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Research article

Stereotactic body radiotherapy for moderately central and ultra-central oligometastatic disease: Initial outcomes

Rosie Cooke [a,b,*], Philip Camilleri [b], Kwun-Ye Chu [a,b], Séan M. O'Cathail [a], Maxwell Robinson [a,b], Frank Van Den Heuvel [a,b], Maria A. Hawkins [c]

[a] Oxford Institute for Radiation Oncology, Department of Oncology, University of Oxford, Old Road Campus Research Building, Roosevelt Drive, Oxford OX3 7DQ, United Kingdom
[b] Oxford University Hospitals NHS FT, Churchill Hospital, Old Road, Oxford OX3 7LE, United Kingdom
[c] Medical Physics and Biomedical Engineering, Malet Place Engineering Building, University College London, Gower Street, London WC1E 6BT, United Kingdom

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ABSTRACT

Background: Delivery of SBRT to central thoracic tumours within 2 cm of the proximal bronchial tree (PBT), and especially ultra-central tumours which directly abut the PBT, has been controversial due to concerns about high risk of toxicity and treatment-related death when delivering high doses close to critical mediastinal structures. We present dosimetric and clinical outcomes from a group of oligometastatic patients treated with a risk-adapted SBRT approach.

Methods: Between September 2015 and October 2018, 27 patients with 28 central thoracic oligometastases (6 moderately central, 22 ultra-central) were treated with 60 Gy in 8 fractions under online CBCT guidance. PTV dose was compromised where necessary to meet mandatory OAR constraints. Patients were followed up for toxicity and disease status.

Results: Mandatory OAR constraints were met in all cases; this required PTV coverage compromise in 23 cases, with V100% reduced to <70% in 11 cases. No acute or late toxicities of Grade $\geq$ 3 were reported. One and 2 year in-field control rates were 95.2% and 85.7% respectively, progression-free survival rates were 42.8% and 23.4% respectively, and overall survival rates were 82.7% and 69.5% respectively. No significant differences were seen in control or survival rates by extent of PTV underdosage or between moderately and ultra-central cases.

Conclusion: It appears that compromising PTV coverage to meet OAR constraints allows safe and effective delivery of SBRT to moderately and ultra-central tumours, with low toxicity rates and high in-field control rates. This treatment can be delivered on standard linear accelerators with widely available imaging technology.

Introduction

Stereotactic body radiotherapy (SBRT) is an established treatment modality for peripheral early stage non-small cell lung cancers (NSCLC) in patients who are unsuitable for surgery, achieving excellent local control rates and low toxicity [1]. More recently SBRT has emerged as an important treatment modality in the management of oligometastases, with promising outcomes following SBRT to pulmonary metastases [2]. In particular, the recent SABR-COMET trial reported an increase in median survival of 13 months associated with SBRT to oligometastatic disease [3].

The use of SBRT in treating central thoracic tumours, both primary and metastatic, has been controversial, following Timmerman et al.'s [4] phase II study showing severe toxicity and treatment-related death when treating central early stage NSCLC with 60–66 Gy in 3 fractions. This led to the definition of the "no fly zone" (NFZ): the area within 2 cm of the proximal bronchial tree (PBT) within which SBRT was not recommended. Several single-centre studies have now demonstrated that acceptable toxicity rates can be achieved when treating central tumours with lower doses per fraction [5–11].

More recently a subgroup of tumours within the central chest has been recognised as potentially being at higher risk of treatment-related toxicity, termed "ultra-central" [12], and generally defined as those tumours directly abutting the PBT. Published data on the safety of treating ultra-central tumours with SBRT is

* Corresponding author at: Oxford University Hospitals NHS FT, Churchill Hospital, Old Road, Oxford OX3 7LE, United Kingdom.
E-mail address: rosie.cooke@ouh.nhs.uk (R. Cooke).

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limited, and while some report similar toxicity rates to those in patients treated for central or peripheral tumours [12–14], others report high toxicity rates [15–17].

When treating tumours within the NFZ there is a trade-off between delivering an ablative dose to the tumour and avoiding causing excessive toxicity by overdosing OARs. There is currently no consensus regarding the best approach, with a variety of dose fractionations and OAR constraints being used, and some groups prioritising PTV dose coverage while others prioritise OAR sparing. It is therefore difficult to draw conclusions on the safety and efficacy of SBRT to central tumours.

At our centre, central pulmonary or nodal oligometastases are treated with SBRT using a risk-adapted approach: a dose fractionation of 60 Gy in 8 fractions is prescribed, and dose coverage of up to 30% of the PTV is compromised where necessary to meet mandatory OAR constraints. This study examines our approach to planning, verification and delivery of SBRT to pulmonary or nodal oligometastases within the NFZ. Specifically, we aim to investigate whether PTV coverage compromises have a significant effect on control rates or possible implications relating to survival, and whether low acute and late toxicity rates are achieved.

Materials and methods

Patients

All patients who received SBRT at our centre for oligometastases within the NFZ between September 2015 and October 2018 were included in analyses. All patients gave written informed consent for use of their information for research purposes, data was collected retrospectively and was anonymised prior to analysis. Work was carried out in accordance with the Declaration of Helsinki.

Metastases were described as ultra-central if the GTV directly abutted the PBT, or moderately central otherwise.

Treatment planning

Patients were positioned for treatment supine with arms above the head supported by a vacuum bag. A 2.5 mm slice planning scan consisting of a contrast-enhanced 3DCT and non-enhanced 4DCT was acquired using a GE Optima CT580 CT scanner and the Varian Real-Time Position Management System (Varian Medical Systems, Palo Alto, CA).

The GTV and OARs – PBT, oesophagus, heart (including pericardial sac), lungs and spinal canal – were outlined on 3DCT. An ITV was outlined using the maximum inhale and exhale phases of the 4DCT, and all other respiratory phases were reviewed to ensure the full range of tumour motion was encompassed. A 3–5 mm margin was added to the ITV to generate the PTV; choice of margin in each case was individualised by the SBRT MDT following qualitative assessment of the challenges of image matching in each individual case.

All patients received a prescribed dose of 60 Gy in 8 fractions, delivered on alternate week days. Prescription dose was not prescribed to a specific isodose line but rather by direct optimisation within the treatment planning software for prescription dose to cover 95% of PTV with compromise to meet mandatory OAR constraints as necessary. Maximum dose within PTV was constrained to greater than 120% and less than 130% of prescription to allow for suitable dose fall off associated with a SBRT treatment. Coverage criterion of 95% of PTV receiving prescription dose was relaxed to a minimum of 70% of PTV receiving prescription dose to allow for OAR constraints being respected. Mandatory dose constraints are shown in Table 3. Where the PTV overlapped with mediastinal structures, dose to the overlap portion was maintained to the highest level achievable while respecting the relevant mandatory OAR constraints, as shown in Fig. 1. Treatments were planned in Varian Eclipse v13 (Varian Medical Systems, Palo Alto, CA) using the AAA dose calculation algorithm and a 0.15 cm dose calculation grid size.

Treatment was delivered on Varian Clinac iX linear accelerators using IMRT or VMAT.

Treatment verification

Before each fraction a kV cone beam CT (CBCT) was acquired and reviewed, and a couch correction performed for any displacement of >1 mm on the right-left (RL), superior-inferior (SI) or anterior-posterior (AP) axes. The PBT position was prioritised in the online match to ensure planned doses to this structure were not exceeded, while also ensuring the lesion was well covered by the PTV. Treatment verification was performed by a team of radiation therapists (RTTs) who are experienced in reviewing CBCTs.

Treatment accuracy was assessed by analysing data on initial set-up errors (discrepancy between the initial couch position and online CBCT match) for all fractions, and residual set-up errors (displacement between the online match and an offline re-match) for fractions 1–5 for the first 10 patients in the cohort.

Follow-up

Patients were assessed for toxicity and disease status at 3, 6, 12, 18 and 24 months post-treatment, with an additional follow-up 1 month post-treatment to assess toxicity only. Toxicity was categorised according to CTCAE version 4.0, and defined as acute if occurring within 3 months of treatment, or late. Disease status was assessed using the most appropriate imaging and/or biochemical investigation according to disease histology. Progression was defined as in-field if occurring within the treated volume, locoregional if outside the treated volume but in adjacent nodal regions, or distant otherwise. Patients were followed up either at our centre or locally if referred from elsewhere.

Statistical analysis

Differences in dose metrics were assessed for significance using the Mann-Whitney U test. In-field control (IFC), progression-free survival (PFS), and overall survival (OS) were calculated using Kaplan-Meier methods, with comparisons between groups performed using the log-rank test. Patients were censored at date of last disease assessment for IFC and PFS analyses, and at date of last contact in analyses of OS. Statistical analyses were performed using R (R Foundation for Statistical Computing, Vienna, Austria). A p-value of < 0.05 was considered to represent statistical significance.

Results

Patient and tumour characteristics

Twenty-seven patients were included in analyses. Median age was 71 years (range 38–89 years), 11 were female and 16 male. Most frequent primary sites were colorectal (16, 59.3%) and renal (5, 18.5%). Patient details are shown in Table 1.

Tumour characteristics are summarised in Table 2. One patient had 2 central tumours treated concurrently. Twenty-two (78.6%) ultra-central and 6 (21.4%) moderately central tumours were treated, 10 (35.7%) were pulmonary metastases and 18 (64.3%) were nodal: 8 (29.6%) mediastinal and 10 (35.7%) hilar. Tumour locations in relation to the PBT are illustrated in Fig. 2.

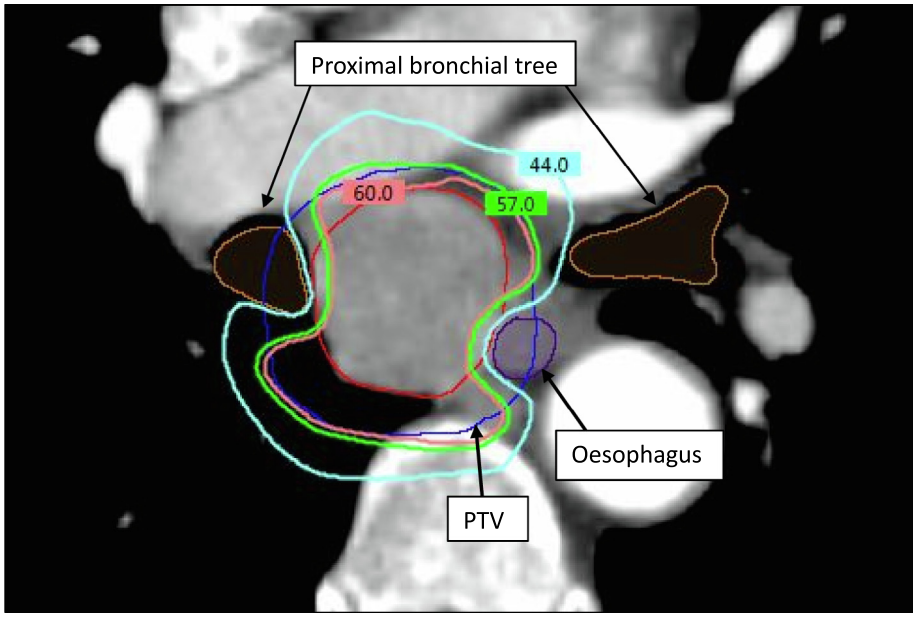

Fig. 1. Axial image from planning CT for a case where PTV overlapped with proximal bronchial tree and oesophagus, requiring compromise to PTV dose coverage. Isodose lines represent absolute dose in Gray.

Table 1
Characteristics of cohort.

	n	%	Median	Range
Primary site				
Colorectal	16	59.3		
Renal	5	18.5		
Lung	2	7.4		
Melanoma	1	3.7		
Pancreas	1	3.7		
Prostate	1	3.7		
Thyroid	1	3.7		
Performance status				
0	13	48.1		
1	14	51.9		
Lung function				
FEV1 %			93.2	59.1–127.0
FVC %			98.3	74.9–148.0
Previous lung treatment				
None	10	37.0		
Surgery	13	48.1		
Radiofrequency ablation (RFA)	2	7.4		
Surgery & RFA	2	7.4		
Previous chemotherapy				
Yes	16	59.3		
No	11	40.7		
Total	27			

GTV volumes ranged from 0.5 cm^3 to 48.3 cm^3 (median 6.6 cm^3). GTV motion on 4DCT ranged between 0 and 14 mm longitudinally (median 6 mm), 0 and 11 mm laterally (median 3 mm), and 0 and 16 mm anteroposteriorly (median 3 mm). An ITV to PTV margin of 3 mm was used in 10 cases, and 5 mm was used in 18 cases. PTV volumes ranged from 8.3 cm^3 to 106.4 cm^3 (median 32.8 cm^3), and 26 (92.9%) PTVs overlapped with mediastinal structures: 25 (89.3%) with the PBT, 13 (46.4%) with the heart, and 3 (10.7%) with the oesophagus. The volume of PTV-OAR overlap ranged from 0.0 cm^3 to 25.1 cm^3 (median 2.1 cm^3), which was between 0.0% and 48.6% of the total PTV volume (median 6.3%).

Dosimetry

A PTV D95% ≥100% of prescribed dose was achieved in only 4 (14.3%) cases (3 moderately central, 1 ultra-central); for the remaining 24 (85.7%) cases it was necessary to underdose the PTV to meet mandatory OAR constraints. A significantly higher PTV D95% was achieved for moderately than ultra-central cases, and similarly for GTV and ITV D95%, as shown in Table 3. The volume of PTV receiving 100% of prescription dose ranged from 35.5% to 99.5%, was significantly higher for moderately than ultra-central cases, and was <70% in 11 cases, all ultra-central. Minimum dose delivered to 0.1 cm^3 of the PTV ranged from 32.1 Gy to 60.5 Gy, with significantly higher minimum doses delivered to moderately than ultra-central cases, see Table 3. Median PTV dose was >60 Gy for all moderately central cases, and all but 3 ultra-central cases.

For the non-overlap portion of the PTV, minimum dose to 0.1 cm^3 was again significantly higher in moderately central than ultra-central cases. The volume of non-overlap PTV receiving 100% prescription dose was significantly lower for ultra-central cases and <70% in 6 cases.

Median D95% to GTV was 88.3% for cases treated with a 3 mm PTV margin (range 74.1–109.1%) and for those with a 5 mm margin median D95% was 89.7% (range 70.7–117.9%). For ITV, median D95% was 73.2% (range 80.9–107.6%) for 3 mm margin and 76.1% (range 68.0–118.3%) for 5 mm margin. Differences in D95% for cases treated with 3 mm and 5 mm margins were non-significant ($p = 0.90$ and $p = 0.13$ for GTV and ITV respectively).

OAR doses were kept below mandatory constraints in all cases. All OAR dose metrics, with the exception of lung V20Gy, were higher for ultra-central than moderately central cases, as shown in Table 3. Differences were significant for PBT and spinal canal.

Two patients received concurrent SBRT to an ipsilateral peripheral pulmonary metastasis. In one case the peripheral GTV abutted the central GTV and both were encompassed in a single PTV. In the other case separate plans were delivered, with the peripheral tumour receiving 60 Gy in 5 fractions. Cumulative doses from the two plans were used in analyses.

Set-up error

The mean (range) absolute initial set-up error was 2.0 mm (0–12 mm) on the RL axis, 4.0 mm (0–17 mm) on the SI axis, and

Table 2
Characteristics of tumours treated in the cohort.

	n	%	Median	Range
Tumour location				
Moderately central	6	21.4		
Ultra-central	22	78.6		
Metastasis type				
Lung	10	35.7		
Mediastinal node	8	28.6		
Hilar node	10	35.7		
OARs overlapped by PTV				
None	2	7.1		
PBT	13	46.4		
Oesophagus	0	0.0		
Heart	1	3.6		
PBT & oesophagus	0	0.0		
PBT & heart	9	32.1		
Oesophagus & heart	0	0.0		
PBT, oesophagus & heart	3	10.7		
GTV volume (cm^3)			6.6	0.5–48.3
PTV volume (cm^3)			32.8	8.3–106.4
Overlapping PTV volume				
cm^3			2.1	0.0–25.1
% of PTV			6.3	0.0–48.6
Non-overlapping PTV volume (cm^3)			28.9	6.0–94.3
Total	28			

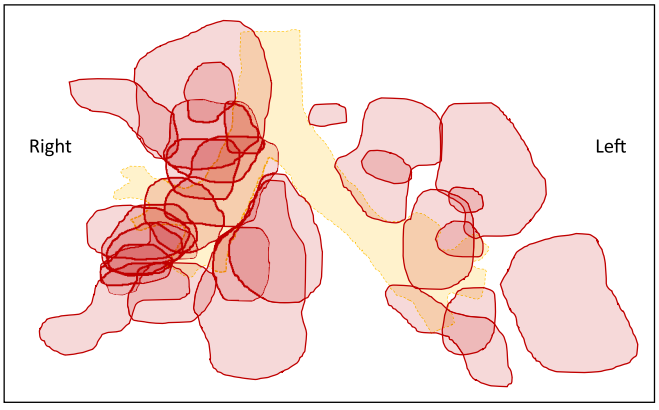

Fig. 2. Illustration of approximate location and size of GTVs (red, solid outline) with respect to the proximal bronchial tree (orange, dashed outline). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

4.4 mm (0–17 mm) on the AP axis. Additional CBCT imaging was required at 15 (6.9%) fractions: in 13 cases this was following correction of a large displacement, in 1 case following repositioning of the patient due to excessive rotation, and in 1 case following an equipment fault. Mean (range) absolute residual set-up error was 0.4 mm (0–2 mm) RL, 0.8 mm (0–3 mm) SI, and 0.5 mm (0–2 mm) AP.

Follow-up

Median follow-up for disease status was 11.6 months (interquartile range 6.5–19.4 months). Two patients (7.4%) experienced in-field progression, both of whom had ultra-central hilar nodal metastases treated. The volume of PTV receiving prescription dose in these two patients was 65.5% and 62.2%. In one patient this was the first and only progression event, occurring at 14.3 months following SBRT. The other patient had distant progression first at 2.6 months, with in-field progression occurring 5.1 months following SBRT. Locoregional progression occurred in 6 patients (22.2%). Distant progression occurred in 13 patients (48.1%). Four patients (14.8%) have received systemic therapy following progression.

One and 2 year IFC rates were 95.2% (95% confidence interval [CI] 86.6–100.0%) and 85.7% (95% CI 68.3–100.0%) respectively. One and 2 year PFS rates were 42.8% (95% CI 26.1–70.1%) and 23.4% (95% CI 9.8–55.9%) respectively. There were no significant differences in IFC or PFS by tumour location, metastasis type, primary site, GTV volume or PTV coverage (see Table 4). Kaplan-Meier plots for IFC and PFS are shown in Fig. 3.

Median follow-up for vital status was 14.3 months (interquartile range 9.4–24.6 months). Six patients (22.2%) died during follow-up; disease progression had occurred in 5 of these cases. One and 2 year OS rates were 82.7% (95% CI 68.6–99.7%) and 69.5% (95% CI 51.0–94.7%) respectively; Fig. 3 shows the Kaplan-Meier plot for OS. Patients whose primary disease was colorectal or renal had significantly higher 1 year OS rates than those with other primary diagnoses, as shown in Table 4. No other significant differences in OS were seen with varying tumour characteristics or dose coverage.

Treatment was tolerated well, with no Grade $\geq$ 3 toxicities observed. Three (11.1%) cases of Grade 2 acute toxicity were seen, all in patients treated for ultra-central tumours: 1 Grade 2 dysphagia which was seen at 1 month following SBRT and had resolved by the 3 month follow-up, and 2 cases of Grade 2 radiation pneumonitis which resolved with steroid treatment. One (3.7%) Grade 2 late toxicity has been reported; this was fatigue, which was reported at 6 months and had resolved by the subsequent follow-up.

Discussion

Oligometastasis is increasingly being recognised as a state during which radical local therapy can lead to long-term control and delay the need for systemic therapy with its associated toxicities, maximising quality of life. Surgical resection of metastases in the central chest is a major undertaking with high risk of complications [18], and will be unsuitable in many cases due to co-morbidities. Data on treating central thoracic metastases with SBRT is limited, as the delivery of SBRT within the NFZ has been controversial since an early study in NSCLC demonstrated severe toxicity and high rates of treatment-related death [4]. Although several retrospective studies have now demonstrated that moderately central primary and metastatic tumours can be treated safely

Table 3
Dosimetry achieved in moderately and ultra-central cases, compared using the Mann-Whitney U test.

	Mandatory dose constraint	Moderately central		Ultra-central			All	
		Median	Range	Median	Range	*p value*	Median	Range
PTV								
D95% (%)		100.4	96.1–103.2	73.6	64.3–100.0	*<0.001*	75.9	64.3–103.2
V100% (%)		91.9	81.7–99.5	70.3	35.5–95.0	*0.001*	77.4	35.5–99.5
Minimum dose (Gy)		54.2	44.3–60.5	41.2	32.1–46.9	*<0.001*	42.0	32.1–60.5
Maximum dose (Gy)		74.2	71.9–77.1	77.0	67.5–83.5	*0.10*	76.2	67.5–83.5
Median dose (Gy)		66.7	63.5–68.2	64.4	56.7–68.8	*0.13*	64.5	56.7–68.8
Non-overlapping portion of PTV								
V100% (%)		96.3	83.7–99.5	78.3	42.1–95.4	*0.001*	82.6	42.1–99.5
Minimum dose (Gy)		57.3	46.3–60.5	42.9	32.1–49.5	*<0.001*	44.2	32.1–60.5
Maximum dose (Gy)		74.2	71.9–77.1	76.7	65.9–81.5	*0.19*	76.2	65.9–81.5
Median dose (Gy)		66.7	64.3–68.2	65.1	58.1–69.1	*0.19*	65.2	58.1–69.1
GTV D95% (%)		112.8	99.9–117.9	86.3	70.7–114.4	*0.003*	89.1	70.7–117.9
ITV D95% (%)		112.3	99.2–118.3	83.1	68.0–109.7	*0.003*	86.8	68.0–118.3
Organs at risk								
PBT Dmax 0.5 cm^3 (Gy)	44 Gy	27.4	13.7–43.9	43.3	34.4–44.0	*0.045*	42.9	13.7–44.0
Oesophagus Dmax 0.5 cm^3 (Gy)	40 Gy	17.8	10.7–24.9	22.3	14.1–39.9	*0.10*	19.6	10.7–39.9
Heart Dmax 0.5 cm^3 (Gy)	60 Gy	26.4	4.6–60.0	37.9	1.1–60.0	*1.00*	34.5	1.1–60.0
Spinal canal 0.1 cm^3 (Gy)	32 Gy	10.1	5.5–16.6	20.5	10.9–30.5	*0.001*	19.0	5.5–30.5
Lungs excluding GTV V20Gy (%)	10%	4.7	4.1–8.0	4.0	1.2–9.6	*0.55*	4.1	1.2–9.6
Lungs excluding GTV V12.5 Gy (%)	15%	8.3	6.9–13.3	9.2	3.2–15.0	*0.80*	9.0	3.2–15.0

Table 4
Kaplan-Meier estimates of in-field control, progression-free survival and overall survival rates, compared using the log-rank test.

	1 year IFC	95% CI	1 year PFS	95% CI	1 year OS	95% CI
Tumour location						
Moderately central	100.0		37.5	8.4–100.0	75.0	42.6–100.0
Ultra-central	94.1	83.6–100.0	42.4	24.7–72.7	84.4	69.7–100.0
p value	*0.49*		*0.59*		*0.22*	
Metastasis type						
Lung	100.0		77.8	54.9–100.0	87.5	67.3–100.0
Mediastinal node	100.0		16.7	2.8–99.7	68.6	40.3–100.0
Hilar node	88.9	70.6–100.0	36.0	15.0–86.5	88.9	70.6–100.0
p value	*0.31*		*0.27*		*0.09*	
Primary site						
Colorectal	92.3	78.9–100.0	47.7	28.1–81.0	85.7	69.2–100.0
Renal	100.0		0.0		100.0	
Other	100.0		40.0	9.4–100.0	50.0	18.8–100.0
p value	*0.53*		*0.79*		*0.02*	
GTV volume						
<7.5 cm^3	90.9	75.4–100.0	45.6	23.3–89.2	90.0	73.2–100.0
≥7.5 cm^3	100.0		38.1	17.9–81.1	75.0	54.1–100.0
p value	*0.79*		*0.10*		*0.49*	
Minimum PTV dose						
<42 Gy	100.0		43.5	22.8–83.0	82.5	63.1–100.0
≥42 Gy	88.9	70.6–100.0	43.7	20.9–91.8	83.3	64.7–100.0
p value	*0.81*		*0.89*		*0.99*	
PTV coverage						
V100% <70%	88.9	70.6–100.0	50.5	27.3–93.3	80.8	60.0–100.0
V100% >70%	100.0		35.6	15.8–80.5	84.6	67.1–100.0
p value	*0.13*		*0.95*		*0.78*	
Overall	95.2	86.6–100.0	42.8	26.1–70.1	82.7	68.6–99.7

using moderated dose fractionations [5,6,8–10,18], other studies report high toxicity rates [19,20].

The evidence for ultra-central tumours is more equivocal. Three studies have reported no significant difference in toxicity following SBRT to moderately central and ultra-central (and in one case peripheral) lesions [12–14]. However others have reported increased rates of toxicity and treatment-related death compared with moderately central tumours [15–17]. Chaudhuri et al. [21] suggest that these high toxicity rates may be due to increased risk of haemorrhage caused by use of anti-angiogenic, anti-coagulant or anti-platelet medications, tumour invasion of proximal bronchi or pulmonary vasculature, or high doses to these structures. The variation in reported toxicity rates may also be partly due to the lack of consensus on the most appropriate dose fractionation schedule, OAR constraints and method of managing the trade-off between PTV coverage and OAR sparing. The use of the terms "central" and "ultra-central" within the literature, as summarised by Adebahr et al. [22] and Rim et al. [23] respectively, is also inconsistent which may result in comparisons between patient groups that are not directly comparable.

By prioritising mandatory OAR constraints, we have demonstrated an apparent initial low toxicity rate for patients who received SBRT to moderately and ultra-central tumours, as per our definition. The compromise to PTV coverage required to meet these constraints exceeded our criterion of 70% PTV receiving 100% prescribed dose in several cases. Although PTV coverage was <70% in both cases of in-field failure, no significant difference in in-field control was found based on whether or not this criterion was met. In-field control rates in this cohort are comparable to those seen in another series of patients receiving 60 Gy in 8 frac-

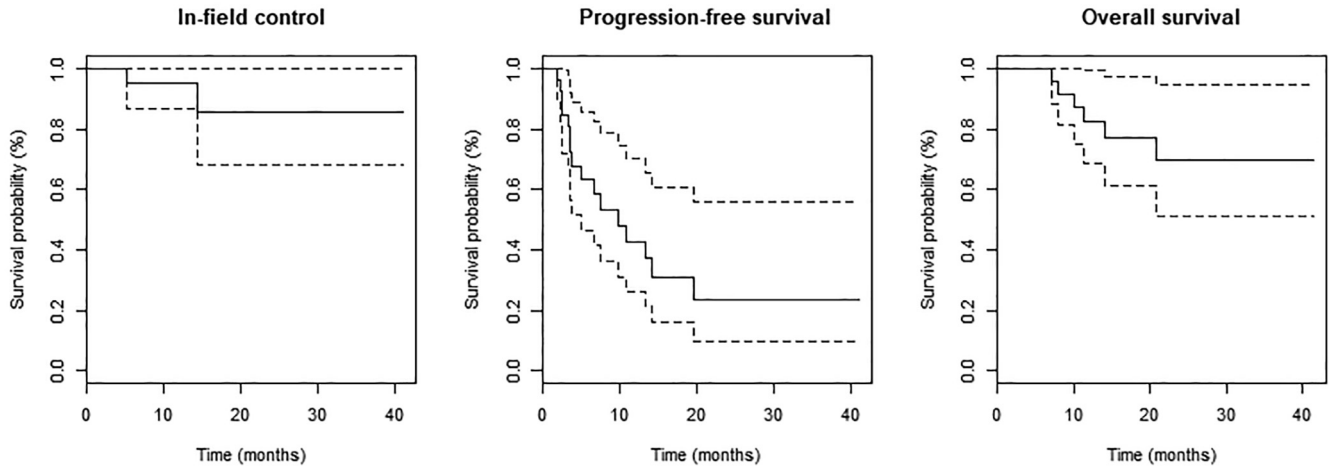

Fig. 3. Kaplan Meier plots of in-field control, progression-free survival and overall survival for the whole cohort, with 95% confidence interval.

tions to central thoracic tumours [6], as well as cohorts receiving a range of more intensive dose fractionations [7,9–12,15,16,24]. Similar in-field control rates were also seen in patients treated with 57.5–60 Gy in 5 fractions in the RTOG0813 trial [25]. OS rates in this cohort are comparable with rates from other metastasis-only series [8,26]. We saw no significant difference in in-field control or survival between moderately and ultra-central cases. Other groups comparing these groups have found no significant difference in control or survival [12–14,16]; Chaudhuri et al. [12] also found no significant differences in comparisons with peripheral cases. The only statistically significant difference in control or survival identified in our cohort was a higher OS rate in patients with colorectal or renal diagnoses compared with other primary diagnoses. No difference was seen between control rates in these groups, and due to the variety of diagnoses in the "other" category it is difficult to draw any meaningful conclusion from this result.

Due to dose being sculpted around OAR-PTV overlap and OAR doses often being near constraints, treatment delivery must be highly accurate, to ensure that delivered dose distributions are as close as possible to those planned. The small residual set-up errors demonstrate that restricting SBRT image matching to an experienced team of RTTs can ensure consistent and accurate delivery of central thoracic SBRT. Treatments in this study were delivered under 3DCBCT image guidance with no respiratory motion management, however, and increased precision could be achieved with more specialised image guidance such as 4DCBCT or real-time fiducial tracking, or motion management techniques such as active breathing control or deep inspiration breath-hold [27]. A recent study [28] demonstrates the potential of stereotactic MR-guided adaptive radiotherapy to improve PTV coverage and OAR sparing when treating ultra-central tumours. However, it is unclear the degree to which motion management and/or specialist image guidance may improve outcomes through increased precision or simply through reduction in PTV volume leading to reduced need for dose compromise in the first instance. Future research in this area would be prudent.

A limitation of this work is that a variable 3/5mm PTV margin has been used and this is a potential confounding factor when linking degree of PTV compromise with outcomes. However, GTV/ITV compromise was comparable when looking at patients treated with a 3 or 5 mm PTV margin, with no significant difference in D95% for either volume, and therefore delivered dose to tumour was similarly compromised irrespective of PTV margin used.

Our study is limited by a small number of patients and short follow-up times in some cases, which could result in being underpowered to detect significant differences between groups. It is also possible that toxicity rates may have been underestimated due to difficulties in obtaining complete follow-up information for some patients being followed up at their referring hospital. However, the use of SBRT in this patient population is not widespread and a cohort of this size adds to the current body of work supporting delivery of SBRT.

SBRT appears to be a promising local treatment option for central chest oligometastases, but the range of approaches taken, discrepancies in terminology, and heterogeneity of patient populations within the published literature make it difficult to reach firm conclusions on the safety of SBRT in this scenario. It is important that consensus is reached to harmonise SBRT delivery in this clinical context in order to provide patients with the best chance of long-term control and low risks of toxicity. Where possible clinical trials such as LungTech [22] and SUNSET [29] should be supported to help achieve this aim.

Our results from a strictly defined patient group in whom SBRT was planned and delivered consistently provide important additional evidence for the efficacy and safety of SBRT within the NFZ. Furthermore, we present novel data on dosimetry achieved when compromising PTV coverage to meet OAR constraints, details on an effective treatment verification approach which ensures these doses are delivered accurately, and reassuring outcomes demonstrating that this approach resulted in a low toxicity rate and did not appear to significantly affect control or survival. While specialised equipment and novel technological developments have the potential to improve treatment precision which may lead to improvements in control and decreased toxicity, this study demonstrates that SBRT can be safely and effectively delivered to central thoracic tumours on a conventional linear accelerator, with no respiratory management, and with widely available imaging technology.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] Murray P, Franks K, Hanna GG. A systematic review of outcomes following stereotactic ablative radiotherapy in the treatment of early-stage primary lung cancer. Br J Radiol 2017;90(1071):20160732.

[2] Siva S, Slotman BJ. Stereotactic ablative body radiotherapy for lung metastases: where is the evidence and what are we doing with it? Semin Radiat Oncol 2017;27(3):229–39.

[3] Palma DA, Olson R, Harrow S, Gaede S, Louie AV, Haasbeek C, et al. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial. Lancet 2019;393(10185):2051–8.

[4] Timmerman R, McGarry R, Yiannoutsos C, Papiez L, Tudor K, DeLuca J, et al. Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. J Clin Oncol 2006;24(30):4833–9.

[5] Davis JN, Medbery C, Sharma S, Pablo J, Kimsey F, Perry D, et al. Stereotactic body radiotherapy for centrally located early-stage non-small cell lung cancer or lung metastases from the RSSearch((R)) patient registry. Radiat Oncol 2015;10:113.

[6] Haasbeek CJA, Lagerwaard FJ, Slotman BJ, Senan S. Outcomes of stereotactic ablative radiotherapy for centrally located early-stage lung cancer. J Thorac Oncol 2011;6:2036–43.

[7] Mangona VS, Aneese AM, Marina O, Hymas RV, Ionascu D, Robertson JM, et al. Toxicity after central versus peripheral lung stereotactic body radiation therapy: a propensity score matched-pair analysis. Int J Radiat Oncol Biol Phys 2015;91(1):124–32.

[8] Mazzola R, Ruggieri R, Figlia V, Rigo M, Giaj Levra N, Ricchetti F, et al. Stereotactic body radiotherapy of central lung malignancies using a simultaneous integrated protection approach: A prospective observational study. Strahlenther Onkol 2019.

[9] Modh A, Rimner A, Williams E, Foster A, Shah M, Shi W, et al. Local control and toxicity in a large cohort of central lung tumors treated with stereotactic body radiation therapy. Int J Radiat Oncol Biol Phys 2014;90(5):1168–76.

[10] Nuyttens JJ, van der Voort NC, van Zyp J, Praag S, van Aluwini RJ, Klaveren C, et al. Outcome of four-dimensional stereotactic radiotherapy for centrally located lung tumors. Radiother Oncol 2012;102(3):383–7.

[11] Park HS, Harder EM, Mancini BR, Decker RH. Central versus peripheral tumor location: influence on survival, local control, and toxicity following stereotactic body radiotherapy for primary non-small-cell lung cancer. J Thorac Oncol 2015;10(5):832–7.

[12] Chaudhuri AA, Tang C, Binkley MS, Jin M, Wynne JF, von Eyben R, et al. Stereotactic ablative radiotherapy (SABR) for treatment of central and ultra-central lung tumors. Lung Cancer 2015;89(1):50–6.

[13] Chang JH, Poon I, Erler D, Zhang L, Cheung P. The safety and effectiveness of stereotactic body radiotherapy for central versus ultracentral lung tumors. Radiother Oncol 2018;129(2):277–83.

[14] Raman S, Yau V, Pineda S, Le LW, Lau A, Bezjak A, et al. Ultracentral tumors treated with stereotactic body radiotherapy: single-institution experience. Clin Lung Cancer 2018;19(5):e803–10.

[15] Haseltine JM, Rimner A, Gelblum DY, Modh A, Rosenzweig KE, Jackson A, et al. Fatal complications after stereotactic body radiation therapy for central lung tumors abutting the proximal bronchial tree. Pract Radiat Oncol 2016;6(2):e27–33.

[16] Nguyen KNB, Hause DJ, Novak J, Monjazeb AM, Daly ME. Tumor control and toxicity after SBRT for ultracentral, central, and paramediastinal lung tumors. Pract Radiat Oncol 2019;9(2):e196–202.

[17] Tekatli H, Haasbeek N, Dahele M, De Haan P, Verbakel W, Bongers E, et al. Outcomes of hypofractionated high-dose radiotherapy in poor-risk patients with "ultracentral" non-small cell lung cancer. J Thorac Oncol 2016;11(7):1081–9.

[18] Senthi S, Haasbeek CJ, Slotman BJ, Senan S. Outcomes of stereotactic ablative radiotherapy for central lung tumours: a systematic review. Radiother Oncol 2013;106(3):276–82.

[19] Aoki S, Yamashita H, Haga A, Ota T, Takahashi W, Ozaki S, et al. Stereotactic body radiotherapy for centrally-located lung tumors with 56 Gy in seven fractions: A retrospective study. Oncol Lett 2018;16(4):4498–506.

[20] Lindberg K, Bergström P, Brustugun OT, Engelholm S, Grozman V, Hoyer M, et al. Lewensohn, OA24.05 the Nordic HILUS-trial - first report of a phase II trial of SBRT of centrally located lung tumors. J Thoracic Oncol 2017;12(1).

[21] Chaudhuri AA, Chen K, Diehn M, Loo Jr BW. Stereotactic ablative radiotherapy for central and ultra-central lung tumors. Ther Radiology Oncology 2019;3.18-18.

[22] Adebahr S, Collette S, Shash E, Lambrecht M, Le Pechoux C, Faivre-Finn C, et al. LungTech, an EORTC Phase II trial of stereotactic body radiotherapy for centrally located lung tumours: a clinical perspective. Br J Radiol 2015;88(1051):20150036.

[23] Rim CH, Kim Y, Kim CY, Yoon WS, Yang DS. Is stereotactic body radiotherapy for ultra-central lung tumor a feasible option? A systemic review and meta-analysis. Int J Radiat Biol 2019:1–9.

[24] Song SY, Choi W, Shin SS, Lee SW, Ahn SD, Kim JH, et al. Fractionated stereotactic body radiation therapy for medically inoperable stage I lung cancer adjacent to central large bronchus. Lung Cancer 2009;66(1):89–93.

[25] Bezjak A, Paulus R, Gaspar LE, Timmerman RD, Straube WL, Ryan WF, et al. Safety and efficacy of a five-fraction stereotactic body radiotherapy schedule for centrally located non–small-cell lung cancer: NRG oncology/RTOG 0813 trial. J Clin Oncol 2019;37(15):1316–25.

[26] Lischalk JW, Malik RM, Collins SP, Collins BT, Matus IA, Anderson ED. Stereotactic body radiotherapy (SBRT) for high-risk central pulmonary metastases. Radiat Oncol 2016;11:28.

[27] Caillet V, Booth JT, Keall P. IGRT and motion management during lung SBRT delivery. Phys Med 2017;44:113–22.

[28] Henke LE, Olsen JR, Contreras JA, Curcuru A, DeWees TA, Green OL, et al. Stereotactic MR-guided online adaptive radiation therapy (SMART) for ultracentral thorax malignancies: results of a phase 1 trial. Adv Radiat Oncol 2019;4(1):201–9.

[29] Giuliani M, Mathew AS, Bahig H, Bratman SV, Filion E, Glick D, et al. SUNSET: stereotactic radiation for ultracentral non-small-cell lung cancer-a safety and efficacy trial. Clin Lung Cancer 2018;19(4):e529–32.