Radiotherapy and Oncology 134 (2019) 178–184

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

Risk-adapted stereotactic ablative radiotherapy for central and ultra-central lung tumours

Alexis Lenglet [a,b,*,1], Marie-Pierre Campeau [a], Dominique Mathieu [a], Houda Bahig [a], Louise Lambert [a], Toni Vu [a], David Roberge [a], Laurent Bilodeau [a], Edith Filion [a]

[a] Centre Hospitalier de l'Université de Montréal, Canada; and [b] Institut du Cancer de Montpellier, France

ARTICLE INFO

Article history:
Received 5 September 2018
Received in revised form 29 January 2019
Accepted 30 January 2019
Available online 18 February 2019

Keywords:
Stereotactic body radiation therapy
Stereotactic ablative radiotherapy
Central Tumours
Non-small-cell lung cancer
Toxicity

ABSTRACT

Background: SABR is a widely accepted treatment for early-stage lung cancer but there are safety concerns for central and ultra-central tumours. Herein we report our experience using risk-adapted fractionation (prescribed doses: 40–60 Gy in 3–8 fractions) with prioritization of dose to organs at risk.

Methods: Patient declining or unsuitable for surgery with primitive or recurrent lung cancer were included. Tumours inside a 2 cm area around proximal bronchial tree (PBT) were classified as central while tumours with PTV overlapping PBT, oesophagus, great vessels and pericardial pleura were classified as ultra-central. We assessed overall survival (OS), disease-free survival (DFS), local control (LC) and toxicities.

Results: From 2009 to 2016, 137 patients were treated (median age: 75 years), with 60 central and 77 ultra-central tumours. Median follow-up was 36 months. Median tumour size, GTV and PTV were 2.5 cm (0.9–7), 7.8 cm^3 (0.7–94.2) and 30.6 cm^3 (6.5–274.3), respectively. For the whole population, median OS and DFS were 46 months and 33 months. One- and 2-years LC rates were 95% and 81%. Median OS between central and ultra-central tumours was statistically different with 57 vs 37 months (HR 0.48, $p = 0.017$), but LC was not different among them. We observed 4 Grade 3 and 6 Grade 5 toxicities (no grade 4).

Conclusions: SABR for central and ultra-central tumours is associated with good OS, DFS and LC rates, with 7.3% grade 3–5 toxicities. Central tumours had a better prognosis in our cohort.

 Radiotherapy and Oncology 134 (2019) 178–184

Stereotactic ablative radiotherapy is a therapy of choice in management of early stage lung cancer. However, in 2006, RTOG 0236 phase II trial raised safety concerns for SABR of centrally located lung tumours. Other publications reinforced this hypothesis, describing partial or complete bronchial strictures, proximal bronchial tree necrosis (PBT, defined as last 2 cm of trachea, carina, right and left main bronchi and bronchial tree up to the second bifurcation), fatal haemoptysis and oesophageal fistulas, thus leading to dosimetric guidelines to avoid such severe late effects [1–5].

Firstly the "no-fly zone" was defined as an isotropic 2 cm expansion around PBT. Later, the RTOG 0813 study expanded this definition to include tumours immediately adjacent to mediastinal or pericardial pleura ("PTV touching pleura"). For the International Association for the Study of Lung Cancer, a central tumour is a lesion within a 2 cm isotropic expansion of any mediastinal critical structure (PBT, oesophagus, heart, brachial plexus, major vessels, spinal cord, phrenic and recurrent laryngeal nerve) [6].

Moreover, the concept of ultra-central tumours was developed for lesions with GTV or PTV directly abutting or overlapping the PBT or oesophagus. Definition of central and ultra-central tumours varies among authors [6–8].

To reduce the incidence of those toxicities, less intensive dose fractionation were used. Modh et al. have published the largest central tumours cohort with 125 patients treated with doses ranging from 45 to 50 Gy in 4 to 5 fractions. Local control stayed high, with 6% grade 3–4 toxicities and two fatal events [9].

Nowadays, central tumours can safely be treated with an adapted dose fractionation. In our institution, we prioritize organs-at-risk, as we decrease dose prescription to meet dose con-

Abbreviations: C, central tumours; CCI, Charlson's Comorbidity Index; CTCAE, Common Terminology Criteria for Adverse Events; PBT, proximal bronchial tree; R-SABR, Robotic Stereotactic Ablative Radiotherapy; UC, ultra-central tumours; VMAT-SABR, Volumetric Modulated Arc Therapy Stereotactic Ablative Radiotherapy.

* Corresponding author at: Centre. Hospitalier de l'Université de Montréal, 1055 rue Sanguinet, Montréal, H2X 0C1 Québec, Canada.
E-mail address: alexis.lenglet@icm.unicancer.fr (A. Lenglet).
[1] Present address: Institut du Cancer de Montpellier, 208 Avenue des Apothicaires, 34298 Montpellier, France

https://doi.org/10.1016/j.radonc.2019.01.035
0167-8140/

straints. Moreover, we wanted to compare outcome and toxicities between central and ultra-central tumours. To address this question, we assessed survival, local control and toxicities in our cohort of central and ultra-central tumours.

Material and methods

Patients and tumours eligibility

We retrospectively reviewed our lung SABR database after approval by our institutional board of ethics.

Patients with primary or recurrent lung cancer, medically inoperable or declining surgical resection were included. Recurrent lung cancer was defined by appearance of a new lesion of same histology from 6 months up to 5 years after a first treatment for lung cancer (performed by surgery or radiation therapy ± chemotherapy). New lesions after 5 years were also included but classified as new primary.

Diagnosis was performed either by biopsy, cytology or a pattern of gross lesion progression on lung computed tomography (CT), repeated every 3–12 months associated with an increase in standardized uptake value on fluorodeoxyglucose (18F) positron emission tomography (PET) if pathologic sampling was not achievable.

Classification was done using 2010 American Joint Committee on Cancer staging system (7th edition). Staging was performed before treatment using body CT, brain magnetic resonance imaging (MRI) and 18F-PET. Patients with pathologically proved or suspected nodal invasion (enlarged nodes on chest CT with 18F uptake) were excluded. Patients with synchronous metastases were also excluded. All NSCLC subtypes of lung cancer were accepted, but metastases from other primary sites were excluded.

Central and ultra-central classification of tumours

Tumours were classified as central if their GTV was within a 2 cm area around the PBT or mediastinal pleura, as in RTOG 0813. If their PTV (5 mm isotropic expansion around the GTV) was abutting or overlapping PBT, trachea, great vessels (aorta, pulmonary arteries, superior and inferior cava veins) or pericardial pleura, they were classified as ultra-central.

Each treatment planning CT was reviewed by two radiation oncologists to ensure that rigorous anatomical landmarks (previously described by Kong et al. in his thoracic atlas for organ-at-risk) were applied to avoid misclassification [10].

SABR planning and treatment

Treatment was performed either with Robotic SABR (R-SABR, using a CyberKnife®, Accuray, Sunnyvale, USA) or Volumetric Modulated Arc Therapy SABR (VMAT-SABR, using a Truebeam®, Varian Medical Systems, Palo Alto, USA or a TomoTherapy®, Accuray, Sunnyvale, USA) at physician's discretion. All patients had a 3-mm slice thickness 4-dimensional non-contrast planning CT. Both lungs, oesophagus, trachea, main and secondary bronchi up to the second bifurcation, heart and great vessels (aorta, superior and inferior cava veins, pulmonary arteries) were delineated on average phase of planning CT.

GTV was delineated using window width of 1600 Hounsfield units (HU) and window level of −600 HU. A geometric 5 mm expansion around the GTV was used to create the PTV.

For VMAT-SABR, Internal Target Volume delineation (ITV) was delineated using respiratory phases of the 4D-CT. Lesions treated with R-SABR were tracked using near-real time imaging or fiducial markers implanted prior to treatment based on applicability parameters previously described by our team [11].

All patients had immobilization with customized dual vacuum immobilization device (BodyFIX, Elekta, Stockholm, Sweden) for VMAT-SABR or a custom foam cushion for R-SABR. Lower lobes tumour movement could be minimized using an abdominal compression system (Aktina Medical® respiratory compression belt or custom homemade belt), if needed after prior predictive movement study.

Prescribed dose varies from 40 Gy to 60 Gy delivered in 3–8 fractions (see Table 1), depending on organs-at-risk dosimetry. We tried to deliver the maximum tolerable dose (up to 60 Gy in 3 fractions) as long as organs-at-risk constraints were kept acceptable. If high dose prescription was not achievable, we reduced it step-by-step until organs-at-risk constraints were met. In some cases, 95% coverage by isodose prescription of a smaller PTV (3 mm around the GTV) was accepted.

Typical isodose prescription was 65–85%, depending on tumour size and location. Maximum 120% of the prescribed dose was allowed in the GTV. Maximum point dose allowed to organs at risk was defined as D0.035 cc. Dose constraints used for organs-at-risk were previously published by AAPM, and vary with treatment fractionation [12].

Follow-up and time-to-events

Patients were assessed at 3, 6, and 12 months and at least yearly thereafter with clinical evaluation, toxicity grading and chest imaging. Local control was assessed by lung CT and local relapse was defined as mass progression on 2 successive CT at least 6 months after SABR. Time-to-events (death, progressive disease or local progression) was calculated from the last day of radiation treatment to first suspicion of event. Time of death, if so, was obtained for all patients through our provincial health insurance system services.

Toxicity assessment

Medical records from our institution and referring hospitals were reviewed to assess for pulmonary, cardiac, oesophageal or haemorrhagic events. Toxicities were scored using CTCAE v4.03. If the link between a medical event and radiation treatment was doubtful, it was considered as the worst-case hypothesis (i.e. linked to SABR) to avoid underestimation of potential toxicities.

Statistical analysis

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS, IBM, version 25.0). Median follow-up time was calculated from the last day of radiation treatment with the reverse Kaplan–Meier method. Time-to-event outcomes were calculated with the Kaplan–Meier method. Log-rank test was used for univariate analysis and Cox hazard regression model for multivariate analysis. Stepwise selection of all variables with a p value <0.15 on univariate analysis was done to build multivariate regression model. Crude rates of toxicity events were reported, without any adjustment.

Results

Patients, tumours and treatment characteristics

From July 2009 to December 2016, 878 patients were treated for primary or recurrent lung cancer by SABR in our institution; 137 patients have central (n = 60) or ultra-central (n = 77) tumours meeting our inclusion criteria. Median age was 75 years (range: 51–94). Most of them (n = 122) were not suitable for surgical resection (insufficient lung function or other comorbidities). The median

Table 1
Patients, tumours and treatment characteristics.

	Total (n = 137)	Central (n = 60)	Ultra-central (n = 77)
Patients characteristics			
Sex (%)			
– M	66 (48)	28 (53)	34 (44)
– F	71 (52)	32 (47)	43 (56)
Median Age (years, range)	75 (51–94)	75 (56–92)	75 (51–94)
Median KPS (range)	90 (50–100)	90 (50–100)	90 (50–100)
Charlson Comorbidity Index (range)	4 (1–9)	3 (1–7)	4 (2–9)
Tobacco (%)			
– Current smokers	37 (27)	15 (25)	22 (29)
– Former smokers	95 (69)	43 (72)	52 (67)
– Never	4 (3)	2 (3)	2 (3)
– Unknown	1 (1)	0 (0)	1 (1)
Choice for SABR (%)			
– Not suitable for surgery	122 (89)	53 (88)	69 (90)
– Declined surgery	15 (11)	7 (12)	8 (10)
Median FEV1 (L)	1.3 (0.5–3.1)	1.3 (0.6–2.5)	1.3 (0.5–3.1)
Tumours characteristics			
First cancer (%)	106 (77)	43 (72)	63 (82)
Recurrence (%)	31 (23)	17 (28)	14 (18)
Prior treatment (if recurrence)			
Surgery only	18	10	8
Surgery and adjuvant chemo	2	1	1
Surgery and CRT	1	1	0
Concomitant CRT	4	1	3
Conformal RT	1	1	0
SABR	3	2	1
Radiofrequency ablation	2	1	1
Histology (%)			
– Adenocarcinoma	39 (28)	19 (32)	20 (26)
– Squamous Cell Carcinoma	41 (30)	14 (23)	27 (35)
– Other	17 (13)	8 (13)	9 (12)
– Unknown	40 (29)	19 (32)	21 (27)
Diameter (cm, range)	2.5 (0.9–7)	2.3 (1–6.3)	2.7 (0.9–7)
GTV (cm^3, range)	7.8 (0.7–94.2)	6.7 (1–52.8)	8.2 (0.7–94.2)
PTV (cm^3, range)	30.6 (6.5–274.3)	23.2 (6,5–111.2)	31.1 (6.6–274.3)
T-stage (%)			
– T1a	31 (23)	22 (37)	9 (12)
– T1b	45 (33)	17 (28)	28 (36)
– T2a	30 (22)	11 (18)	19 (25)
– T2b	3 (2)	1 (2)	2 (2)
– T3	28 (20)	9 (15)	19 (25)
Treatment characteristics			
SABR type (%)			
- Robotic	65 (47)	24 (40)	41 (53)
- VMAT	72 (53)	36 (60)	36 (47)
Median dose (Gy, range)	50 (40–60)	50 (40–60)	50 (40–60)
Fractionation	5 (3–8)	5 (3–5)	5 (3–8)
Median BED_{10} (Gy, range)	100 (72–180)	100 (72–180)	100 (72–180)
– 72 Gy (40 Gy–5 fx)	2 (1)	1 (2)	1 (1)
– 80 Gy (40 Gy–4 fx)	1 (1)	0 (0)	1 (1)
– 95.2 Gy (56 Gy–8 fx)	1 (1)	0 (0)	1 (1)
– 100 Gy (50 Gy–5 fx)	88 (64)	35 (58)	53 (69)
– 105 Gy (60 Gy–8 fx)	7 (5)	0 (0)	7 (9)
– 112.5 Gy (50 Gy–4 fx)	8 (6)	4 (7)	4 (5)
– 132 Gy (60 Gy–5 fx)	19 (14)	11 (18)	8 (11)
– 180 Gy (60 Gy–3 fx)	11 (8)	9 (15)	2 (3)

Karnofsky Performance Score (KPS) was 90% (range 50–100). Active or former smokers accounted for 132 patients. Median Charlson Comorbidity Index was 4.

Primary lung cancer with no prior treatment accounted for 106 (77%) tumours (43 in central tumours cohort, 63 in ultra-central cohort). Pathologic proof of diagnosis was obtained in 109 (80%) cases. Squamous cell carcinomas (SCC) and adenocarcinomas (ADC) accounted for 80 (58%) tumours. Most of tumours (n = 106) were classified as T1 (T1a or T1b) tumours. Median tumour size, GTV and PTV were 2.5 cm (0.9–7), 7.8 cm^3 (0.7–94.2) and 30.6 cm^3 (6.5–274.3), respectively.

SABR treatment was delivered with R-SABR and VMAT-SABR for 65 and 72 patients, respectively. Most used dose-fractionation scheme was 50 Gy in 5 fractions. BED_{10} was $\geq$100 Gy for 133 (97%) patients.

Details of patients, tumours and treatment characteristics are listed in Table 1.

For central tumours, GTV was in the 2-cm area around mediastinum only, PBT only, or both for respectively 30, 24 and 6 patients. For ultra-central tumours, which can often be close to several critical structures, GTV was abutting or overlapping major vessels for 50 patients, PBT for 24 patients, pericardial pleura for 12 patients and oesophagus for 2 patients.

Survival and local control

Median follow-up was 36 months (range: 1–92 months). For the whole cohort, median overall survival (OS) was 46 months (95% CI: 39–53 months) and median disease-free survival (DFS) was 33 months (95% CI: 23–43 months).

One-, 2- and 3-years OS rates were 87%, 70% and 62%, respectively. One-, 2- and 3-years DFS rates were 82%, 59% and 45%, respectively.

Local control (LC) was 95.1%, 81.4% and 66% at 1-, 2- and 3 years, respectively.

Comparison between central and ultra-central tumours

OS and DFS were statistically different between central and ultra-central tumours on univariate models. Median OS for central tumours was 57 months vs 37 months for ultra-central tumours ($p = 0.027$, Fig. 1). This significant difference remains after multivariate analysis with a Hazard Ratio (HR) for death of 0.48 (95% CI: 0.26–0.88, $p = 0.017$) for central tumours (see Table 2). Median DFS for central tumours was 37 months vs 22 months for ultra-central tumours ($p = 0.034$, Fig. 2).

LC was not different between central and ultra-central tumours ($p = 0.186$, Fig. 3) with 100%, 92% and 72% at 1–2- and 3 years for central tumours, respectively, vs 92%, 73% and 61% for ultra-central tumours. After multivariate analysis, the only remaining predictive factor for LC was $BED_{10} \geq 100$ Gy (HR = 0.12, 95% CI: 0.25–0.54, $p = 0.006$) (see Supplementary files).

Toxicity

Grade 2 toxicities occurred 17 times in 15 patients for a cumulative incidence of 12%. Mostly were radiation pneumonitis ($n = 9$), atelectasis/bronchial stricture ($n = 6$) and haemoptysis ($n = 2$). Grade 3 toxicities occurred in 4 patients (3%), with atelectasis/bronchial strictures ($n = 2$) and myocardial infarctions ($n = 2$). There was no grade 4 toxicity. Fatal events (i.e. grade 5) occurred in 6 patients (4%): 4 radiation pneumonitis (in which one occurred in a patient with interstitial lung disease) and 2 myocardial infarctions. Cumulative incidence of grade 3–5 events was 7.3% (Fig. 4). Grade 3–5 toxicity occurred after a median of 6.5 months (range: 1.3–58.2 months). No oesophagitis, massive bleedings nor fistulas were seen. No grade ≥3 brachial plexopathy or chest wall pain was seen in our cohort (data not shown).

There was no difference in the occurrence of grade 3–5 toxicity between central and ultra-central tumours ($p = 0.7$, Supplementary material). Grade 3–5 toxicities were only observed in patients unsuitable for surgical resection. Two patients with prior lung surgery, both in ultra-central cohort, experienced severe toxicities: one grade 3 myocardial infarction and one grade 5 radiation pneumonitis. Detailed characteristics of comorbidities, tumours and treatments of those patients are available in Supplementary files.

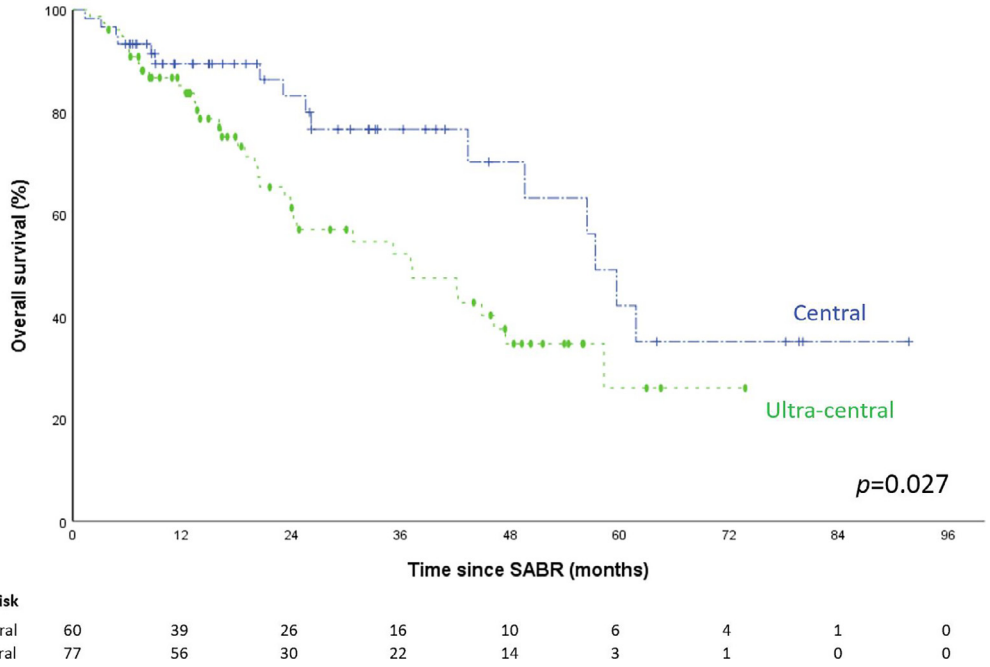
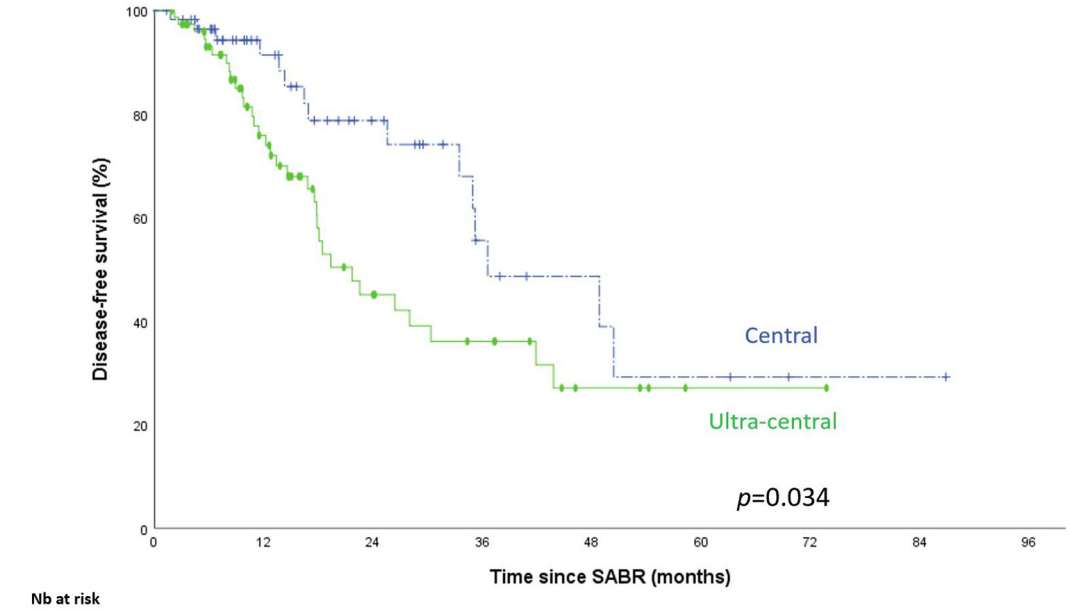


Fig. 1. Overall survival curves. Median OS for central tumours was 57 months vs 37 months for ultra-central tumours. This difference was significant ($p = 0.027$).

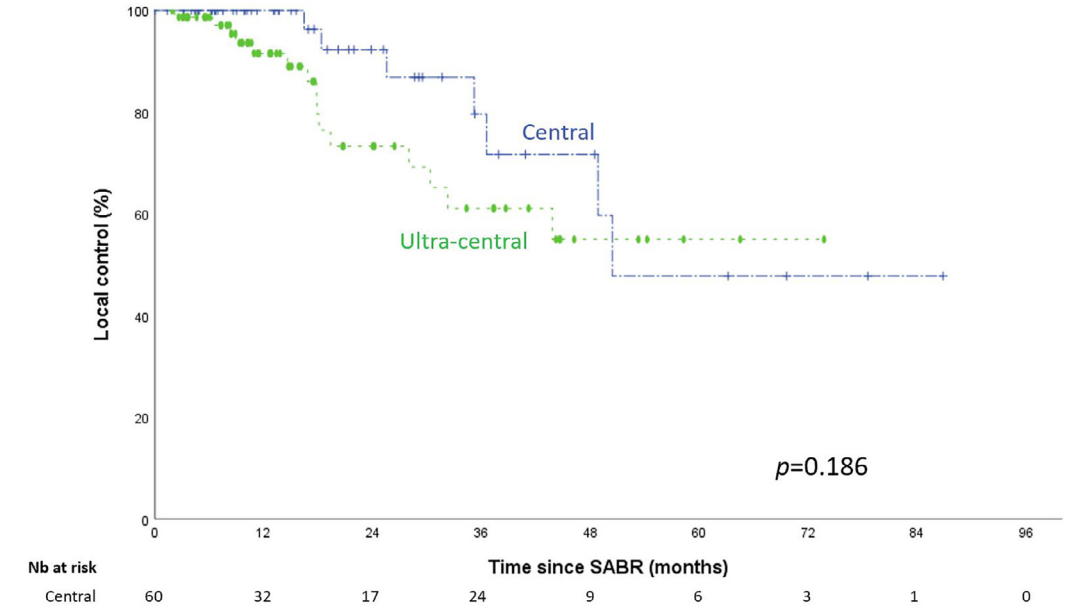
Table 2
Analysis of predictive factors for OS and LC.

Factors	Univariate analysis		Multivariate analysis	
	OS (p value)	LC (p value)	OS (p value)	LC (p value)
Age ≥75	0.973	–	–	–
Charlson ≤4	0.038	–	0.060	–
Diameter ≥25 mm	0.865	0.579	–	–
Primary (vs recurrent)	0.132	0.114	0.103	0.073
Central (vs ultra-central)	0.027	0.186	0.017 HR = 0.48 (95% CI: 0.26–0.88)	0.123
R-SABR (vs VMAT-SABR)	0.698	0.626	–	–
$BED_{10} \geq 100$ Gy	0.198	0.003	–	0.006 HR = 0.12 (95% CI: 0.25–0.54)



Nb at risk									
Central	60	32	18	8	5	3	1	1	0
Ultra-central	77	40	16	11	4	1	1	0	0

Fig. 2. Disease-free survival curves. Median DFS for central tumours was 37 months vs 22 months for ultra-central tumours. This difference was significant ($p = 0.034$).



Nb at risk									
Central	60	32	17	24	9	6	3	1	0
Ultra-central	77	40	20	13	4	1	0	0	0

Fig. 3. Local control curves. No significant difference was seen ($p = 0.186$).

Discussion

This study presents the largest cohort of central and ultra-central lung tumours to date. It shows that our approach with prioritization to organ-at-risk (i.e. decreasing prescribed dose to meet organ-at-risk dose constraints) is safe without jeopardizing survival or local control. With a median follow-up of 36 months, we have a long-term view of prognosis and toxicities.

Our definition of central tumours is reliable with the RTOG 0813 study. However, we assume to include tumours with PTV touching pericardial pleural into the ultra-central cohort, as cardiac events may be linked to SABR. Therefore, we choose that PTV abutting or overlapping the PBT, trachea, oesophagus, major vessels or pericardium as the definition for our ultra-central tumours. Haasbeek et al. and Raman et al. used a similar definition [13,14].

For some authors, only tumours with PTV abutting or overlapping the PBT may be considered as ultra-central. If we look only at this subset of ultra-central tumours in our cohort ($n = 24$), no difference in OS or DFS was observed, but local control was superior in central tumours ($p = 0.045$, see Supplementary files). Nevertheless the definition of ultra-central tumours changes between studies. In the ongoing SUNSET trial, ultra-central tumours are

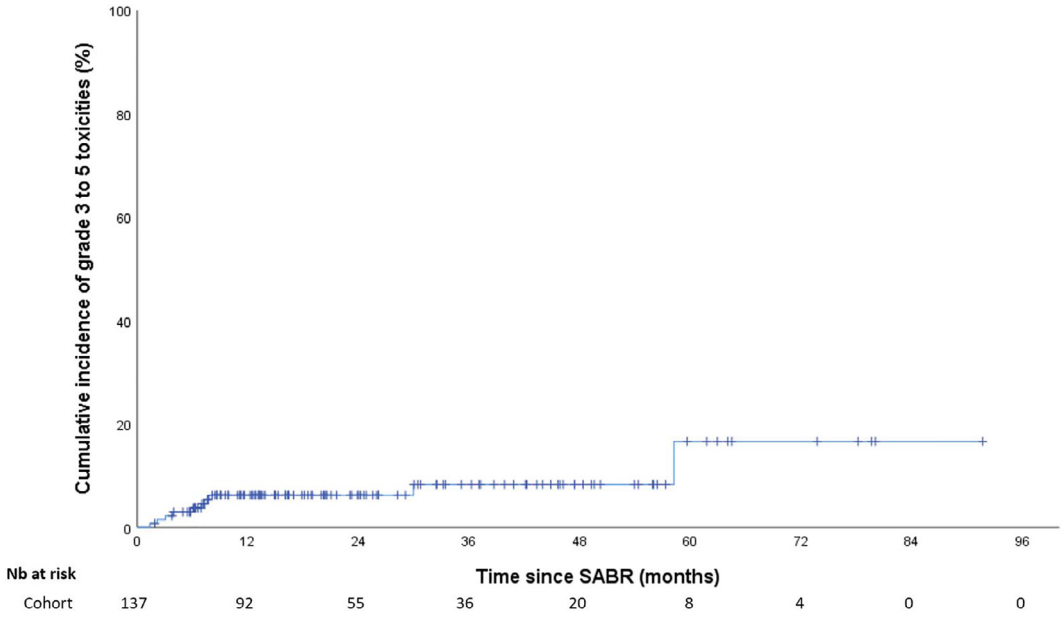


Fig. 4. Cumulative incidence of severe toxicities (grade ≥3) for the whole cohort.

those whose PTV touches or overlaps the PBT, oesophagus, pulmonary veins and arteries [15].

It is the first time that a direct comparison between central and ultra-central tumours is made, showing a better OS and DFS for central vs ultra-central tumours. A more aggressive behaviour of ultra-central tumours cannot be excluded. Close contact or direct invasion of critical mediastinal structures inherent in the definition of such lesion may be an explanation. It is also possible that the most "peripheral" tumours from central location may benefit from more aggressive treatment with higher BED_{10} and less compromises in target coverage than in ultra-central tumours. But no local control difference between the two groups was found. This warrants further investigation.

Overall survival in our population is similar with outcome previously described for central but also peripheral tumours. Median OS ranged from 15.9 to 29.1 months in Fakiris et al., Modh et al. and Tekatli et al. studies. Chaudhuri et al. found that 2-years OS rates were similar between ultra-central, central, and peripheral tumours (80.0%, 63.2% and 86.6%, respectively) [2,7–9].

Local control was also an endpoint of interest because delivered doses were less intensive than those used for the treatment of peripheral tumours. Delivering doses above 50 Gy in 5 fractions was possible in only 33% of our cohort because of our prioritization to organs-at-risk politics. Therefore, LC was still good at 1-, 2- and 3 years with 95%, 81% and 66% respectively. With the delivery of BED_{10} ≥80 Gy, Modh et al. experienced 14% local failure at 1 year and 21% at 2 years [9].

We found on multivariate analysis that delivering a BED_{10} ≥100 Gy is associated with a better probability to achieve local control and it was feasible in 97% of cases in our cohort. Other published study already shows that a BED_{10} ≥100 Gy is associated with better local control, and it is consistent with actual guidelines to prescribe such BED. However, in central tumours, Modh et al. failed to show that BED is associated with local control, and only GTV size remains significant after multivariate analysis [9,16–18].

Safety of SABR is reassuring in our study. We observed 7% of grade 3–5 toxicities. No unexpected or unusual toxicities were seen. It does not seem that central or ultra-central tumours have a different risk of severe toxicities, but the low incidence would make our study underpowered to detect a small difference among them. We are consistent with other series who find an 8% rate of grade 3–5 toxicities [9,18].

With studies finding as high as 38% grade 3–5 toxicities in ultra-central tumours, treated by less intensive regimen (60 Gy in 12 fractions, BED_{10} = 90 Gy), we cannot deny that something may be misunderstood in the prediction of such severe events. However, reporting of toxicity is also questionable [8,19].

Although no oesophageal toxicity was noted, only 2 patients had ultra-central tumours close to the oesophagus, which is underpowered to assess the risk.

The only early death in our cohort (at 1.3 months) was due to myocardial infarction, in a patient treated for a left lower lobe ultra-central tumour touching mediastinum. Plan was reviewed, and heart doses were kept acceptable, but we cannot rule out a link with SABR and included it for analysis. One patient with grade 5 radiation pneumonitis had prior interstitial lung disease, as it is now well-known at high-risk for radiation pneumonitis. For other patients with radiation pneumonitis, lung doses were kept below accept threshold [20].

Our study is limited by its retrospective nature and by fractionation heterogeneity, as emphasis to organ-at-risk was the rule. Our wide range of dose prescription may be confusing, but is led by dose constraints to organs-at-risk. Missing data may lead to underscoring of toxicities but our large research for data from our institution and referring hospitals may have limited this caveat. At last, our definition of ultra-central tumours can be discussed but it stays coherent with recent studies and ongoing trials.

Practice for central tumours is heterogeneous even among radiation oncologist. Thus, we are eagerly awaiting the results of the RTOG 0813 dose escalation study and SUNSET trial to help us to draw more definitive conclusions about outcome and safety in treatment of central and ultra-central tumours [21].

In conclusion, in our cohort of central and ultra-central lung tumours treated by SABR with prioritization to organ-at-risk, we observed good local control and survival rates with an acceptable amount (7%) of severe toxicity. However, survival may be affected by the location of the tumour, as we observed a better outcome for central tumours.

Declaration of interest

None declared.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2019.01.035.

References

[1] Timmerman R 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;24:4833–9.
[2] Fakiris AJ et al. Stereotactic body radiation therapy for early-stage non-small-cell lung carcinoma: four-year results of a prospective phase II study. Int J Radiat Oncol Biol Phys 2009;75:677–82.
[3] Song SY et al. Fractionated stereotactic body radiation therapy for medically inoperable stage I lung cancer adjacent to central large bronchus. Lung Cancer 2009;66:89–93.
[4] Corradetti MN, Haas AR, Rengan R. Central-airway necrosis after stereotactic body-radiation therapy. N Engl J Med 2012;366:2327–9.
[5] Stephans KL et al. Esophageal dose tolerance to hypofractionated stereotactic body radiation therapy: Risk factors for late toxicity. Int J Radiat Oncol Biol Phys 2014;90:197–202.
[6] Chang JY, Bezjak A, Mornex F. Stereotactic ablative radiotherapy for centrally located early-stage non-small-cell lung cancer: what we have learned on behalf of the IASLC advanced radiation technology committee. J Thorac Oncol 2014;10:577–85.
[7] Chaudhuri AA et al. Stereotactic ablative radiotherapy (SABR) for treatment of central and ultra-central lung tumors. Lung Cancer 2015;89:50–6.
[8] Tekatli H et al. Outcomes of hypofractionated high-dose radiotherapy in poor-risk patients with "ultracentral" non-small cell lung cancer. J. Thorac. Oncol. 2016;11:1081–9.
[9] Modh A 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;90:1168–76.
[10] Kong FM et al. Consideration of dose limits for organs at risk of thoracic radiotherapy: atlas for lung, proximal bronchial tree, esophagus, spinal cord, ribs, and brachial plexus. Int J Radiat Oncol Biol Phys 2011;81:1442–57.
[11] Bahig H et al. Predictive parameters of cyberknife fiducial-less (XSight Lung) applicability for treatment of early non-small cell lung cancer: a single-center experience. Int J Radiat Oncol Biol Phys 2013;87:583–9.
[12] Benedict SH et al. Stereotactic body radiation therapy: the report of AAPM Task Group 101. Med Phys 2010;37:4078–101.
[13] 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.
[14] Raman S et al. Ultracentral tumors treated with stereotactic body radiotherapy: single-institution experience. Clin Lung Cancer 2018;19:e803–10.
[15] Giuliani M et al. SUNSET: stereotactic radiation for ultracentral non-small-cell lung cancer—a safety and efficacy trial. Clin Lung Cancer 2018;19:e529–32.
[16] Onishi H et al. Stereotactic hypofractionated high-dose irradiation for stage I nonsmall cell lung carcinoma: clinical outcomes in 245 subjects in a Japanese multiinstitutional study. Cancer 2004;101:1623–31.
[17] Guckenberger M et al. ESTRO ACROP consensus guideline on implementation and practice of stereotactic body radiotherapy for peripherally located early stage non-small cell lung cancer. Radiother Oncol 2017;124:11–7.
[18] Senthi S, Haasbeek CJA, Slotman BJ, Senan S. Outcomes of stereotactic ablative radiotherapy for central lung tumours: a systematic review. Radiother Oncol 2013;106:276–82.
[19] Oskan F. The quality of toxicity reporting and the story of the lung SBRT 'No-Fly Zone'. Int J Radiat Oncol Biol Phys 2015;92:514–5.
[20] Bahig H et al. Severe radiation pneumonitis after lung stereotactic ablative radiation therapy in patients with interstitial lung disease. Pract Radiat Oncol 2016;6:367–74.
[21] Roesch J et al. SBRT for centrally localized NSCLC – What is too central? Radiat Oncol 2016;11:157.