Received: 9 April 2019 | Revised: 29 July 2019 | Accepted: 24 August 2019

DOI: 10.1111/cas.14185

ORIGINAL ARTICLE

Cancer Science WILEY

Risk-adapted stereotactic body radiation therapy for central and ultra-central early-stage inoperable non-small cell lung cancer

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Funding information
the National Natural Science Foundation of China, Grant/Award Number: 81872465 and 81502660

Abstract

To determine the therapeutic efficacy and safety of risk-adapted stereotactic body radiation therapy (SBRT) schedules for patients with early-stage central and ultra-central inoperable non-small cell lung cancer. From 2006 to 2015, 80 inoperable T1-2N0M0 NSCLC patients were treated with two median dose levels: 60 Gy in six fractions (range, 48-60 Gy in 4-8 fractions) prescribed to the 74% isodose line (range, 58%-79%) for central lesions (ie within 2 cm of, but not abutting, the proximal bronchial tree; n = 43), and 56 Gy in seven fractions (range, 48-60 Gy in 5-10 fractions) prescribed to the 74% isodose line (range, 60%-80%) for ultra-central lesions (ie abutting the proximal bronchial tree; n = 37) on consecutive days. Primary endpoint was overall survival (OS); secondary endpoints included progression-free survival (PFS), tumor local control rate (LC), and toxicity. Median OS and PFS were 64.47 and 32.10 months (respectively) for ultra-central patients, and not reached for central patients. Median time to local failure, regional failure, and any distant failures for central versus ultra-central lesions were: 27.37 versus 26.07 months, 20.90 versus 12.53 months, and 20.85 versus 15.53 months, respectively, all $P < .05$. Multivariate analyses showed that tumor categorization (ultra-central) and planning target volume ≥52.76 mL were poor prognostic factors of OS, PFS, and LC, respectively (all $P < .05$). There was one grade 5 toxicity; all other toxicities were grade 1-2. Our results showed that ultra-central tumors have a poor OS, PFS, and LC compared with central patients because of the use of risk-adapted SBRT schedules that allow for equal and favorable toxicity profiles.

KEYWORDS
efficacy, non-small cell lung cancer, risk-adapted stereotactic body radiation therapy, safety, ultra-central tumor

M-B Meng, H-H Wang, and N-G Zaorsky contributed equally to the work.

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1 | INTRODUCTION

Stereotactic body radiation therapy (SBRT) delivers an ablative dose to the tumor with a sharp dose fall off that minimizes dose to surrounding critical normal structures.[1] SBRT is a treatment option for peripheral early-stage non-small cell lung cancer (NSCLC) with clinical outcomes comparable to surgery.[2,3] However, not only optimal dose-fractionation schedules, but also safety and efficacy for central early-stage NSCLC with SBRT are not yet clear, in part because there are varying definitions of "central" tumors.[4,5]

Radiation Therapy Oncology Group (RTOG) 0236 defines a "central" tumor as being within 2 cm of the proximal bronchial tree (PBT), including the carina, right and left main bronchi, and bronchial tree to the second bifurcation.[6] Importantly, central and peripheral tumors were treated with doses used for peripheral lesions, and excessive toxicity was noted primarily among patients with central lesions.[7]

Subsequently, RTOG 0813 defines a "central" tumor as being from RTOG0236, and adds tumors that are immediately adjacent to mediastinal or pericardial pleura. RTOG 0813 evaluated the safety and efficacy of SBRT to lesions near the central "no-fly zone".[8] Phase I data from this trial showed a maximum tolerated dose of 60 Gy/5 fractions[9]; phase II data reported tumor local control rate (LC), progression-free survival (PFS), and overall survival (OS) at 2 years of 87.9%, 54.5%, and 72.7%, respectively.[10] Although these control rates are encouraging, even conservative dose-fractionation schemes from these trials have been shown to cause severe damage to bronchial structure, bronchial necrosis, and fatal hemoptysis in approximately 5% of patients.[11,12]

In the 2010s, a new subgroup within the cohort of patients with central tumors was designated as "high-risk" or "ultra-central" tumors, or those that abut the PBT.[7,13-32] Ultra-central tumors have increased grade 4+ toxicity, even with conservative radiotherapy fractionation.[25] Of concern, Haseltine et al reported that in patients with PBT-abutting tumors who received conservative dose-fractionation SBRT plus bevacizumab, two patients experienced grade 5 pulmonary hemorrhages.[23] Thus, there is great interest in defining risk-adapted dose-fractionation schedules for "high-risk/ultra-central" and "standard-risk/central" early-stage NSCLC.[19,33]

In the present study, we report our experience with risk-adapted SBRT for central and ultra-central early-stage inoperable NSCLC. Our hypothesis is that those with ultra-central tumors have poorer OS, PFS, LC, or higher toxicity rates than those with central tumors. The results of this study may provide clinical guidance in the use of SBRT for early-stage NSCLC patients, and they may be used to interpret the results from the RTOG 0813,[34,35] EORTC LungTech,[36] and SUNSET[18] prospective clinical trials. It would be very interesting if these studies subdivided their results into central and ultra-central tumors.

2 | MATERIALS AND METHODS

2.1 | Study design and eligible patients

This was a retrospective review of patients with central and ultra-central early-stage inoperable American Joint Committee on Cancer (AJCC) 7th edition T1-2N0M0 NSCLC treated with SBRT. Patients treated from 1 November 2006 to 31 December 2015 were identified from our prospective SBRT database. All patients were examined in a multidisciplinary setting by a thoracic surgeon, medical oncologists, radiologist, and radiation oncologists at the time of treatment. This study was carried out in accordance with the ethical guidelines of the Declaration of Helsinki and was approved by the independent ethics committees at our hospital (no. Ek2017106).

Inclusion criteria were defined as follows: (i) any age; (ii) Karnofsky Performance Scale (KPS) ≥70; (iii) located centrally early-stage T1-2N0M0 NSCLC with histological confirmation and/or positron emission tomography/computed tomography (PET-CT) images consistent with malignancy; (iv) patients with tumor ≤2 cm of the PBT. "Standard-risk/central" lesions were those within 2 cm of the PBT, but without abutment of the PBT. "High-risk/ultra-central" lesions had abutment of the PBT; (v) unamenable to resection either because of anatomical tumor characteristics, patient comorbidities, elderly, or patient refusal; and (vi) patient provided written informed consent for the treatment and database. Exclusion criteria were as follows: (i) recurrent disease or new primary lung cancer with previous history of lung cancer; (ii) prior use of local therapy (eg radiotherapy and/or surgery); (iii) prior use of systemic therapy (eg chemotherapy, antiangiogenic agents, or biological targeted agents); (iv) contraindication to receiving SBRT (eg change in performance status); and (v) uncontrolled comorbid condition (metabolic or psychiatric).

2.2 | Stereotactic body radiation therapy treatment schedule, organs at risk contouring and normal tissue constraints

Treatments were carried out using the CyberKnife (CK; Accuray Inc.), a robotic image-guided radiosurgical system, equipped with Synchrony (Accuray Inc.) on consecutive days, which allowed respiratory motion tracking during irradiation. Briefly, CK treatment involves fiducial placement, CT simulation, target volume delineation, treatment planning, and normal tissue constraints.

2.2.1 | Fiducial placement

Patients had one gold fiducial (gold seeds 3 × 0.8 mm; Best Medical International) implanted inside or near the treatment target for targeting purposes in real time. Patients with contraindications to fiducials (eg high-risk pneumothorax, anticoagulant use) were treated with the fiducial-free Xsight (Accuray Inc.) spine-tracking system.

2.2.2 | Computed tomography simulation

Patients were immobilized using a vacuum bag, and a CT was obtained after injection of i.v. radiographic contrast to highlight the tumor. CT simulation was carried out approximately 7 days after fiducial placement to avoid fiducial migration. In the case of Xsight,

four-dimensional CT (4-D CT) allowed visible tumor position verification of its range of motion.

2.2.3 | Target volume delineation

Gross tumor volume (GTV) was defined as tumor disease based on simulation, CT, and +/− PET-CT. Planning target volume (PTV) was defined as GTV with the appropriate margin in the x-, y-, and z-axis direction, which was obtained by detection of the motion of gold fiducial markers. If patients were treated with the Xsight spine-tracking system, internal target volume (ITV) was defined as the GTV with the appropriate margins obtained by 4-D CT detection of the motion of the lesions, and then expanded by 5 mm to generate the PTV.

2.2.4 | Treatment planning

A treatment plan was generated based on tumor geometry and location. Plans were optimized and dose calculations were carried out using the ray-tracing dose calculation algorithm. Heterogeneity correction using appropriate CT density models were applied for dose calculation.

2.2.5 | Organs at risk, normal tissue constraints, and biologically effective doses

Organs at risk contouring was adopted from RTOG 0813,[35] EORTC LungTech,[36] SUNSET,[18] and RTOG 1106 contouring atlas,[37] and normal tissue constraints were adopted from RTOG 0813 and previous HILUS studies.[6,13-32] Meanwhile, maximum point dose and volumetric maximum dose analyses were evaluated for OAR including esophagus, heart, pulmonary artery, pulmonary vein, spinal cord, ipsilateral lung, contralateral lung, lung total, trachea, mainstem bronchi, lobe bronchi, and proximal bronchial tree. Treated doses were converted to biologically effective doses (BED) based on the formula: $nd\ [1 + d/(\alpha/\beta)]$, where n is number of fractions, and d is dose/fraction (Gy); assuming α/β value of 10 for NSCLC (ie BED_{10}) and α/β value of 3 for normal tissues (ie BED_3).

2.3 | Follow up and endpoints

Patients were seen in the clinic at 1 month after completion of treatment, then every 3 months for the first year; then every 6 months until July 31, 2018. Imaging and toxicity of all patients were monitored for the follow-up period using our clinical database.

Primary endpoint was OS, defined as the time between the date of SBRT and date of death or date of the last follow up for censored patients. Secondary endpoints were: (i) PFS, defined as the time between the date of the SBRT and the date of disease progression (based on RECIST 1.1) or the date of the last follow up for censored patients; (ii) LC, defined as no progression of treated disease on follow-up scans); and (iii) Common Terminology Criteria for Adverse Events (CTCAE v4.0) grade toxicity. Acute toxicity was defined as a treatment-related side-effect occurring within 90 days of the first fraction; late toxicity was one that occurred after this time. All toxicities were assessed in a multidisciplinary setting.

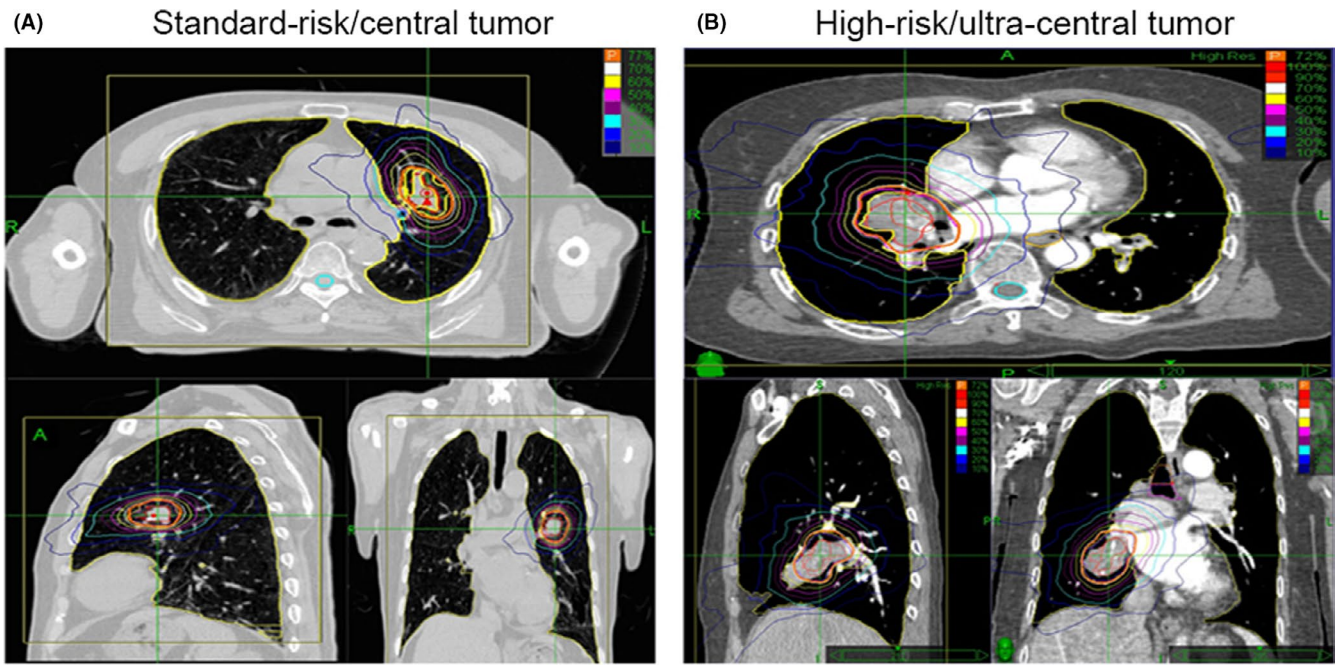

FIGURE 1 Tumor categorization. (A,B) All patients had tumor ≤2 cm of the proximal bronchial tree (PBT) (ie "central" tumors) and were divided into "standard-risk/central" and "high-risk/ultra-central" lesions. "Standard-risk/central" lesions were those within 2 cm of the PBT, but without abutment of the PBT. "High-risk/ultra-central" lesions had abutment of the PBT

TABLE 1 Characteristics of patients with central and ultra-central early-stage inoperable AJCC 7th edition T1-2N0M0 NSCLC treated with SBRT

	All patients (n = 80)	Tumor categorization			
		High-risk/ultra-central tumors (n = 37)	Standard-risk/central tumors (n = 43)	F/χ^2 value	*P* value
Age (y), median (range)	71 (51-85)	71 (51-85)	71 (53-83)	0.0003	.99
Gender					
Male	56 (70%)	27 (73%)	29 (67.4%)	0.29	.59
Female	24 (30%)	10 (27%)	14 (32.6%)		
Diagnosis type					
Pathology	72 (90%)	34 (91.9%)	38 (88.4%)	0.45	.80
CT/PET-CT	6 (7.5%)	2 (5.4%)	4 (9.3%)		
CT	2 (2.5%)	1 (2.7%)	1 (2.3%)		
Pathology					
Squamous cell	36 (45%)	15 (40.6%)	21 (48.8%)	5.25	.15
Adenocarcinoma	33 (41.3%)	16 (43.2%)	17 (39.6%)		
Other	3 (3.7%)	3 (8.1%)	0		
NR	8 (10.0%)	3 (8.1%)	5 (11.6%)		
Reason for inoperability					
Organ dysfunction	34 (42.5%)	15 (40.6%)	19 (44.2%)	0.12	.99
Tumor location	6 (7.5%)	3 (8.1%)	3 (7.0%)		
Elderly	21 (26.3%)	10 (27.0%)	11 (25.6%)		
Refusal	19 (23.7%)	9 (24.3%)	10 (23.2%)		
Presence of symptoms					
Yes	57 (71.3%)	30 (81.1%)	27 (62.8%)	3.25	.07
No	23 (28.7%)	7 (18.9%)	16 (37.2%)		
T-stage[a]					
T1	37 (46.3%)	18 (48.6%)	19 (44.2%)	3.71	.16
T2a	33 (41.2%)	12 (32.5%)	21 (48.8%)		
T2b	10 (12.5%)	7 (18.9%)	3 (7.0%)		
Lesion site					
RUL	23 (28.8%)	9 (24.3%)	14 (32.6%)	19.03	**.004**
RML	1 (1.3%)	0	1 (2.3%)		
RLL	13 (16.3%)	8 (21.6%)	5 (11.6%)		
R hilar	3 (3.7%)	2 (5.4%)	1 (2.3%)		
LUL	22 (27.5%)	4 (10.9%)	18 (41.9%)		
LLL	11 (13.7%)	8 (21.6%)	3 (7.0%)		
L hilar	7 (8.7%)	6 (16.2%)	1 (2.3%)		
Tracking modality type					
Xsight	41 (51.3%)	23 (62.2%)	18 (41.9%)	3.28	.07
Synchrony	39 (48.7%)	14 (37.8%)	25 (58.1%)		
PTV volume (mL), median (range)	52.8 (2.8-264.5)	55.0 (9.9-264.5)	49.2 (2.8-159.7)	0.45	.50
Risk-adapted SBRT schedule					
48 Gy/4 fr	1 (1.2%)	0	1 (2.3%)	44.54	**.0001**
48 Gy 6 fr	1 (1.2%)	1 (2.7%)	0		
49 Gy/7 fr	4 (5.0%)	3 (8.1%)	1 (2.3%)		
50 Gy/5 fr	6 (7.5%)	2 (5.4%)	4 (9.3%)		
50 Gy/8 fr	1 (1.2%)	1 (2.7%)	0		

(Continues)

TABLE 1 (Continued)

	All patients (n = 80)	Tumor categorization			
		High-risk/ultra-central tumors (n = 37)	Standard-risk/central tumors (n = 43)	F/χ^2 value	*P* value
50 Gy/3 fr	1 (1.2%)	0	1 (2.3%)		
51 Gy/6 fr	3 (3.8%)	1 (2.7%)	2 (4.7%)		
52 Gy/8 fr	1 (1.2%)	1 (2.7%)	0		
54 Gy/6 fr	5 (6.3%)	3 (8.1%)	2 (4.7%)		
55 Gy/5 fr	3 (3.8%)	0	3 (7.0%)		
56 Gy/7 fr	9 (11.3%)	7 (18.9%)	2 (4.7%)		
56 Gy/8 fr	11 (13.8%)	10 (27.0%)	1 (2.3%)		
56 Gy/9 fr	1 (1.2%)	1 (2.7%)	0		
60 Gy/4 fr	3 (3.8%)	0	3 (7.0%)		
60 Gy/5 fr	10 (12.5%)	2 (5.4%)	8 (18.6%)		
60 Gy/6 fr	12 (15.0%)	0	12 (27.9%)		
60 Gy/7 fr	2 (2.5%)	0	2 (4.7%)		
60 Gy/8 fr	5 (6.3%)	4 (10.8%)	1 (2.3%)		
60 Gy/10 fr	1 (1.2%)	1 (2.7%)	0		
BED_{10} (Gy), median (range)	102.6 (81.3-150.0)	96.0 (81.3-132.0)	120.0 (83.3-150.0)	23.98	**.0001**
Isodose line, median (range)	74% (58%-80%)	74% (60%-80%)	74% (58%-79%)	0.72	.40

Note: Bold face denotes *P* value < .05.

Synchrony (Accuray Inc.); Xsight (Accuray Inc.).

Abbreviations: BED_{10}, biologically equivalent dose at α/β value of 10; CT, computed tomography; fr, fraction; Gy, Gray; L, left; LLL, left lower lobe; LUL, left upper lobe; NR, none report; NSCLC, non-small cell lung cancer; PET-CT, positron emission tomography-CT; PTV, planning target volume; R, right; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe; SBRT, stereotactic body radiation therapy.

[a]American Joint Committee on Cancer (AJCC) 7th edition.

Given patient comorbidities and the relatively unreliable negative predictive value of biopsy, tissue diagnosis of local recurrence was not always possible. Patients with three or more of the following high-risk features (HRF) were suggestive of local failure: (i) enlarging opacity at primary site; (ii) sequential enlarging opacity; (iii) enlarging opacity after 12 months; (iv) bulging margin; (v) loss of linear margin; (vi) cranio-caudal growth; and (vii) air bronchogram loss. Local recurrence was classified as having at least three HRF and a PET-CT standard uptake value (SUV) >2.5 or >3 HRF without PET-CT.[38] Regional failure was defined as tumor regrowth in the hilar, mediastinal, or supraclavicular lymph nodes or at the bronchial margin of SBRT, as visualized by CT and/or PET-CT scanning by independent oncologist and radiologist who were blinded to the treatment to ensure accuracy and precision of the data. Recurrences beyond these sites were deemed distant failures.

2.4 | Statistical analysis

The χ^2-test or Fisher's exact test was carried out for qualitative data. Quantitative data were expressed as median and range, and *t* test or nonparametric Mann-Whitney *U* test was used. OS, PFS, and LC curves were estimated by using the Kaplan-Meier technique and compared by stratified log-rank test. Multivariate analyses were carried out using a Cox regression model. $P < .05$ was considered to indicate statistical significance. Data were analyzed using statistical software Intercooled Stata version 8.2 for Windows (Stata Corporation).

3 | RESULTS

3.1 | Patient characteristics

A total of 80 patients were included in this analysis, including 37 high-risk/ultra-central patients and 43 standard-risk/central patients. Dose fractionation schedules were established at the discretion of the treating physician, using a formulaic risk-adapted approach to minimize toxicity while maximizing cancer killing, and were used mainly based on central versus ultra-central location, with examples shown in Figure 1. Median prescription dose/fraction were 60 Gy/6 fractions (range, 48-60 Gy in 4-8 fractions) with median BED_{10} = 120.0 Gy (range, 83.3-150.0 Gy) prescribed to the 74% isodose distribution (range, 58%-79%) for the "central" patients versus 56 Gy/7 fractions (range, 48-60 Gy in 5-10 fractions) with median BED_{10} = 96.0 Gy (range, 81.3-132.0 Gy) prescribed to the 74% isodose distribution (range, 60%-80%) for "ultra-central" patients on consecutive days (all $P < .05$). However, there were no significant differences in age, gender, diagnosis type, pathology, reason for inoperability, presence of symptoms, T-stage, tracking modality type and PTV volume between the

clinical groupings (all $P > .05$). Characteristics of all patients are shown in Table 1.

3.2 | Overall survival, PFS, and LC

In Figure 2A-C, median OS was not reached, and median PFS was 56.67 months for the entire cohort with a median follow up of 44.47 months (range, 2.8-101.57), respectively. Median OS and PFS were 64.47 months and 32.10 months for ultra-central patients, but they were not reached for central patients, respectively.

In Figure 2A,D, the 1, 3, and 5-year actuarial LC rates were 97.4%, 92.6%, and 85.4% for the entire cohort; they were 94.5%, 88.0%, and 72.7% for ultra-central patients; and they were 100.0%, 96.9%, and 96.9% for central patients, respectively. There were significant differences in OS, PFS, and LC between the ultra-central patients and the central patients (all $P < .05$).

In order to explore the prognostic factors for OS, PFS, and LC, median value of age (71 years), PTV volume (52.76 mL), and BED_{10} (102.6 Gy) in all patients were used to divide the patient cohort into high and low groups. Univariate analyses showed that patients with pathological diagnosis, those without symptoms, PTV volume <52.76 mL, and those with central lesions experienced significantly greater OS (all $P < .05$). Patients with PTV volume <52.76 mL and those with central lesions experienced significantly greater PFS and LC, respectively (all $P < .05$). Results of univariate analyses for clinical factors affecting OS, PFS, and LC are presented in Table 2.

3.3 | Patterns of failure

Patterns of failure are summarized in Figure 3. Median time to local failure, regional failure, and any distant failures were 26.72 months (range, 6.47-50.57), 18.13 months (range, 3.23-50.57), and 15.63 months (range, 3.23-56.93), respectively, for the entire cohort. Median time to local failure, regional failure, and any distant failures for central versus ultra-central lesions were: 27.37 versus 26.07 months, 20.9 versus 12.53 months, and 20.85 versus 15.53 months, respectively, all $P < .05$.

At the time of last follow up, the most common failure was distant. Crude initial distant failure was noted in 33 patients (33/80, 41.25%). The most common site of initial distant failure was lung; other sites were brain, bone, adrenal gland, and liver. Eight patients relapsed within PTV with a median of 26.72 months (range, 6.47-50.57); seven patients had ultra-central tumors and one patient had central tumor. Crude initial regional recurrence occurred in 16

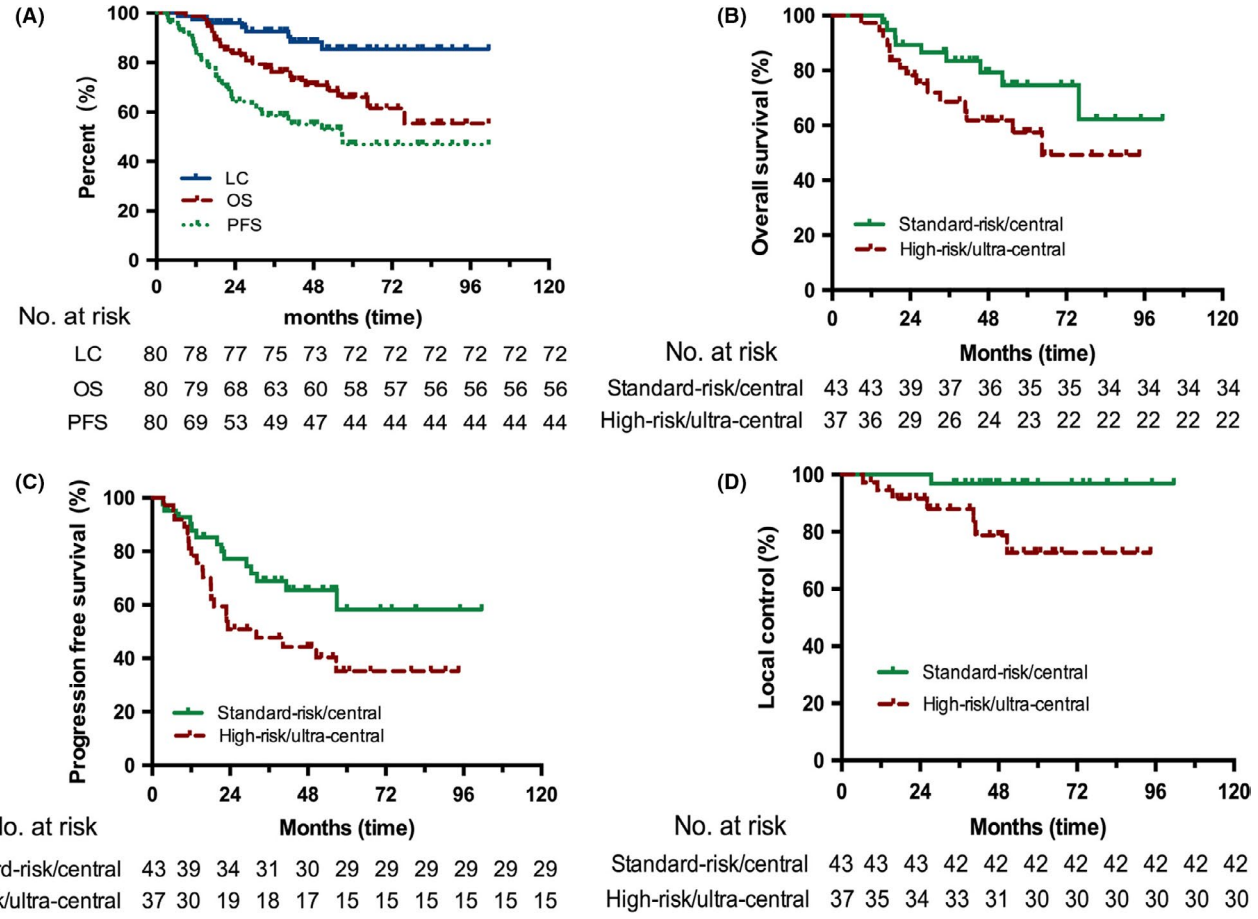

FIGURE 2 Kaplan-Meier curves showing overall survival (OS), progression-free survival (PFS), and tumor local control rate (LC) over time and pattern of failures using cumulative analyses for competing risks of death. A, OS, PFS, and LC for entire group; B-D, OS, PFS, and LC for standard-risk/central and high-risk/ultra-central tumors, respectively

TABLE 2 Univariate analyses of the prognostic factors for OS, PFS and LC in patients with central early-stage inoperable NSCLC treated with SBRT

	OS					PFS					LC			
Characteristic	MST (mo)	3-y (%)	5-y (%)	χ^2	*P*	MST (mo)	3-y	5-y	χ^2	*P*	3-y	5-y	χ^2	*P*
Age (y)														
≤71	NR	73.50	66.40	0.013	.908	56.93	61.2	44.50	0.006	.937	97.30	89.50	0.353	.552
>71	75.83	79.30	64.50			NR	55.40	50.30			91.20	84.20		
Gender														
Male	NR	65.40	62.00	0.481	.488	56.67	58.10	49.50	0.001	.977	95.50	92.20	2.113	.146
Female	NR	81.80	76.00			56.93	59.10	38.80			91.50	76.40		
Diagnosis type														
Pathology	NR	78.50	69.70	11.084	**.004**	56.93	59.90	46.20	0.660	.719	95.50	87.40	0.372	.830
CT/PET/CT	55.53	66.70	50.00			29.03	50.00	50.00			83.30	83.30		
CT	14.53	N/A	N/A			13.73	N/A	N/A			N/A	N/A		
Pathology														
Squamous	75.83	76.10	63.20	2.885	.410	41.30	53.00	48.90	0.177	.981	91.40	91.40	0.461	.927
Adenocarcinoma	NR	79.50	75.30			56.67	67.30	39.10			100.00	81.30		
Other	NR	100.00	N/A			NR	66.70	66.70			N/A	N/A		
NR	55.53	58.30	43.80			29.03	45.00	45.00			83.30	83.30		
Reason for inoperability														
Organ dysfunction	NR	76.30	57.20	0.903	.825	NR	54.60	51.00	2.217	.529	93.10	88.20	2.543	.468
Tumor location	NR	83.30	83.30			NR	83.30	83.30			100.00	100.00		
Elderly	NR	83.50	75.90			50.57	54.30	45.30			100.00	87.50		
Refusal	NR	66.20	66.20			56.67	61.50	20.20			88.80	78.90		
Presence of symptoms														
Yes	75.83	70.30	58.90	4.206	**.040**	41.30	53.30	41.20	3.012	.083	92.00	81.10	3.290	.070
None	NR	90.70	83.10			NR	71.40	61.20			100.00	100.00		
T stage[a]														
T1	NR	86.80	74.00	4.622	.099	56.67	67.00	48.10	1.484	.476	100.00	84.80	0.454	.929
T2a	75.83	71.00	61.70			56.93	53.40	47.50			89.50	89.50		
T2b	NR	55.60	N/A			32.33	41.70	N/A			87.50	87.50		
PTV volume														
<52.76 mL	NR	87.90	80.60	8.901	**.003**	NR	66.70	60.70	5.725	**.017**	100.00	95.80	4.601	**.032**
≥52.76 mL	64.47	64.80	51.90			32.33	49.90	32.50			88.10	77.00		

(Continues)

TABLE 2 (Continued)

Characteristic	OS					PFS					LC			
	MST (mo)	3-y (%)	5-y (%)	χ^2	*P*	MST (mo)	3-y	5-y	χ^2	*P*	3-y	5-y	χ^2	*P*
Tracking modality type														
Xsight	NR	83.40	70.60	1.761	.184	NR	65.90	51.50	0.958	.328	91.60	77.60	3.172	.075
Synchrony	75.83	68.90	61.20			41.30	50.90	41.60			97.30	97.30		
BED_{10}														
<102.6 Gy	75.83	74.50	67.10	0.061	.805	56.67	58.80	46.60	0.007	.933	91.20	81.90	1.264	.261
≥102.6 Gy	NR	77.90	64.50			56.93	58.40	46.90			97.30	92.70		
Tumor categorization														
High-risk/ultra-central tumor	64.47	68.70	57.40	4.215	**.042**	32.10	47.70	35.20	4.559	**.033**	88.00	72.70	8.516	**.004**
Standard-risk/central tumor	NR	83.40	74.60			NR	68.90	58.20			100.00	100.00		

Note: Bold face denotes *P* value < .05. Synchrony (Accuray Inc.); Xsight (Accuray Inc.).

Abbreviations: BED_{10}, biologically equivalent dose at α/β value of 10; CT, computed tomography; Gy, Gray; LC, local control rate; MST, median survival time; N/A, not available; NR, not reached; NSCLC, non-small cell lung cancer; OS, overall survival; PET-CT, positron emission tomography-CT; PFS, progression-free survival; PTV, planning target volume; SBRT, stereotactic body radiation therapy.

[a]American Joint Committee on Cancer (AJCC) 7th edition.

patients (16/80, 20%) after SBRT. Patient characteristics with local failure are provided in Table S1.

3.4 | Prognostic factors associated with OS, PFS and LC

On multivariate analyses, PTV volume and tumor categorization were statistically significant prognostic factors for OS, PFS, and LC, respectively (all $P < .05$, Table 3).

3.5 | Toxicities

Toxicity analysis between ultra-central patients and central patients are presented in Table 4. Toxicities included fatigue, pneumonitis, esophagitis, bronchial stenosis, bronchial occlusion, pleural effusion, pericardial effusion, bronchial fistula, esophageal fistula, and bronchopulmonary hemorrhage. CTCAE v4.0 ≥grade 3 toxicities occurred in only one patient who died from radiation pneumonitis. He was a 71-year-old man treated with 60 Gy in six fractions for a 6.3 × 3.1 cm adenocarcinoma with a central lesion. He developed radiation pneumonitis 2.6 months after SBRT and was treated intensively to help with healing. However, his condition of radiation pneumonia was not effectively controlled, and he died of respiratory failure. In addition, he had interstitial lung disease (ILD) for 15 years and had a bilateral lung V20 of 13.28%.

Except for the above patient, all toxicities in patients were grade 2 or lower. Early toxicities occurred in 40 patients (40/80, 50%), late toxicities in 16 patients (16/80, 20%), and one central patient had pneumonitis and bronchial stenosis (1/80, 1.25%). Pneumonitis (25/80, 31.25%) and bronchial occlusion (14/80, 17.5%) were the most common acute and late toxicities. No significant difference between the ultra-central patients and the central patients was found for toxicities.

3.6 | Dosimetric evaluation

Dosimetric details are summarized in Table S2. Doses to the esophagus, PBT, main bronchus, lobar bronchus, and contralateral lung dosimetry were higher in the ultra-central group than in the central group because the ultra-central tumor is closer to the mediastinum. However, there were no significant differences in spinal cord, heart, trachea, pulmonary artery, pulmonary vein, total lung, and ipsilateral lung dosimetry between the two groups. In addition, patients who had grade 2 bronchial occlusion or stenosis were found to have bronchial involvement and several dosimetric differences.

4 | DISCUSSION

In the present study, we report on our experience in comparing OS, PFS, LC, and toxicity profiles of high-risk/ultra-central versus standard-risk/central early-stage inoperable NSCLC treated with risk-adapted SBRT. When following risk-adapted SBRT dose-fractionation regimens, ultra-central tumors have worse OS, PFS, and

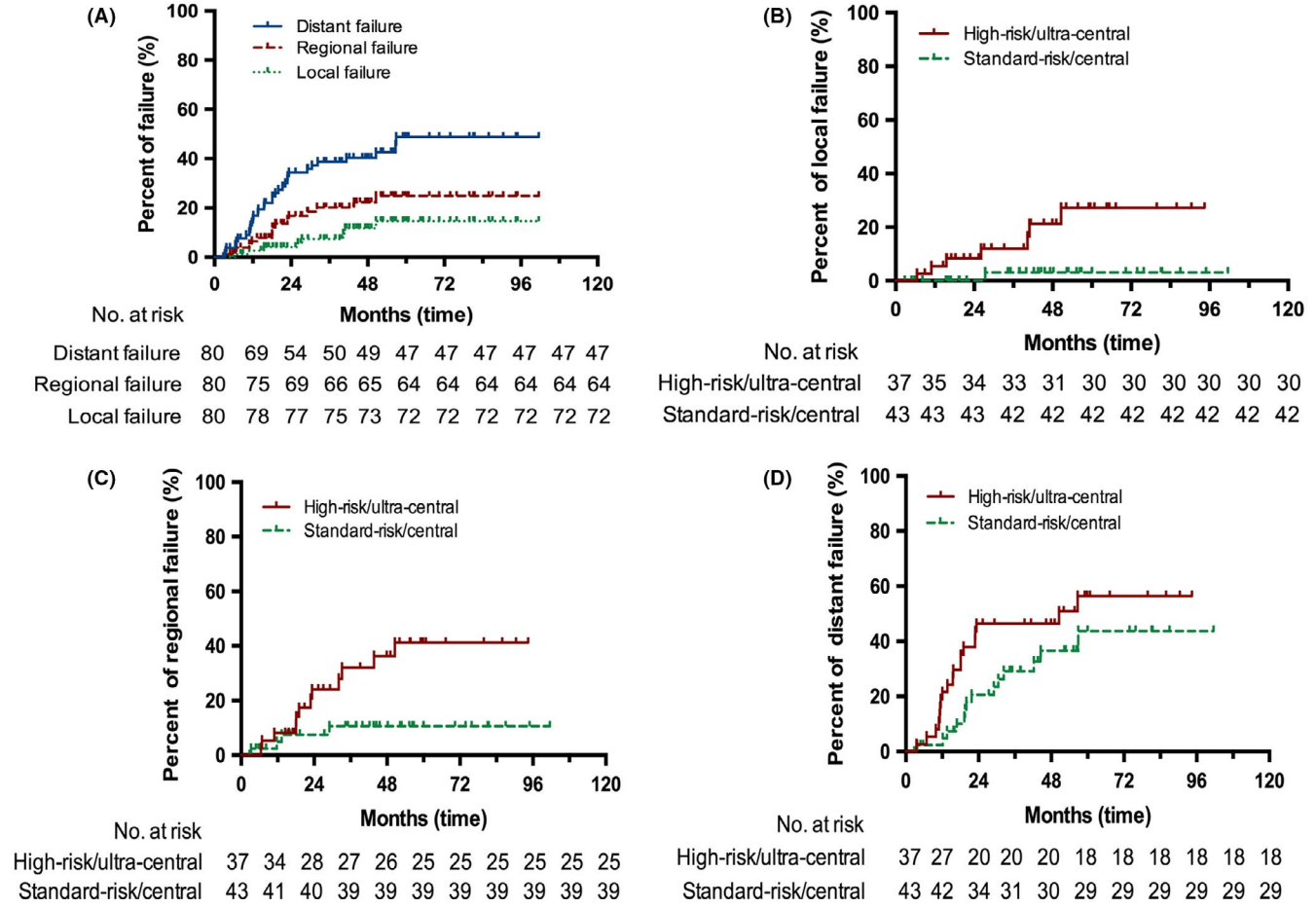

FIGURE 3 Kaplan-Meier curves showing pattern of failures using cumulative analyses for competing risks of death. A, local failure, regional failure, and distant failure for entire group; B-D, local failure, regional failure, and distant failure for standard-risk/central and high-risk/ultra-central tumors, respectively

LC compared with central lesions. However, the toxicity profiles of the two groups are similar, with almost no patients having grade 3 or higher toxicity. These results suggest that future studies should focus on augmentation of tumor control probability in ultra-central lesions while maintaining low rates of toxicity.

Our findings showed that, compared with central lesions, ultra-central tumors have worse OS, PFS, and LC because of risk-adapted SBRT dose-fractionation regimens. Furthermore, OS, PFS, and LC in this study were superior to those reported in other studies of risk-adapted dose-fractionation SBRT schedules for early-stage central NSCLC. These differences may be related to the different definitions of ultra-central tumors (listed in Table S3), use of risk-adapted SBRT dose-fractionation regimens, and different follow-up schedules in these studies. Intriguingly and importantly, our findings concurred with published data that showed that conservative dose-fractionation schedules for central lesions reduced toxicities at the expense of worse efficacy.[39-41]

At the time of last follow up, our study corroborated with other studies showing that the majority of patients ultimately die of systemic disease progression.[42,43] However, adjuvant treatment such as chemotherapy, molecular targeted therapy, or biotherapy after SBRT for these patients was undoubtedly understudied and potentially underused. In the present study, only 14 (14/80, 17.5%), five (5/80, 6.3%), and seven (7/80, 8.8%) patients received chemotherapy, molecular targeted therapy, or biotherapy, respectively, after SBRT. Few studies suggest that the treatment strategy of SBRT following chemotherapy is associated with improved PFS and OS for patients with early-stage NSCLC.[44,45] However, recent studies showed that adjuvant chemotherapy following definitive SBRT is not associated with survival and reduced regional-distant failure benefits for patients with early-stage NSCLC.[45,46] Unfortunately, a prospective study evaluating the addition of chemotherapy to SBRT in early-stage NSCLC (NCT02319889) has been terminated due to lack of funding. Together, these previous findings indicate that adjuvant treatment after SBRT remains poorly understood and warrants further investigation.

In our study, patients with high-risk/ultra-central and standard-risk/central early-stage inoperable NSCLC treated with risk-adapted dose-fractionation SBRT regimens similarly experienced very little toxicity; all toxicities in central tumor patients were grade 2 or lower. Also, Mangona et al used a propensity score matched-pair approach to compare central and peripheral lung

TABLE 3 Multivariate analyses of predictors for OS, PFS, and LC in patients with central early-stage inoperable NSCLC treated with SBRT

	OS (n = 80)			PFS (n = 80)			LC (n = 80)		
Characteristic	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value
Age (≤71 vs >71 y)	1.024	0.407-2.578	.96	1.203	0.587-2.466	.614	1.233	0.099-15.345	.87
Gender (male vs female)	0.919	0.326-2.587	.872	1.317	0.629-2.756	.465	2.542	0.288-22.436	.401
Diagnosis type (pathology vs CT/PET-CT vs CT)	7.118	0.923-54.874	.06	1.631	0.359-7.417	.526	7.271	0.029-1807.6	.481
Pathology (squamous cell vs adenocarcinoma vs other vs none reported)	0.586	0.255-1.346	.208	0.849	0.447-1.612	.617	0.397	0.036-4.422	.452
T stage (T1 vs T2a vs T2b)[a]	0.947	0.439-2.045	.891	0.824	0.464-1.461	.507	0.493	0.097-2.499	.393
PTV volume (<52.76 mL vs ≥52.76 mL)	3.652	1.149-11.607	**.028**	2.593	1.116-6.025	**.027**	19.23	1.493-247.67	**.023**
Reason for inoperability (organ dysfunction vs tumor location vs elderly vs refusal surgery)	0.960	0.729-1.264	.769	1.017	0.826-1.252	.874	0.792	0.375-1.674	.542
Presence of symptoms (Yes vs No)	0.379	0.102-1.404	.147	0.548	0.228-1.315	.178	0.001	0.001-	.924
Tracking modality type (Xsight vs Synchrony)	1.955	0.768-4.977	.160	1.626	0.789-3.351	.187	0.656	0.04-10.778	.768
BED_{10} (≥102.6 Gy vs <102.6 Gy)	0.331	0.112-0.983	.056	0.469	0.199-1.106	.083	0.25	0.013-4.888	.361
Tumor categorization (high-risk/ultra-central tumor vs standard-risk/central tumor)	0.263	0.092-0.754	**.013**	0.304	0.136-0.682	**.004**	0.476	0.124-0.783	**.029**

Note: Bold face denotes *P* value < .05. Synchrony (Accuray Inc.); Xsight (Accuray Inc.).
Abbreviations: BED_{10}, biologically effective dose at α/β value of 10; CI, confidence interval; CT, computed tomography; Gy, Gray; HR, hazard ratio; LC, local control; NSCLC, non-small cell lung cancer; OS, overall survival; PET-CT, positron emission tomography/computed tomography; PFS, progression free survival; PTV, planning target volume; SBRT, stereotactic body radiation therapy.
[a]American Joint Committee on Cancer (AJCC) 7th edition.

TABLE 4 Early and late toxicity analysis between ultra-central patients and central patients

	High-risk/ultra-central/tumors (n = 37)		Standard-risk/central tumors (n = 43)	
Characteristic	<Grade 3	≥Grade 3	<Grade 3	≥Grade 3
Early toxicity				
Fatigue	0	0	1 (2.3%)	0
Pneumonitis	12 (32.4%)	0	10 (23.2%)	1 (2.3%)[a]
Esophagitis	0	0	0	0
Bronchial stenosis	4 (10.8%)	0	0	0
Bronchial occlusion	3 (8.1%)	0	1 (2.3%)	0
Pleural effusion	4 (10.8%)	0	3 (7.0%)	0
Pericardial effusion	1 (2.7%)	0	0	0
Late toxicity				
Pneumonitis	0	0	2 (4.7%)	0
Esophageal fistula	0	0	0	0
Bronchial stenosis	1 (2.7%)	0	0	0
Bronchial occlusion	6 (16.2%)	0	4 (9.3%)	0
Bronchial fistula	0	0	0	0
Bronchopulmonary hemorrhage	0	0	0	0
Pleural effusion	1 (2.7%)	0	3 (7.0%)	0

[a]Grade 5 pneumonitis occurred in one patient with poor lung function.

tumor SBRT, and similar safe toxicity profiles for both central and peripheral lung cancer were seen.[47] It is worth noting that only one patient died from radiation pneumonitis after SBRT. This patient had interstitial lung disease (ILD) for 15 years and had a bilateral lung V20 of 13.28%; thus, the cause of death was likely a combination of cancer, underlying comorbidities, and toxicity of SBRT.

Radiation pneumonitis is the most frequent toxicity observed after SBRT, and the reported incidence of radiation pneumonitis after SBRT in this study was parallel with those reported in other studies ranging from 10% to 30%.[48] Pre-existing ILD is thought to be a risk factor for fatal radiation pneumonitis after SBRT and, accordingly, severe ILD was regarded as a relative contraindication in the clinical guidelines for SBRT published by the Japanese Society for Therapeutic Radiation and Oncology.[49] Therefore, further studies are necessary to show that prescreening for ILD is important for predicting the risk of radiation pneumonitis when planning SBRT.

Limitations of the present study include those inherent to retrospective analyses. Selection bias of patients and treatment approaches (particularly with dose) is likely present because of violation of normal tissue constraints. Furthermore, the SBRT treatment protocol changed over time and this study period evolved during the long 13-year timespan, meaning that dose-fraction schedule heterogeneity might have existed. Second, there are conflicting data in the literature as to what actually defines "standard-risk/central" versus "high-risk/ultra-central" with varying definitions. Third, because grade 3-5 toxicity events were rare, it was necessary to include less clinically significant grade 2 events to facilitate statistically meaningful analysis. Finally, in some patients in whom real-time tracking for SBRT was not used, ITV was defined as GTV with the appropriate margins obtained by 4-D CT detection of the motion of the lesions, and then expanded by 5 mm to generate the PTV.

In conclusion, ultra-central tumors have a poor OS, PFS, and LC versus central patients because of the use of risk-adapted dose-fractionation radiotherapy schedules that allow for equal and favorable toxicity profiles. Future studies should focus on augmentation of tumor control probability in ultra-central lesions while maintaining low rates of toxicity. We are currently awaiting the final results from the RTOG 0813, EORTC LungTech, and SUNSET prospective clinical trials of SBRT for central or ultra-central lung tumors. The results of the current study may be used to interpret the results of these trials, and it would be very interesting if these studies subdivided their results into central and ultra-central tumors.

ACKNOWLEDGMENT

This work was supported by the National Natural Science Foundation of China (No. 81872465 and No. 81502660).

DISCLOSURE

Authors declare no conflicts of interest for this article.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Meng M-B, Wang H-H, Zaorsky NG, et al. Risk-adapted stereotactic body radiation therapy for central and ultra-central early-stage inoperable non-small cell lung cancer. *Cancer Sci*. 2019;110:3553-3564. https://doi.org/10.1111/cas.14185