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Literature Review

A forward planned treatment planning technique for non-small-cell lung cancer stereotactic ablative body radiotherapy based on a systematic review of literature

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Abstract

Purpose and Method: A systematic literature review of six computerised databases was undertaken in order to review and summarise a forward planned lung stereotactic ablative body radiotherapy (SABR) treatment planning (TP) technique as a starting point for clinical implementation in the author's department based on current empirical research. The data were abstracted and content analysed to synthesise the findings based upon a SIGN quality checklist tool.

Findings: A four-dimensional computed tomography scan should be performed upon which the internal target volume and organs at risk (OAR) are drawn. A set-up margin of 5 mm is applied to account for inter-fraction motion. The field arrangement consists of a combination of 7–13 coplanar and non-coplanar beams all evenly spaced. Beam modifiers are used to assist in the homogeneity of the beam, although a 20% planning target volume dose homogeneity is acceptable. The recommended fractionations by the UK SABR Consortium are 54 Gy in 3 fractions (standard), 55–60 Gy in 5 fractions (conservative) and 50–60 Gy in 8–10 fractions (very conservative). Conformity indices for both the target volume and OAR will be used to assess the planned distribution.

Conclusion: An overview of a clinically acceptable forward planned lung SABR TP technique based on current literature as a starting point, with a view to inverse planning with support from the UK SABR Consortium mentoring scheme.

Keywords: SABR; SBRT; Stereotactic ablative body radiotherapy; Stereotactic ablative body radiation therapy; Stereotactic radiotherapy

INTRODUCTION

Stereotactic ablative body radiotherapy (SABR) is a non-invasive technique that is based on the principles of stereotaxis where multiple radiation beams are precisely targeting the tumour. It permits a dramatic reduction in irradiated volumes facilitating hypofractionation with large daily doses

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[higher Biological Effective Dose (BED)] and a reduced overall treatment time.[1]

There is now a wealth of publications on lung SABR, mainly institutional series/phase I/II trials. SABR is considered the gold standard for appropriate patients where surgery is contra-indicated. It may be considered an acceptable standard of care for peripheral medically inoperable stage 1 non-small-cell lung cancer (NSCLC) as the local control (LC) and overall survival (OS) results are very promising ranging from 73 to 97% [local control rate (LCR)] and 62 to 81% (OS).[1–15] Table 1 provides further details of LC and OS between external beam radiotherapy and SABR.

The evidence presented in literature overwhelmingly supports such a technique and understandably explains why it may be considered unethical not to offer an SABR service. Indeed, many articles suggest that it is comparable with surgical resection.[13,16,17] Presently, there are only two studies that have compared SABR and surgery in operable patients only.[13,18] Most studies have included inoperable patients, which can increase case selection bias into the research. The most current study supports the above results by showing the 1- and 3-year survival rates to be 94·7 and 84·7%, respectively and the LCR at 1 and 3 years were 98 and 93%, respectively.[18]

Even so a direct comparison of SABR and surgery is required. To date only the ROSEL study[19] aimed to do this. This was a phase III randomised trial, but owing to poor recruitment the study was terminated in September 2011. Nevertheless, it's treatment planning (TP) and organs at risk (OAR) constraints have been recommended for use by the UK SABR Consortium.[20,21]

The aim of this literature review focusses on the forward planned SABR TP technique as this would be the starting point for any clinical implementation in the author's department. The most recent UK SABR Consortium report[21] states that the majority of centres (7 out of 14) employ volumetric-modulated arc therapy (VMAT) delivery and 10 out of 14 use some sort of inverse planning technique for SABR.[22]

RESEARCH METHODOLOGY

The primary literature sources used were academic and medical journals, online databases, e-journals, Encore (SHU library catalogue) and clinical trials. The online databases used were as follows: ScienceDirect (Elsevier), Medline, Embase, Cochrane Library, Cinahl (EbscoHost) and the independent resource of Google Scholar.

The secondary sources were grey literature. Government department reports and information from professional bodies were used. The two databases searched were Zetoc and OpenGrey.

Overall, 77 pieces of evidence have been reviewed for this study.

Literature was included/excluded if they fulfilled the following criteria as shown in Table 2.

Literature search process

Advanced searches

For the advanced searches, the PICO system was used to identify information gained through the literature search. For each key clinical question, a PICO table was created.

Table 1. *NSCLC SABR local control rate (LCR) and overall survival (OS) rates for stage 1 tumours*[1–15]

	LCR (%)		OS (%)	
	EBRT	**SABR**	**EBRT**	**SABR**
1 year	72–85[5,6]		65·8[17]	79–81[13,15]
2 years	48–64[5,7]	94–96[10–12,14]	55·7[17]	63–72[13,15,12]
3 years	22–66[5,6,8,9]	88·1–97[13–15]	34 ± 9[18]	
5 years	13·9–56[8,9]	73 (T2)–92 (T1)[16]	21 ± 8–25·3[17,18]	62 (1B)–72 (1 A)[16]

Abbreviations: NSCLC, non-small-cell lung cancer; SABR, stereotactic ablative body radiotherapy; EBRT, external beam radiotherapy.

Table 2. *Methodology inclusion and exclusion criteria*

Inclusion criteria	Exclusion criteria
English language literature only. This is due to possible translation errors in the text or omission of important information	As the first work on lung SABR by the Karonlinska Institute in Sweden was published in 1994/95,[23] the search for evidence will be limited to articles from 1994 onwards. This will ensure that any classical pioneering research would not be omitted carelessly. However, information from the past 10 years will hold the most value, thus a further time limit was set depending upon the number of results
The primary focus of the research considers/answers the overall research question as well as the subareas of interest	They do not help to answer the overall research question
Human studies only	They are non-English language articles
Ideally randomised controlled trials quantitative in nature and relevant to the research question. This will increase the reliability and validity of the data reported. However, owing to the lack of randomised trials reported by Rowell and Williams,[24] non-randomised trials will also be used	
Articles in Press. These would have been subject to the peer review process and as such should be treated as published work	
Supplement Abstracts. These too have been subject to peer review	
Systematic Reviews and Service Evaluation retrospective studies	
Grey literature, professional websites and clinical trials relevant to the research question as well as subareas of interest	
Only studies that use 4DCT or equivalent imaging method will be reviewed for the purpose of the treatment planning aspect and future recommendations section of the literature review	

Abbreviations: SABR, stereotactic ablative body radiotherapy; 4DCT, four-dimensional computed tomography.

Advanced searching using Boolean logic was undertaken. For each PICO column, the 'keywords' were entered (using OR) and the resultant search saved. These searches were then combined (using OR) to achieve a search string that included all related term/words for that column (i.e., P: Patient/Population/Problem). Each search was date limited by refining the search by year. 'AND' was used to combine all of the 'PICO' columns.

'AND' meant that all the search words appeared in the article and 'OR' collects similar search terms. Phrase marks ("") were used to ensure searching of whole terms/keywords (i.e., stereotactic body radiotherapy).

All searches were attempted twice. The first was to establish how to use the database and to familiarise the researcher to the interface. The second being the actual search.

All searches were done using the 'Subject Heading' box ticked on and ticked off and the 'explode' tool was also used for all searches. The 'major concept/focus' tool was not used for searching as this reduced the amount of articles retrieved.

Keywords

Numerous searches and keywords were used for each column. Briefly, the summarised key searched terms can be seen in Table A1.

However, the outcome column was felt to be too broad to achieve suitable results, and thus was refined further, as seen in Table A2.

Key author searches

The following key researchers were used to identify any further research of relevance. The key researchers searched were as follows: Lagerwaard F, Timmerman R, Onishi H, Nagata Y and Hurkmans C.

Data extraction and analysis

A quantitative checklist method was used for data extraction based upon the quality assessment/ critical appraisal tool SIGN. The data were collected and analysed manually and data

synthesis was primarily via descriptive analysis of the extracted data.

DISCUSSION

SABR TP technique

Gross tumour volume (GTV) and clinical target volume (CTV) delineation

The accepted standard in the majority of SABR trials and practice is that the CTV is the GTV with no margin for microscopic disease extension.[20] In order to contour the GTV/CTV, a four-dimensional (4D) view of the tumour is required, with the breathing motion being the fourth dimension.

Internal target volume (ITV) delineation

For SABR, a four-dimensional computed tomography (4DCT) scan is preformed upon which an ITV created to take account of the breathing motion of the tumour within the patient.[25] This is defined as a tumour volume, which is obtained using a 4DCT scan on either a (i) maximum intensity projection (MIP) (this displays the 'maximum' extent of breathing, thus the maximum extent of the tumours position during the breathing cycle. It corresponds to the greatest voxel intensity values throughout the 4DCT), (ii) maximum inspiratory and expiratory scans or (iii) as contoured on all ten phases of a 4DCT scan.[20] Thus, for SABR patients the ITV includes the mobile GTV and CTV.

The tumour is contoured on an MIP created from a 4DCT scan and an average intensity projection (AIP) is created. The AIP displays the 3DCT scan with voxels equal to the arithmetic mean of the 4DCT electron density. As the voxel density values in a 3D AIP dataset are more representative of the true density values that would be present during treatment, AIPs can be used for dose calculation.

It is important that all ITV contours are reviewed by two consultant oncologists with an additional review by a consultant radiologist highly recommended and considered best practice certainly for non-standard or complex treatments.[20]

PTV delineation

A set-up margin (SM) is applied to the ITV to create the PTV for SABR treatments. This is to account for potential set-up errors and external patient movement. Numerous studies (Table A3) using 4DCT or equivalent imaging modality to delineate the ITV have used margins of 3–5 mm.[8,10,19,26–30] Other studies that have used larger margins of 5–15 mm overall have used 3D helical scanning as the imaging modality.[1,7,11,12,14,31,32] It would therefore be advisable to begin with an ITV to PTV SM of 5 mm.

OAR delineation

In addition to the OAR outlined as standard (heart, total lungs and spinal cord), the consortium also recommend that the major airways are also contoured (trachea and proximal bronchial tree, the proximal brachial tree, the proximal trachea and the proximal bronchial tree plus a further 2 cm).[20,21]

When non-coplanar beams are used the whole liver should be scanned (especially for lower lobe lesions) and additional OAR outlined (stomach, bowel, spleen, brachial plexus, oesophagus and liver). In addition, skin dose should be kept to a minimum to reduce cutaneous and subcutaneous toxicity. This is assisted by ensuring that beam entry points do not overlap on the skin.[21]

All OAR are outlined on the AIP of a 4DCT scan.[19]

Dose and fractionation schedules

Various dose fractionation schedules have been researched, ranging from a single fraction to ten or more and with a total dose (TD) of between 24 and 72 Gy.[1,7,8,10–14,17,23,31,33,34]

Dose fractionation regimes supported by the lung consortium[20,21] are as provided in Table 3.

The standard dose has been informed by the results of the RTOG 0236 trial.[35] This was a multicentre phase II study. The prescription dose was 20 Gy/fraction over 3 fractions (60 Gy TD) without proper tissue heterogeneity. Subsequent analysis with heterogeneity correction showed the actual dose to be only 54 Gy total. This dose

Table 3. *Dose/fractionation regimes supported by the Lung Consortium*[20,21]

Standard	54 Gy in 3 fractions (NB 60 Gy in 3 fractions is not allowed)
Conservative	55–60 Gy in 5 fractions
Very conservative	50–60 Gy in 8–10 fractions

Notes: Each fraction is given on alternative days and resting at weekends. This is a risk-adapted fractionation approach.

was associated with acceptable treatment-related morbidity.

The conservative dose fractionation is recommended when any a part of the PTV is in contact with the chest wall. The inter-fraction interval is recommended to be at least 40 hours, with a maximum interval of ideally 4 days between treatment fractions.[19] If the dose constraints cannot be met at 55 Gy in 5 fractions, the very conservative fractionation schedules can be used. The conformity constraints are as per 55 Gy in 5 fractions.

It is important to mention that the doses are prescribed depending on the algorithm used.[19]

Biological Effective Dose (BED) and SABR

There has been much debate and discussion on the contribution of the BED for hypofractionated SABR, particularly as the underlying mechanisms of cell killing and the biological dose–response relationship between observed effects and hypofractionation is far from understood.[36] In fact, after a review of literature, Partridge et al.[37] suggested that owing to the high daily dose it is inappropriate to employ this, as the model does not accurately explain clinical outcomes as it is based upon the radiobiology rules of conventional fractionation, which is different to hypofractionation radiation therapy.

Nevertheless, the BED remains the only well-established and researched model as an estimation of radiation effect and as such needs consideration when deciding a dose/fractionation schedule for SABR. The general consensus in literature is that higher BED over a shorter period must be given to achieve a successful LCR.[38]

Onishi et al.[19] undertook a retrospective evaluation of 245 patients. After a median follow-up (FU) of 24 months, local recurrence rate was 8·1% for a BED $\geq$ 100 Gy compared with 26·4% for a BED $<$ 100 Gy ($p < 0{\cdot}05$) and 3-year OS rate for medically operable patients was 88·4% for BED $\geq$ 100 Gy compared with 69·45 for a BED $<$ 100 Gy ($p < 0{\cdot}05$).

In two FU studies, Onishi et al.[17,16] concluded that a BED $>$ 100 Gy is considered to be a satisfactory SABR dose for stage 1 NSCLC, giving an LCR better than 85%. The BED was calculated at the isocentre and the median calculated BED was 116 Gy (range, 100–141 Gy).[17] This is echoed by Xia et al.[9]

Similarly in America, Timmerman et al.[1,7] concluded that 60 Gy over three fraction was the optimum dose. This is a calculated BED of 180 Gy. With proper tissue heterogeneity correction, the dose was 54 Gy in 3 fractions, which is a BED of 151·2 Gy.

Field arrangement (forward planned)

In order to achieve adequate target coverage using SABR while sparing critical structures including the skin surface, a multiple-beam field arrangement with the isocentre placed at the centre of the PTV is the conventional technique for SABR, which can range between 7 and 13 fields.[1,31,39–44]

All fields are non-opposing, evenly spaced and most of the literature supports a non-coplanar technique,[1,12–14,17,31,39–44] although it is also possible to use coplanar beam configuration depending on the size and location of the lesion. Han et al.[28] and Nyman et al.[45] both used a combination of co-planar and non-coplanar beams. The large limitation of non-coplanar angles is the increase in delivery time.[42] However, with the advent of flatness filter-free linacs, treatment times for SABR have been shown to be halved.[46]

Beam angles should be directed so that the spinal cord receives the lowest dose possible;

Timmerman et al.[1] asked for no more than 6 Gy/fraction and beam weightings manipulated to deliver roughly equal absolute dose to the isocentre[1] and minimum beam segment area set to 4 cm.[21]

Beam energy

The lower megavoltage energies such as 4–6 MV should be used[13,14,17,39,40,43,44,47] owing to the wide penumbra of high-energy beams, the small beam apertures used in SABR and the problems associated with build up. The plan is recommended to be calculated on a small dose grid (no more than 2·5 cm) to ensure the accuracy of the dose volume histogram calculations. For lung SABR treatments, all patients should be treated with 0·5 cm MLC or better capable linear accelerator.[32]

Tissue heterogeneity correction

Dose delivered to the PTV and OARs for SABR of lung tumours are largely influenced by tissue density corrections.[47] For SABR, it is strongly recommended that Type B algorithms should be used.[43] This is calculated based upon the electron density matrix of the attenuated tissues rather than equivalent path lengths. It is a more accurate estimation of dose near tissue/air interfaces.

Assessing the clinical acceptability of a plan

PTV conformity indices (CI)

From the review of literature there were several standard CI used to assess the clinical acceptability of a plan. They are seen in Table 4, assuming the standard prescription dose.

Prescription point

Owing to the highly inhomogeneous distributions accepted with SABR, target dose homogeneity in the PTV should be within 20%[14,17,39,40] and the target reference point dose should be defined at the isocentre of the beam.[39,40]

PTV dosimetric criteria

In order to critically assess the clinical acceptability of a plan, the conformity of the PTV coverage will be judged as given in the tables below, incorporating constraints used in the ROSEL study (Table 5).[19]

OAR dose constraints

The OAR constraints recommended by the Lung Consortium are also from the ROSEL trial (Table 6).[19] They are based on the highest

Table 4. *PTV conformity indices*

PTV coverage constraints	
Ratio calculations	
R100% [Vol (100%)/ Vol (PTV)]	The ratio of the 100% (54 Gy) isodose to the PTV. This is calculated by dividing the volume of 100% isodose of the dose prescription isodose with the PTV volume It is a calculated in order to decide whether the volume is an adequate size for SABR planning. The R100 should be a value of 1·0–1·2 for SABR treatments For acceptable values see Table 5
R50% [Vol (50%)/ Vol (PTV)]	The ratio of the 50% isodose (27 Gy) to the PTV. This is calculated by dividing the volume of 50% isodose of the dose prescription isodose with the PTV volume For acceptable values see Table 5
PTV constraints	
PTV V50%	The percentage of the volume of the PTV that receives 50% of the prescribed dose
PTV V99%	The percentage of the volume of the PTV that receives 99% of the prescribed dose. It should be above 90% for SABR treatments
PTV V100%	The percentage of the PTV that receives 100% of the prescribed dose. It should be above 95% for SABR treatments
Max dose >2 cm	The maximum dose (% of nominal prescription dose) at least 2 cm from the PTV in any direction. A D2cm (PTV + 2 cm) is created to determine this constraint For acceptable values see Table 5
Max dose	The max dose within the PTV should preferably not be <59·4 Gy (110%) or >75·6 Gy (140%). A minor deviation will be scored in cases where the max dose lies between either 56·7 and 59·4 Gy or between 75·6 and 78·3 Gy

Abbreviations: PTV, planning target volume; SABR, stereotactic ablative body radiotherapy.

Table 5. Dose conformity requirements for Type B models (54 Gy in 3 fractions and 55 Gy in 5 fractions and 60 Gy in 8 and 50 Gy in 10 fractions)[19]

	Vol (100%)/Vol (PTV)		Vol (50%)/Vol (PTV)		Max dose >2 cm		V20 (%)	
Vol (PTV) (cc)	Tolerance	Minor deviation	Tolerance	Minor deviation	Tolerance (Gy)	Minor deviation (Gy)	Tolerance	Minor deviation
54 Gy in 3 fractions								
<20	<1·25	1·25–1·40	<12	12–14	<35·1	35·1–40·5	<5	5–8
20–40	<1·15	1·15–1·25	<9	9–11	<37·8	37·8–43·2	<6	6–10
> 40	<1·10	1·10–1·20	<6	6–8	<37·8	37·8–43·2	<10	10–15
60–90	<1·10	1·10–1·20	<5	5–7	<37·8	37·8–43·2	<10	10–15
> 90	<1·10	1·10–1·20	<4·5	4·5–6·5	<37·8	37·8–43·2	<10	10–15
55 Gy in 5 fractions (and 60 Gy in 8 and 50 Gy in 10 fractions)								
<20	<1·25	1·25–1·40	<12	12–14	<35·8	35·8–41·3	<5	5–8
20–40	<1·15	1·15–1·25	<9	9–11	<38·5	38·5–44·0	<6	6–10
> 40	<1·10	1·10–1·20	<6	6–8	<38·5	38·5–44·0	<10	10–15
60–90	<1·10	1·10–1·20	<5	5–7	<38·5	38·5–44·0	<10	10–15
> 90	<1·10	1·10–1·20	<4·5	4·5–6·5	<38·5	38·5–44·0	<10	10–15

Abbreviations: Vol (100%)/Vol (PTV), ratio of prescription isodose (e.g., 54 or 55 Gy) volume to the PTV; Vol (50%)/Vol (PTV), ratio of 50% prescription isodose (27 or 27·5 Gy) volume to the PTV; Max dose >2 cm, maximum dose (% of nominal prescription dose) at least 2 cm from the PTV in any direction; V20, percentage of total lung volume—GTV receiving >20 Gy; PTV, planning target volume; GTP, gross tumour volume.

Table 6. OAR dose constraints Administrator[19]

		3 fraction regime		5 fraction regime		10 fraction regime	
Organ	Volume	Tolerance	Minor deviation	Tolerance	Minor deviation	Tolerance	Minor deviation
Spinal cord	Any point	18 Gy	>18–22 Gy	25 Gy	>25–28 Gy	25 Gy	>25–28 Gy
Oesophagus	1 cc^3	24 Gy	>24–27 Gy	27 Gy	>27–28·5 Gy	27 Gy	>27–28·5 Gy
Ipsilateral brachial plexus	1 cc^3	24 Gy	>24–26 Gy	27 Gy	>27–29 Gy	27 Gy	>27–29 Gy
Heart	1 cc^3	24 Gy	>24–26 Gy	27 Gy	>27–29 Gy	50 Gy	>50–60 Gy
Trachea/ipsilateral bronchus	1 cc^3	30 Gy	>30–32 Gy	32 Gy	>32–35 Gy	32 Gy	>32–35 Gy
Lungs—GTV	V20, V12·5	<10%, <15%	N/A	<10%, <15%	N/A	<10%, <15%	N/A

Abbreviations: OAR, organs at risk; GTP, gross tumour volume.

dose/fractionation regimes reported in lung SABR and therefore should be safe for lower BED regimes used in lung SABR.[20]

SUMMARY

From the literature, SABR is more commonly associated with conventional forward planning,[1,7,8,10,13,14,17,35] with only a few researchers using co-planar inverse planned treatments.[44,47–49] It would therefore be advisable to start any SABR as a forward planned technique initially and then progress to other techniques. Table 7 provides a summary of the technique proposed.

FUTURE DEVELOPMENTS

This review focussed on the forward planned SABR TP technique as this would be the starting point for any clinical implementation in the author's clinical department. However, presently it would seem that VMAT sets the standard for SABR planning and delivery. Ong et al.[50] compared techniques and found that VMAT achieved a superior CI and lower V45 Gy to the chest wall ($p < 0{\cdot}05$) compared with all other techniques and gave far quicker delivery times (of a 7·5 Gy fraction) than other techniques: 3·9 minutes (VMAT), 11·6 minutes (conformal SABR) and 12 minutes (fixed-field intensity-modulated radiotherapy).[50] Indeed, Naviarria et al.[51] found

Table 7. *SABR pre-treatment summary*

Patient selection		
Strict eligibility criteria	Two clinical oncologists and CT radiographers	Patient must fit the eligibility criteria as recommended by the consortium
CT scanning		
Immobilisation	CT therapy radiographers	A 'wing board' with an evacuated bag and foot rest and abdominal compression where indicated
Scanning method	CT therapy radiographers	4DCT with contrast
Scanning limit		The scan will extend from the upper cervical spine to the lower edge of the liver—this should ensure inclusion of all OAR Transverse slice thickness should be 3 mm minimum
Volume definition		
ITV	Two clinical oncologists and radiologist	Outlined on the MIP of the 4DCT scan using diagnostic imaging information including PET-CT ITV geographical position must fit the inclusion criteria by the consortium
SM (PTV)	Physics and treatment planning	0·5 cm margin added isotropically to ITV
OAR definition		
OAR delineation	Two clinical oncologists and radiologist	Outlined on the AIP Spinal cord, liver, heart, trachea, oesophagus, brachial plexus, proximal bronchial tree, the proximal brachial tree, the proximal trachea and the proximal bronchial tree plus 2 cm The consortium proposes that that the spinal cord alone is contoured to the bony limits of the vertebra However, a planning risk volume of 0·5 cm will be applied isotropically to the actual spinal cord as this is the clinical practice at the author's clinical department. This is a more generous margin than that proposed by the consortium. Its use will be assessed during the intended planning studies
Treatment planning		
Algorithm	Physics/treatment planning	A Type B (AAA) algorithm will be used on an Varian Eclipse treatment planning system
Grid size		2·5 mm
Energy		6 MV
Number of fields and arrangement		7–13 non-opposing fields. Directed to reduce OAR doses Combination of co-planar and non-coplanar
Beam modifiers		EDW and static MLCs
Dose prescription and fractionation		Standard; 54 Gy in 3 fractions (NB 60 Gy in 3 fractions is not allowed) Conservative; 55–60 Gy in 5 fractions Very conservative; 50–60 Gy in 8–10 fractions
Conformity indices		Refer to Table 4
Volume constraints		Refer to ROSEL constraints (Table 5)
OAR constraints		Refer to ROSEL constraints (Table 6)

Abbreviations: SABR, stereotactic ablative body radiotherapy; 4DCT, four-dimensional computed tomography; OAR, organs at risk; ITV, internal target volume; MIP, maximum intensity projection; PET-CT, positron emission tomography computed tomography; SM, set-up margin; PTV, planning target volume; AIP, average intensity projection.

that the median beam on time was reduced by 75% for VMAT plans and Boda-Heggemann et al.[46] found by using flatness filter-free linacs during one breath hold, treatment time was reduced by half.

These results are being echoed throughout the most current literature; VMAT gives improved highly conformal dose distributions while achieving accurate dosimetric delivery and improved treatment times.[44,47–49]

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Conflicts of Interest

None.

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APPENDIX

Table A1. *Keyword/term searches*

P Problem/Patient/Population	I Intervention/Indicator	C Comparison	O Outcome
'Non-small cell lung cancer' (indexed term)	'Stereotactic Body Radiotherapy' (indexed term)		'Local Control' (keyword)
T1a	SBRT		'Prognosis' (indexed term)
T1b	'Stereotactic Ablative Body Radiotherapy'		'Cancer Prognosis' (indexed term)
'Early Stage Lung Cancer'	SABR		'Cancer Survival' (indexed term)
'Lung Cancer'	'Stereotactic Body Radiation Therapy'		'Survival Rate' (indexed term)
	'Stereotactic Ablative Body Radiation Therapy'		'Overall Survival' (indexed term)
			'Survival' (indexed term)
			'Treatment Outcome' (indexed term)
			'Treatment Planning'
			'Treatment Planning Technique'
			'Dosimetric Analysis'
			'Volumetric Analysis'
			'Radiotherapy Treatment Planning'
			'Radiation Treatment Planning'
			'RT Treatment Planning'
			'Dosimetry' (indexed term)
			'Treatment Planning' (indexed term)

Abbreviations: SBRT, stereotactic body radiation therapy; SABR, stereotactic ablative body radiotherapy.

Table A2. *Keyword/term searches*

O Outcome					
'Target Volumes'	'Organs at Risk'	'Conformity Indices'	'Forward Planned' OR 'Forward Planning'	'Field Arrangement'	'Dose Prescription'
'Planning Target Volume'	'Dose Constraints'		'Conformity Index'	'Inverse Planned' OR 'Inverse Planning'	'Algorithm' (indexed term)
'Hypofractionated Radiotherapy'					
'Clinical Target Volumes'	Delineation	'Dose Conformity'	'Volumetric Modulated Arc Therapy'	'Photon Beam Energy'	'Prescription' (indexed term)
'Gross Tumour Volumes' 'Tumour Volume' (indexed term)	Outlining	'Dose Constraints'	'Intensity Modulated Radiotherapy' (indexed term)	'Treatment Planning' (indexed term)	'Radiotherapy' (indexed term)
'Tumour Volume' (indexed term)		'Dosimetry' (indexed term)	'Conformal Radiotherapy'	'Radiotherapy' (indexed term)	'Radiation Dose' (indexed term)
Delineation		'Dose Volume Histogram'	'Rapid Arc'	'Dosimetry' (indexed term)	'Radiation Dose Fractionation' (indexed term)
Outlining		Histogram (indexed term)	'Radiotherapy' (indexed term)		
'Internal Target Volumes'		'Treatment Planning' (indexed term)	'Treatment Planning' (indexed term)		
'Treatment Planning' (indexed term)		'Radiation Dose' (indexed term)			

Table A3. *Summary of volumes and margins applied in literature*

Study	Patient number	Imaging method	GTV	CTV	ITV	PTV/SM	Total margin (mm)
4DCT or equivalent							
de Koste et al.[52]	7	3DCT (equivalent of 4DCT) (three rapid CT scans and three slow scans co-registered)	Yes	5 mm	No	5 mm	10
Jin et al.[27]	Phantom Study	3DCT (equivalent of 4DCT) (one gated CTs at end and start of inspiration and expiration and one mid-phase)	As ITV	As ITV	Yes	3 mm (circumferentially), 5 mm superior/inferior for residual motion	3–5
Underberg et al.[26]	10	4DCT	As ITV	As ITV	Yes	3 mm	3
Gukenburger et al.[30]	24	3DCT (equivalent of 4DCT) (three dynamic CT studies in deep inspiration, deep expiration and CT scans) (15 seconds, one image per second)	As ITV	As ITV	Yes	5 mm circumferentially	5
Lagerwaard et al.[8,10]	197–206	4DCT	Yes	No	Yes	3 mm circumferentially	3
Hurkmans et al.[19]	N/A	4DCT	Yes	No	Yes (defined as the GTV on the MIP)	3–5 mm circumferentially	3–5
Han et al.[28]	24	4DCT	Yes	No	Yes (defined as the GTV on the MIP)	5 mm circumferentially	5 (circumferentially)
Li et al.[29]	133	4DCT	Yes	No	Yes (defined as the GTV on the MIP)	5 mm circumferentially	5
3DCT							
Dvorak et al.[32]	10	Helical 3DCT + D3	Not stated	Yes	No	7 mm anterior/posterior, left/right and 10 mm superior/inferior	7–10
Timmerman et al.[11] Phase I; McGarry et al.[31] Phase I; Fakiris et al.[12] Phase II; Timmerman et al.[1] Phase II; Timmerman et al.[7] Phase II (RTOG)	47–70	Helical 3DCT	Yes	As GTV	No	5 mm anterior/posterior, left/right and 10 mm superior/inferior	5–10
Onishi et al.[13]	87	Helical 3DCT	Yes	0–5 mm	2–5 mm (according to individual respiratory motion)	5 mm	7–15

Abbreviations: GTV, gross tumour volume; CTV, clinical target volume; ITV, internal target volume; PTV, planning target volume; SM, set-up margin; 4DCT, four-dimensional computed tomography; MIP, maximum intensity projection.