conclusion

Reducing planning margins can lead to significant sparing of OARs without compromising doses to the target volume, enabling acceptable plans to be generated in patients previously ineligible for lung SABR. IGRT developments, such as MRI guidance, have the potential to broaden indications for lung SABR as a curative option to more NSCLC patients. More work is needed to investigate the impact of such technologies on clinical outcomes and to develop models able to identify patients most likely to benefit from them.

Conflict of Interest

The authors declare no conflict of interest.

Funding Information

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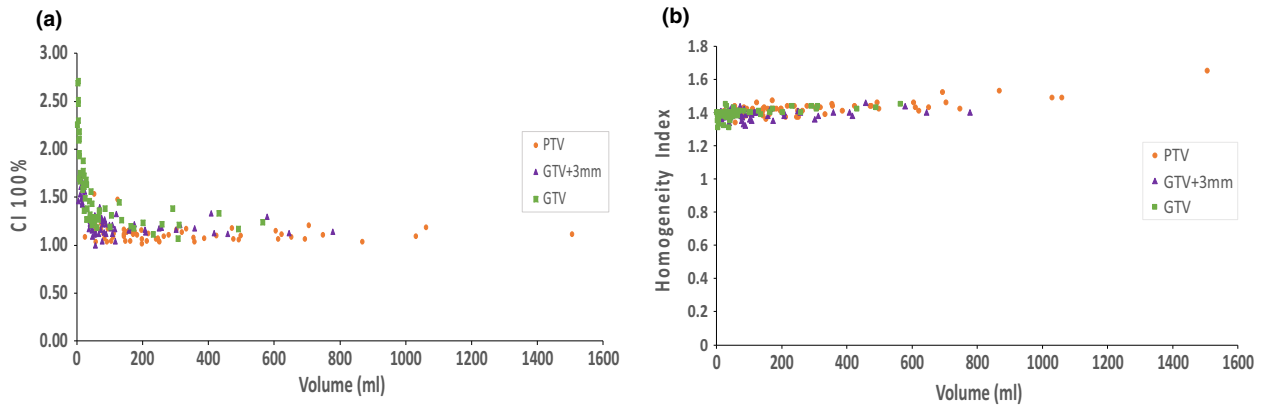
Appendix 1
Summary of the dose constraints for each of the fractionation schedules used:

Organ at risk	Dose constraint	Maximum limit	
		50 Gy/5F	48 Gy/4F
Bronchus and trachea	Max (Gy)	<52.5	<50.4
	$V_{15.6 \text{ Gy}}$ (mL)	–	<4
	$V_{18 \text{ Gy}}$ (mL)	<4	–
	$V_{32 \text{ Gy}}$ (mL)	–	<1
Lungs-GTV	Mean (Gy)	<4	<4
	$V_{20 \text{ Gy}}$ (mL)	<8%	<8%
Heart	Max (Gy)	<52.5	<50.4
	$V_{27 \text{ Gy}}$ (mL)	–	<1
	$V_{32 \text{ Gy}}$ (mL)	<15	–
Brachial plexus	Max (Gy)	<32	<32
	$V_{23.6 \text{ Gy}}$ (mL)	–	<3
	$V_{30 \text{ Gy}}$ (mL)	<3	–
Oesophagus	Max (Gy)	<52.5	<50.5
	$V_{18.8 \text{ Gy}}$ (mL)	–	<5
	$V_{27.5 \text{ Gy}}$ (mL)	<5	<1
Chest wall	$V_{30 \text{ Gy}}$ (mL)	<30	<30
Spinal cord	Max (Gy)	<28	<28
	$V_{13.5 \text{ Gy}}$ (mL)	< 0.5	<1.2
	$V_{20.8 \text{ Gy}}$ (mL)	–	<0.35
	$V_{22.5 \text{ Gy}}$ (mL)	<0.25	–
Vertebrate	Max (Gy)	<54	<54
Great vessels	Max (Gy)	<52.5	<45
	$V_{39 \text{ Gy}}$ (mL)	–	<10
	$V_{47 \text{ Gy}}$ (mL)	<10	–
Skin	Max (Gy)	<32	<32
	$V_{24 \text{ Gy}}$ (mL)	<10	<10
Ribs	Max (Gy)	<52.5	<50.4

$D_{n\text{cc}}$ dose received by a volume of n cc; GTV, gross tumour volume; Max, maximum dose; $V_{50\%}$, volume receiving 50% of prescription dose; $V_{n\text{Gy}}$, volume receiving a dose of n Gy.
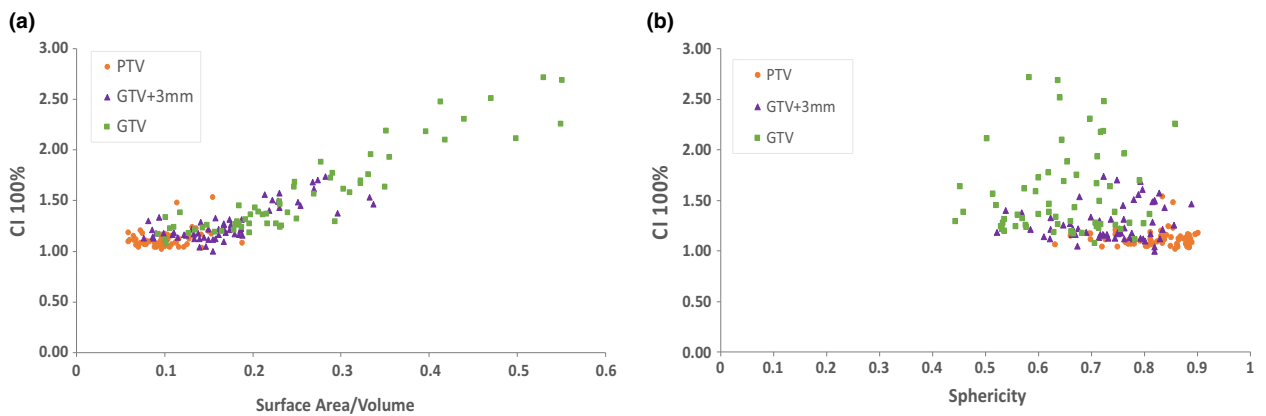
Appendix 2
Plotting target volumes for each of the three margin scenarios: planning target volume (PTV) margins (Red), gross tumour volume +3 mm margin (GTV+3 mm) (Purple) and non-margin (GTV) (Green) against: (a) Conformity index of the prescription isodose line (CI 100%) and (b) homogeneity index:

Appendix 3
Plotting conformity index of the prescription isodose line (CI100%) against two radiomics shape features: (a) Surface/volume ratio and (b) sphericity of the three margin scenarios: planning target volume (PTV) (Red), the gross tumour volume + 3 mm margin (GTV+3 mm) (Purple) and (GTV) with no margins (Green).:

Appendix 4
Summary of correlations among target's radiomics features investigated, along with conformity of the 100% isodose line (CI100), conformity of the 50% isodose line (CI50), gradient index (GI) and homogeneity index (HI).:

Appendix 5
Summary of correlations among plan acceptability and potential predictors. GTV, gross tumour volume; PTV, planning target volume.: