Dose-response relationship of stereotactic body radiotherapy for ultracentral tumor and comparison of efficacy with central tumor: a meta-analysis

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Background: Ultracentral (UC) tumors, a subset of central lung tumors defined as those that abut the proximal bronchial tree (PBT), have been contraindicated for stereotactic body radiotherapy (SBRT). The present meta-analysis evaluated the efficacy of SBRT for UC and central tumors, and dose-response for local control (LC) of UC tumors.

Methods: Databases including MEDLINE and EMBASE were searched up to March, 2020, to identify studies regarding SBRT for UC and/or central tumors. The primary endpoints were LC and overall survival (OS), while secondary endpoints were grade ≥3 and 5 complications.

Results: Fourteen studies including 892 patients were included. In the UC and central tumor groups, the 1-year OS rates were 82.2% and 85.4% (P=0.556), respectively, and the 2-year OS rates were 66.4% and 71.9% (P=0.522), respectively. The 1- and 2-year LC rates in the UC and central tumor groups were 93.9% and 97.8% (P=0.023) and 90.4% and 93.7% (P=0.459), respectively. The pooled grade ≥3 complication rates in the UC and central tumor groups were 9.0% and 4.4% (P=0.06), while the corresponding grade 5 complication rates were 5.7% and 2.1% (P=0.087). The dose-response for LC was shown in the meta-regression (P<0.0001), and 1-year LC rates were significantly different (94.4% *vs.* 59.3%, P<0.001) with very low heterogeneities in both subgroups, with threshold of 85 Gy10. Of the 28 fatalities, 12 (42.8%) were caused by hemorrhage or bronchial stenosis, and another 12 (42.8%) by pneumonia or respiratory failure.

Conclusions: The oncologic outcomes of patients with UC and central tumors were comparable post-SBRT. A dose of at least ≥85 Gy10 is recommended for SBRT of UC tumors. Causes of complications should be further studied as UC tumors are more prone to serious toxicities.

Keywords: Lung cancer; central tumor; ultracentral (UC) tumor; stereotactic body radiotherapy (SBRT); stereotactic ablative body radiotherapy

Introduction

Lung cancer has long been the primary cause of cancer-related deaths (1), and surgical resection has been the standard curative modality for early-stage disease (2,3), Although external beam radiotherapy (EBRT) had previously been applied for locally advanced or metastatic disease, precise tumor targeting using updated technologies namely, stereotactic body radiotherapy (SBRT), enable curative treatment. Unlike conventional EBRT, SBRT delivers a very high dose precisely to the target in a relatively short period, and recent randomized trials have shown that outcomes post-SBRT were comparable to those following surgery (4,5).

The feasibility and efficacy of SBRT for treating peripheral tumors were previously demonstrated, but those for treating central tumors remain unclear. An early trial found that the risk of grade ≥3 toxicity was 11-fold higher when using SBRT to treat central tumors, defined as those within a 2 cm radius of the proximal bronchial tree (PBT), than treating peripheral tumors (6). However, central tumors are commonly inoperable or require more extensive surgery than do peripheral tumors; hence, many researchers have continued administering SBRT to central tumors using more protracted regimens. With the downside of having a moderate risk level of complications (the grade ≥3 complication rate is ~9%), the oncologic outcomes of patients treated with SBRT for central tumors were comparable to those treated for peripheral tumors (7,8).

While careful administration of SBRT to central tumors has been performed, an independent concept of "ultracentral" (UC) tumors was introduced; this generally refers to tumors that abut the PBT (9). When SBRT is applied to such tumors, the target volume must cover the PBT, rendering its irradiation with the full treatment dose inevitable. Corradetti *et al*. (10). described a patient who developed fatal central airway necrosis owing to UC tumor irradiation and, therefore, warned of the risk of such a treatment. However, UC tumors are more intractable and have fewer curative options than do central tumors. In early studies, some investigators reported serious toxicity rates of over 20% (11,12), while other studies reported more favorable results (4,13).

Several researchers eagerly reported their clinical experiences recently, and their data were more encouraging than in the past. A suitable SBRT dose information for UC tumors has been longed by clinicians. At the same time, whether UC tumors have different outcomes post-SBRT

from central tumors is controversial (13-17). Hence, the present meta-analysis was performed to assess the dose-response relationship and feasibility of SBRT for UC tumors and to compare outcomes between UC and central tumors.

We present the following article in accordance with the PRISMA reporting Guideline (available at http://dx.doi.org/10. 21037/tlcr−20−503).

Methods

The present meta-analysis and systematic review were performed to address the following clinical (PICO) questions: "(I) Does SBRT for UC tumors have feasibility and dose-response relationship? (II) Are UC tumors a distinct clinical subset of central tumors for purposes of considering SBRT application?" Databases including MEDLINE and EMBASE were searched for records available up to March 1, 2020. We used the following search terms: (ultracentral OR "ultra central" OR "ultra-central") and lung and ("radiation therapy" or "radiotherapy"). Reference lists from the searched articles were used to locate additional publications. No language or time restrictions were applied. Unpublished literature was considered if it fully satisfied the inclusion criteria.

Inclusion criteria

Eligible studies included in the present meta-analysis met all of the following criteria: (I) clinical trials; (II) inclusion of ≥5 patients with UC tumors who underwent SBRT; (III) definition of UC tumor must include "abutting the PBT" (e.g., tumors described as "<1 cm from the PBT" were not included, as they could encompass central tumors); (IV) SBRT was delivered at either >4 Gy per fraction or in ≤10 fractions; (V) SBRT was not performed in re-irradiation setting and 5) at least one of the primary endpoints was reported. The primary endpoints were rates of local control (LC) and overall survival (OS), while secondary endpoints were of grade ≥3 or grade 5 complications. Initial screening was performed using citations and titles to filter out duplicate studies, reviews, editorials, letters, and *in vivo* or *in vitro* studies. Abstracts were reviewed to exclude studies with irrelevant subjects or formats. Full-text reviews were then performed to identify studies that fulfilled all the inclusion criteria. Multiple studies from the same institutions were sorted using the following criteria—prioritized in numerical order: (I) studies with the largest number of

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patients with UC; (II) published articles were preferred over conference abstracts. We included multiple studies from the same institution if they had no overlapping patients or if the overlap was negligible. Screening for these inclusion criteria was performed by two independent researchers, and final inclusion was decided upon mutual consent.

Data collection

Data collection from the included studies was performed using a pre-designed standardized form to evaluate (I) background information including authors, affiliations, study type, and number of patients; (II) clinical information including T stage, proportion of squamous histology cases, target volume, proportion of metastasis or recurrence cases, SBRT dose, and definition of UC tumor; (III) outcomes of interest including LC, OS, and complication of grade ≥3. LC and OS rates were estimated from descriptive graphs, considering follow-up periods, in the absence of numeral data. The prescribed SBRT doses were converted to the biologically equivalent dose (BED) using an α/β ratio of 10 and equivalent dose in 2 Gy fractions (EQD2) using α/β ratios of 3 and 10. An α/β ratio of 10 represented aggressive biologic behavior in the early responding tissues (i.e., the tumors), while an α/β ratio of 3 represented that in late-responding tissues and was commonly used to estimate complication risks (18). The data collection process was performed by two independent researchers, and disagreements were resolved by conducting an additional literature review and mutual discussion.

Quality assessment

As most of the included studies were retrospective, the Newcastle-Ottawa scale (19) was used for quality assessment. Studies with scores of 7–9 and 4–6 were considered to be of high and medium qualities, respectively.

Statistical analysis

Pooled analyses were performed for all primary and secondary endpoints. The selection of the effects model depended on the nature of the included studies and their data, rather than on the calculated heterogeneity (20). A random-effects model was used considering the inevitable heterogeneity of the patients' characteristics and treatment details (21). Heterogeneity among the studies was assessed using Cochran Q test and I^2 statistics; (22,23). Significant heterogeneity was considered present when P<0.1 and $I^2 \geq 50\%$; I^2 values of 25%, 50%, and 75% corresponded to low, moderate, and high degrees of heterogeneity, respectively. Pooled analyses of 1- and 2-year LC and OS rates were performed for controlled studies, whereas only analyses of 1-year LC and OS rates were performed for all studies because the follow-up durations were short in single-arm UC case series. Subgroup comparisons were performed using Q tests on the basis of analysis of variance, and P values <0.05 indicated significant differences among the subgroups. Meta-regression was performed to quantitatively assess the relationship between the endpoints and BED_{10Gy}, and P values <0.05 represented significant correlations. Publication biases were evaluated via the visual inspection of funnel plots, quantitative results of the Egger's test, and analyzing Rosenthal's fail-safe number (24,25). If funnel plot inspection showed asymmetric distributions and the 2-tailed P value of the Egger's test was <0.1, then the fail-safe number was calculated; if the possibility arose that studies similar to that number may have been missed, Duval and Tweedie's trim and fill method (26) was used to determine the corrected relevant values. All statistical analyses were conducted using the Comprehensive Meta-Analysis software version 3 (Biostat, Inc., Englewood, NJ).

Results

Among the 72 studies that were initially searched, 14 studies including 892 patients (411 and 481 with UC and central tumors, respectively), were finally included (9,11-17,27-32). The study inclusion process is described in *Figure S1*. Eight of the studies were controlled trials that included patients with both UC and other central tumors, whereas six were single-arm observational studies of patients with UC. Two studies from Georgetown University were included in the final list (28,29), as the authors unanimously agreed that the number of overlapping patients was small enough not to yield a significant bias whereas including the data would enrich the pooled analyses. We also included our older data that were reported in a previous publication and subsequently updated (30,33). All the included studies were described in full-text articles. Six single-arm observational studies (11,27-30,32) were categorized as having medium quality according to the Newcastle-Ottawa scale, and 8 controlled studies (9,13-17) were considered high-quality.

The proportions of T1 tumors ranged from 2% to 76% with a median of 51.8%. The median PTV ranged from 23.2 to 111.3 cm³, with a median of 68.5 cm³. The median

prescribed dose ranged from 59.5 to 132 BED_{Gy10}, with a median of 100 BED_{Gy10}. Basic information about the included studies is summarized in *Table 1*, while clinical information is shown in *Table 2*.

Comparison of UC and other central tumors

In pooled analyses of the controlled studies, the 1-year LC rates were 93.9% (95% CI: 95.6–98.9%) and 97.8% (95% CI: 95.6–98.9%) in the UC and central tumor groups, respectively (P=0.023), while the corresponding 2-year LC rates were 90.4% (95% CI: 77.8–96.2%) and 93.7% (95% CI: 88.3–96.7%), respectively (P=0.459). Moreover, the corresponding 1-year OS rates were 82.2% (95% CI: 71.7–89.7%) and 85.4% (95% CI: 78.9–90.1%), respectively (P=0.556), while the 2-year OS rates were 66.4% (95% CI: 51.4–78.7%) and 71.9% (95% CI: 61.0–80.8%), respectively (P=0.522). The pooled grade ≥3 complication rates in the UC and central tumor groups were 9.0% (95% CI: 5.0–15.9%) *vs.* 4.4% (95% CI: 2.8–6.9%) (P=0.06), while the grade 5 complication rates were 5.7% (95% CI: 2.6–11.9%) *vs.* 2.3% (95% CI: 1.1–4.6%) (P=0.087). The results of the pooled analyses are summarized in *Table 3* and are also shown as forest plots in *Figure 1*.

Pooled analyses among all UC cohort

In a pooled analyses of all UC cohorts from controlled and single-arm studies, the 1-year LC and OS rates were 90.2% (95% CI: 80.1–95.4%) and 77.6% (95% CI: 69.5–84.0%), respectively; moreover, grades ≥3 and 5 complication rates were 10.4% (95% CI: 5.9–17.7%) and 6.1% (95% CI: 3.3–11.0%), respectively. Subgroup comparisons were performed according to the percent of patients in a study with recurrence or metastases, and median PTV volume. On subgroup comparisons, the 1-year LC rates were 94.1% (95% CI: 89.2–96.8%) and 83.0% (95% CI: 65.5–92.6%) in the subgroups representing recurrence or metastases incidences of <50% and ≥50%, respectively (P=0.045). The pooled 1-year OS rates were 87.0% (95% CI: 79.0–92.3%) and 69.9% (95% CI: 61.0–77.4%) in the subgroups representing median PTVs of ≤78 and >78 cm³, respectively (P=0.003). Above results are summarized in *Table 4*.

Dose-response for LC among all UC cohort (meta-regression analyses)

The median BED_{10Gy} of the studies was significantly

correlated with the 1-year LC rate (P<0.0001, *Figure 2A*). With the threshold of 85 Gy_{10}, commonly prescribed as 55 Gy in 10 fractions or 45 Gy in 5 fractions, 1-year LC rates were significantly different (94.4% *vs.* 59.3%, P<0.001) with very low heterogeneities in both subgroups (I^2=~0% in both); the result is shown in *Figure 2B* in detail. Meta-regression results were not statistically significant between the median $BED_{10\,Gy}$ and 1-year OS, grade ≥3 complications, and grade 5 complications. The results of meta-regression analyses are shown in *Table 4*. Forest plots and scatterplots of meta-regression were shown in *Figure S2*.

Qualitative analysis of fatal complications

As fatal complications are the most important concern when applying SBRT for UC tumors, we qualitatively analyzed the reported toxicities in addition to the pooled analyses. Data regarding fatal complications were available for all the included studies involving 892 patients (411 and 481 with UC and central tumors); fatal complications were reported in 28 patients. Among them, 24 had UC tumors while 4 had other central tumors. The fatal complications among patients with UC tumors were hemorrhage (9, 37.5%), pneumonia or respiratory failure (9, 37.5%), bronchial stenosis or fistula (3, 12.5%), and cardiac toxicity (3, 12.5%). Fatal complications among patients with central tumors included pneumonitis (3, 75%) and myocardial infarction (1, 25%). The reported complication rates and their suggested risk factors are shown in *Table 5*.

Publication bias assessment

Egger's test showed that possible publication bias was present for the 1-year LC rate (P<0.001), 2-year LC rate (P=0.005), 1-year OS rate (P=0.051), grade ≥3 complication rate (P=0.003), and grade 5 complication rate (P<0.001). The fail-safe numbers (e.g., the numbers of unpublished or unfound studies enough to statistically nullify observed effects) to prevent publication bias were 889, 719, 877, 1,348, and 1,294, respectively. Since it is unreasonable to assume that studies with these numbers were missing from our literature search, the originally observed effect sizes rather than adjusted values were shown as results.

Discussion

Tumors abutting the PBT are generally either inoperable or require extensive surgery such as pneumonectomy

Table 1 Basic information of the included studies

First author	Source of information	Affiliation	Study type	NOS score	Patients (n)	Age [y]	T1; T2; T3 (%)	SQCC (%)	ECOG PS score	Median PTV (range) (cm3)	Metastasis or recurrence (%)	UC definition
Studies of both UC and C tumors												
Raman	*Clin Lung Cancer,* 2018	Princess Margaret Cancer Center, Canada	R	9	UC: 21	74 [44–89]	55; 45; 0	52.6	0–1 (90.5%)	68.5 (20.1–238.3)	0	PTV directly abuts/overlaps the PBT, trachea, esophagus, pulmonary vein/artery
					C: 161	76 [51–91]	66.9; 31.3; 1.9	21.5	0–1 (78.9%)	42.4 (9.7–246.3)	0	
Comparison (P)						0.77	0.41	0.01	0.05	0.004	n/a	
Lenglet	*Radiother Oncol,* 2019	l'Université de Montréal, Canada	R	9	UC: 77	75 [51–94]	48; 27; 25	35	Median KPS 90 (50–100)	31.1 (6.6–274.3)	0	PVT overlaps PBT, trachea, great vessels, pericardium
					C: 60	75 [56–92]	65; 20; 15	23	Median KPS 90 (50–100)	23.2 (6.5–111.2)	0	
Comparison (P)						n/a	n/a	n/a	n/a	n/a	n/a	
Meng	*Cancer Sci,* 2019	Tianjin medical university, China	R	9	UC: 37	71 [51–85]	48.6; 51.1 (T1,2)	40.6		55.0 (9.9–264.5)	0	Abutment of PBT
					C: 43	71 [51–83]	44.2; 48.8 (T1,2)	48.8		49.2 (2.8–159.7)	0	
Comparison (P)						0.99	0.16	0.15		0.5	n/a	
Chang	*Radiother Oncol,* 2018	Sunnybrook Odette Cancer Center, Canada	R	7	UC: 46	72 [63–80, IQR]				78.9 (45.7–136, IQR)	73.9 (mostly oligomets or oligoprogression)	ITV directly abutted the proximal bronchial tree
					C: 61	75 [67–83, IQR]				55.2 (42.5–107, IQR)	41 (mostly oligomets or oligoprogression)	
Comparison (P)						0.16		0.01		0.26	0.0079	
Haseltine	*Pract Radiat Oncol,* 2016	MSKCC, US	R	8	UC: 18	69 [49–84]	67; 33 (T1,2)	44	KPS ≥80 in 83%	Tumor's greatest dimension: ≤3 cm in 67%	~20 was recurrent, but all were cT1, 2N0M0	Touch or invade trachea or mainstem bronchus, or lobar bronchus.
					C: 90	79 [52–95]	76; 24 (T1,2)	77	KPS ≥80 in 70%	≤3 cm in 74%		
Comparison (P)						0.13	NS	0.022	NS	NS	n/a	
Chaudhuri	*Lung Cancer,* 2015	Stanford University, US	R	8	UC: 7	74 [30–90]	62.9; 33.3; 3.7	33.3		44.7 (14.2–224)	not reported	GTV abuts proximal branch or trachea (excluding GTV abuts esophagus)
					C: 21							
Comparison (P)						n/a	n/a	n/a	n/a	n/a	n/a	
Nguyen	*Pract Radiat Oncol,* 2019	University of California Davis, US	R	8	UC: 14	66 [41–87]					7.1	PVT overlap PBT or esophagus
					C: 39	73 [31–92]					30.7	
Comparison (P)						n/a	n/a	n/a	n/a	n/a	n/a	
Cooke	*Tech Innov Patient Support Radiat Oncol,* 2020	University of Oxford, UK	R	7	UC: 22	71 [38–89]			0 (48.1%); 1 (51.9%)	73.6 (64.3–100)	100 (all oligometastasis)	GTV directly abut PBT
					C: 6					100.4 (96.1–103.2)		
Comparison (P)						n/a	n/a	n/a	n/a	n/a	n/a	

Table 1 (*Continued*)

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First author	Source of information	Affiliation	Study type	NOS score	Patients (n)	Age [y]	T1; T2; T3 (%)	SQCC (%)	ECOG PS score	Median PTV (range) (cm3)	Metastasis or recurrence (%)	UC definition
Single-arm studies												
Tekatli	*J Thorac Oncol*, 2016	VU University Medical Center, Netherland	R	6	UC: 4	77.5 [57.7–90.8]	8; 36; 38 (remainders are described as 'recurrent')	49	WHO 0–1 (51%)	104.5 (17.7–508.5)	17	PTV overlaps trachea of main bronchi
Cong	*Thorac Cancer,* 2019	Chinese PLA General Hospital, China	R	4	UC: 51	63 [35–82]	2; 11.8; 31.4; 54.9 (T4)	56.9	0–1 (96.1%)	111.3 (9.8–688.9)	60.8	GTV overlapping trachea or PBT
Lischalk	*Radiat Oncol*, 2016	Georgetown University, US (2008–2011)	R	5	UC: 20	66 [24–82]		20	0–1 (100%)	Mean 111.3 (22.6–300)	100 (Controlled metastases: 65)	"High-risk," with abutment or invasion to mainstem bronchus
Unger	*J Hematol Oncol*, 2010	Georgetown University, US (2005–2009)	R	4	UC: 20	63.5 [13–82]			0–1 (75%)	GTV: 73 (23–324)	85 (Lung primary, 41)	"High-risk," with abutment or invasion to mainstem bronchus
Yang	*Thorac Cancer*, 2020	Peking University	R	5	UC: 21	66 [52–81]	27.3; 31.8; 9.5; 28.6	38.1		36.5 (16.4–133.1)	52.40	PTV abut PBT, heart, great vessel, but not esophagus
Park	*Int J Radiat Biol*, 2019	Korea University, Korea	R	4	UC: 10	66 [51–75]		50	0–1	Mean 83.7 (17.1–144.3)	60	GTV abutting PBT

C, central; ECOG PS, Eastern Cooperative Oncology Group performance status; GTV, gross tumor volume; IQR, interquartile range; KPS, Karnofsky performance status; MSKCC, Memorial Sloan Kettering Cancer Center; NOS, Newcastle-Ottawa scale; NS, not significant; oligomets, oligometastases; PBT, proximal bronchial tree; PTV, planning target volume; R, retrospective; SQCC, squamous cell carcinoma; UC, ultracentral; WHO, World Health Organization; ITV, internal target volume.

Table 2 Clinical outcomes of patients in the included studies

First author	Patients (n)	SBRT dose	EQD2 (α/β 3, 10)	BED$_{10Gy}$	Median FU (months)	1-year LC rate (%)	2-year LC rate (%)	Median OS (months)	1-year OS rate (%)	2-year OS rate (%)
Studies with both UC and C tumors										
Raman	UC, 21	60 Gy/8 F (76.9% of patients)	126, 87.5	105		100	100	23.8	77.3	45.5
	C, 161	60 Gy/8 F (50.6%)	126, 87.5	105	21.4	98.1	96.7	39.4	80.7	62.7
		48 Gy/4 F (32.3%)	144, 88	105.6						
Comparison (P)							0.36			0.4
Lenglet	UC, 77	M50 [40–60] in M5F [3–8]	M130,	M100 [72–180]	36	92	73	37	87	62.3
	C, 60		M83.3			100	92	57	90	83.3
Comparison (P)							0.186			0.027
Meng	UC, 37	M56 Gy [48–60]/7 F [5–10]	M123.2, M84	M96.0 [81.3–132.0]	44.5	94.5	91.9	64.5	97.3	78.4
	C, 43	M60 Gy [48–60]/6 F [4–8]	M100, M156	M120.0 [83.3–150.0]		100	100	not reached	100	88.3
Comparison (P)							0.004			0.042
Chang	UC, 46	Mostly 50 Gy/5 F	–	>100 in 71.7%	16.7	95.7	95.7	24.5	65.2	50.4
	C, 61		–	>100 in 91.8%		98.4	96.6	29.7	83.6	57.7
Comparison (P)							0.92			0.1
Haseltine	UC, 18	M45 Gy/5 F	M108, 71.25	M85.5 [85.5–100]	22.5	–	77.4 (UC&C)*	–	–	63.9 (UC&C)*
	C, 90			M85.5 [85.5–180]						
Comparison (P)						No significant difference in <1 vs. >1 cm from PBT				
Chaudhuri	UC, 7	50 Gy/4 F (70.5%)	155, 93.75	112.5	18.4	100	100	–	100	80
	C, 21					95.2	90.4	–	100	63.2
Comparison (P)							0.64			0.62
Nguyen	UC, 14	M50 [40–60] in M5F [4–8]	M130,	M100 [80–105]	19.7	100	89	–	76.0	76
	C, 39		M83.3			97.4	85	–	84.6	73
Comparison (P)							0.72			0.75

Table 2 (*continued*)

Table 2 (*continued*)

First author		Patients (n)	SBRT dose	EQD2 (α/β 3, 10)	BED$_{10Gy}$	Median FU (months)	1-year LC rate (%)	2-year LC rate (%)	Median OS (months)	1-year OS rate (%)	2-year OS rate (%)
Cooke	UC	22	60 Gy/8 F	126, 87.5	105	11.6	94.1	–	–	84.4	–
	C	6					100	–	–	75.0	–
Comparison (P)							0.49			0.22	
Single-arm studies											
Tekatli	UC	47	60 Gy/5 F	96, 75	132	29.3	100	100	15.9	61.5	28.7
Cong	UC	51	M35 Gy/5 F	M70, 49.6	M59.5	17	54	~47	18	76.5	38.9
Lischalk	UC	20	M40 Gy/5 F	M88, 60	M72	19	70.1	57.4	16.3	75.0	40.0
Unger	UC	20	M35 Gy/5 F	M70, 49.6	M59.5	10	63	N/A	10	54.0	N/A
Yang	UC	21	60Gy/8F	126, 87.5	105	15	92.9	92.9	15	87.5	76.6
Park	UC	10	M55 Gy/10 F	M93.5, 71	M85.2	14	100	N/A	14	90.0	N/A

*, including both ultracentral and central tumors. BED, biologically equivalent dose; C, central; EQD2, equivalent dose in 2 Gy fractions; FU, follow-up; LC, local control; OS, overall survival; PBT, proximal bronchial tree; UC, ultracentral. Capital M prefix refers to the median value.

(11,34). Therefore, the feasibility of SBRT, which can provide a curative opportunity, is of great clinical significance. The application of SBRT for UC tumors had been considered impossible until just a few years ago, and the feasibility of SBRT was gradually acknowledged by pioneering researchers (35). We previously performed a meta-analysis of the literature published until April 2018 (36). Surprisingly, our current study (merely 2 years later) included 3 times as many full-text publications as did the previous meta-analysis; this reflects the rigorous academic interest in the subject. In addition to the merits of including more research articles, the present study confers comparative results between UC and central tumor and dose-response for LC and suggestion of dose prescription of SBRT for UC tumors.

Regarding the primary outcomes of the study, the pooled OS rates at 1 and 2 years were not different between the UC and central tumor groups. Although the 1-year LC rates for the UC and central tumor groups were significantly different (93.9% *vs.* 97.8%, P=0.023), the clinical impact of this difference might be moderate considering that the 2-year LC rates were not significantly different and the 1-year LC rates in both groups were very high. The narrow range of 1-year LC rates reported as well as the very low heterogeneity between the studies might also have produced the statistical difference. Taken together, oncologic outcomes after SBRT for UC and central tumors are thought to be very similar to outcomes in clinical practice.

In the pooled analyses of all UC tumor cohorts, the 1-year LC and OS rates were favorable (90.2% and 77.6%, respectively), demonstrating the efficacy of SBRT. Subgroup comparisons revealed that a higher proportion of recurrence or metastasis influenced the LC rate (P=0.045), while the OS rate was largely affected by tumor size (P=0.003); these results were expected when considering current knowledge of tumor biology (37-39). The dose-response relationship for LC was significant in the meta-regression (P<0.0001, *Figure 2A*). However, an overwhelming majority of studies used SBRT doses near or mildly higher from 100 Gy$_{10}$, reflecting that most oncologists tended to prescribe higher doses than those recommended by Onishi *et al.* (40). and were concerned for possible toxicities simultaneously. The prescription dose of 59.5–72 Gy$_{10}$ was shown to be suboptimal (27-29) as it only showed a pooled 1-year LC rate of 59.3%. With the threshold of 85 Gy$_{10}$, all studies with higher prescription doses reported a 1-year LC rate of over 90%, and the pooled rate was favorable at 94.3%

Table 3 Comparison between ultracentral and central tumor groups

Variable	No of cohorts	Patients (n)	Heterogeneity (P)	I^2 (%)	Heterogeneity	Effect size (95% CI)	Comparison (P)
Local control comparison (controlled studies only)							
UC, 1-year	7	224	0.961	~0.0	Very low	93.9% (95.6–98.9%)	0.023
C, 1-year	7	391	0.896	~0.0	Very low	97.8% (95.6–98.9%)	
UC, 2-year	6	202	0.011	66.1	High	90.4% (77.8–96.2%)	0.459
C, 2-year	6	385	0.076	49.9	Medium	93.7% (88.3–96.7%)	
Overall survival comparison (controlled studies only)							
UC, 1-year	7	224	0.027	58.0	High	82.2% (71.1–89.7%)	0.556
C, 1-year	7	391	0.159	35.3	Medium	85.4% (78.9–90.1%)	
UC, 2-year	6	202	0.002	74.1	High	66.4% (51.4–78.7%)	0.522
C, 2-year	6	385	0.006	69.4	High	71.9% (61.0–80.8%)	
Grade ≥3 complications (controlled studies only)							
Ultracentral	8	247	0.196	29.1	Medium	9.0% (5.0–15.9%)	0.06
Central	8	500	0.532	~0.0	Very low	4.4% (2.8–6.9%)	
Grade 5 complications (controlled studies only)							
Ultracentral	8	247	0.163	33.2	Medium	5.7% (2.6–11.9%)	0.087
Central	8	500	0.697	~0.0	Very low	2.3% (1.1–4.6%)	

C, central; UC, ultracentral.

with very low heterogeneity (*Figure 2B*). Therefore, we suggest the application of SBRT with a dose of at least 85 Gy_{10}, which can be prescribed as either 55 Gy in 10 fractions (30) or 45 Gy in 5 fractions (12). Dose over 100 Gy_{10} can be prescribed with an expectation of a dose-response relationship; however, risk factors should be monitored as SBRT for UC tumors have a higher risk of complications than that for central tumors. Feasibility and additional efficacy regarding long-term LC of dose escalation should be evaluated in future studies.

The main reason UC tumors began to be treated independently of central tumors was that the former were thought to be more vulnerable to serious toxicities. Haseltine *et al*. (12). and Tekatli *et al*. (11), whose studies were performed relatively early, reported overwhelmingly high toxicity rates (grade ≥3 complications rates in these studies were 24.8% and 38%, respectively), thereby causing reluctance regarding the feasibility of SBRT. On the other hand, studies by Lenglet *et al*. (41), Raman *et al*. (13), and Chang *et al*. (15). found that the differences in serious toxicities between central and UC tumors were not

significant. Given the inevitable full-dose irradiation to PBT when treating UC tumors, and results of higher grade ≥3 complications rates (9% *vs*. 4.4%, P=0.06) and grade 5 complication (5.7% *vs*. 2.3%, P=0.087) with UC than with central tumors post-SBRT (with borderline significances), it seems that irradiating UC tumors produces a greater susceptibility to serious toxicities than does irradiating central tumors.

The pooled grade ≥3 complication rate was 10.4%, which was much lower than that revealed in the previous meta-analysis (23.2%) (36). The pooled complication rates in previous meta-analyses were largely affected by those of Tekatli *et al*. (11). and Haseltine *et al*. (12), which reported relatively high rates of 24.8% and 38%. However, in Tekatli *et al*.'s study (11), 60% of the tumors were >5 cm in diameter and 32% were >7 cm; these sizes were much larger than those of tumors commonly indicated for SBRT. In Haseltine *et al*.'s study (12), it was not clear that SBRT was the main cause of complications because some patients also received bevacizumab, exposure to which is a known risk factor for serious hemorrhage when treating
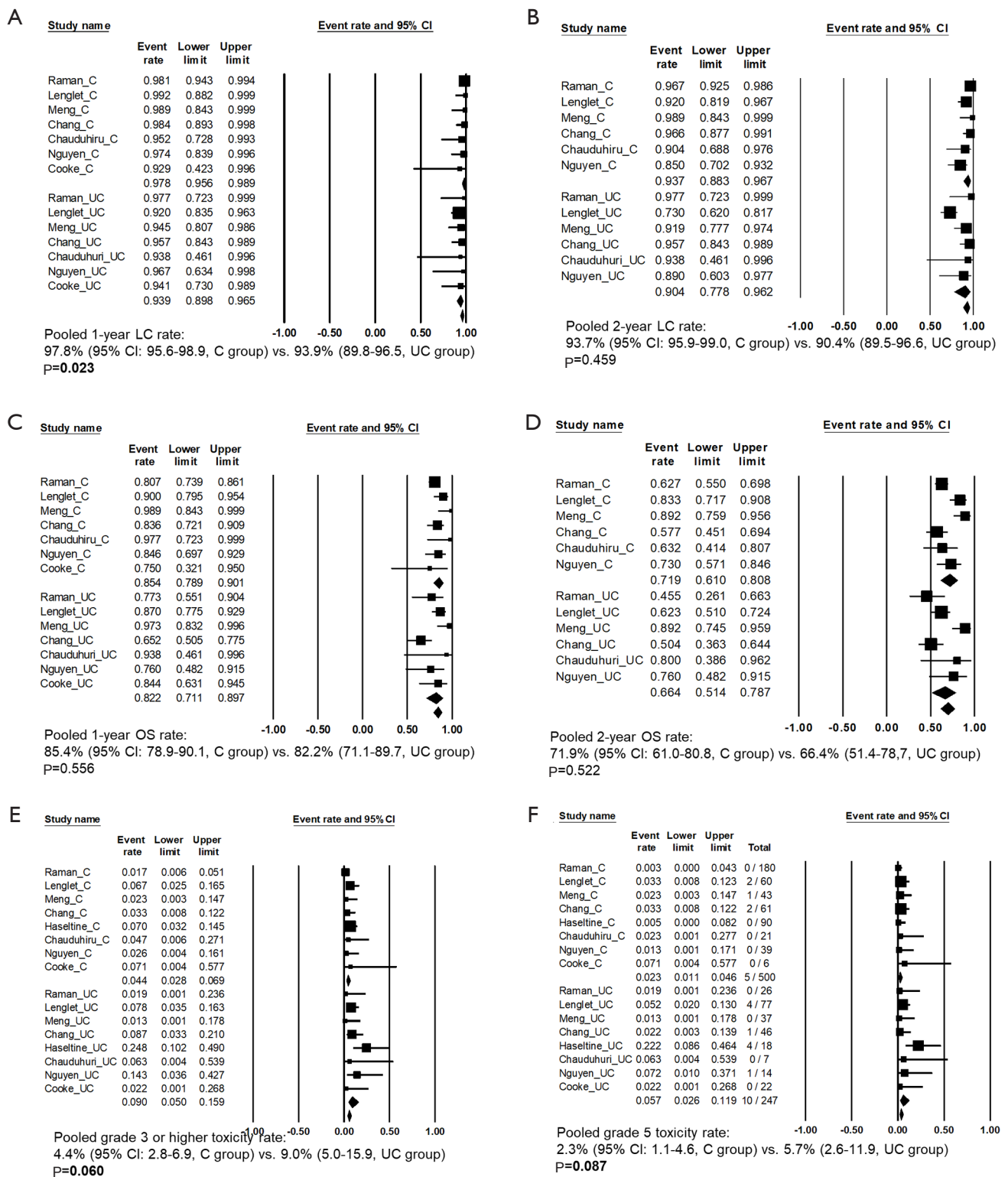
Figure 1 Forest plots for the pooled analyses of controlled studies (comparison between the ultracentral and central tumor groups). (A) 1-year local control rate; (B) 2-year local control rate; (C) 1-year overall survival rate; (D) 2-year overall survival rate; (E) Grade ≥3 complication rate; (F) Grade 5 complication rate.

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Table 4 Pooled analyses of all the ultracentral tumor cohorts

Variable	No. of cohorts	Patients (n)	Heterogeneity (p)	I^2 (%)	Heterogeneity	Effect size (95% CI)	Comparison (P)
Local control at 1 year							
All UC cohorts	13	393	<0.001	78.4	Very high	90.2% (80.1–95.4)	
Median PTV ≤68.5 cm^3	5	163	0.922	~0.0	Very low	93.2% (88.0–96.2)	0.153
Median PTV >68.5 cm^3	7	216	<0.001	79.8	Very high	85.0% (66.7–94.1)	
Recurrence or mets. <50%	5	196	0.584	~0.0	Very low	94.1% (89.2–96.8)	0.045
Recurrence or mets. ≥50%	7	190	<0.001	77.8	Very high	83.0% (65.5–92.6)	
BED$_{10Gy}$*	13	393			Meta-regression P value: <0.0001		
Overall survival at 1 year							
All UC cohorts	13	393	0.006	56.8	High	77.6% (69.5-84.0%)	
Median PTV ≤78 cm^3	5	163	0.315	15.6	Low	87.0% (79.0-92.3%)	0.003
Median PTV >78 cm^3	7	216	0.159	35.3	Medium	69.9% (61.0-77.4%)	
Recurrence or mets. <50%	5	196	0.003	74.6	High	80.9% (64.8-90.8%)	0.422
Recurrence or mets. ≥50%	7	190	0.125	39.9	Medium	74.2% (64.4-82.0%)	
BED$_{10Gy}$	13	393			Meta-regression P value: 0.7177		
Grade ≥3 complications (all UC cohorts)							
All UC	14	416	0.001	63.3	High	10.4% (5.9-17.7%)	
Median PTV ≤78 cm^3	5	163	0.58	~0.0	Very low	5.8% (2.9-11.2%)	0.15
Median PTV >78 cm^3	7	216	0.002	71.4	High	12.3% (5.6-25.0%)	
Recurrence or mets. <50%	6	219	<0.001	78.6	Very high	12.6% (4.7-29.7%)	0.55
Recurrence or mets. ≥50%	7	190	0.772	~0.0	Very low	9.1% (5.6-14.5%)	
BED$_{10Gy}$	14	416			Meta-regression P value: 0.6347		
Grade 5 complications (all UC cohorts)							
All UC	14	416	0.036	44.7	Medium	6.1% (3.3–11.0%)	
Median PTV ≤78 cm^3	5	163	0.826	~0.0	Very low	4.0% (1.8–8.7%)	0.642
Median PTV >78 cm^3	7	216	0.03	56.6	High	5.4% (2.0–14.0%)	
Recurrence or mets. <50%	6	219	0.021	62.2	High	9.3% (3.9–20.5%)	0.079
Recurrence or mets. ≥50%	7	190	0.995	~0.0	Very low	3.3% (1.5–7.1%)	
BED$_{10Gy}$	14	416			Meta-regression P value: 0.2488		

*, median dose, or prescribed dose for the majority of patients. BED, biologically equivalent dose; CI, confidence interval; mets, metastases; PTV, planning target volume; UC, ultracentral.

central lung cancer (42). In fact, the authors also suggested that bevacizumab might have contributed to hemorrhagic complications, and also noted that gram-negative bacterial pneumonia (another serious complication that arose) is generally not caused by non-invasive treatments such as SBRT. Contrarily, more recent trials including those by Lenglet *et al.* (14), Meng *et al.* (17), Raman *et al.* (13), and Chang *et al.* (15). which might avoid such risks previously suggested, found much more acceptable rates of toxicity (0% to ~8%) although all patients in these studies were
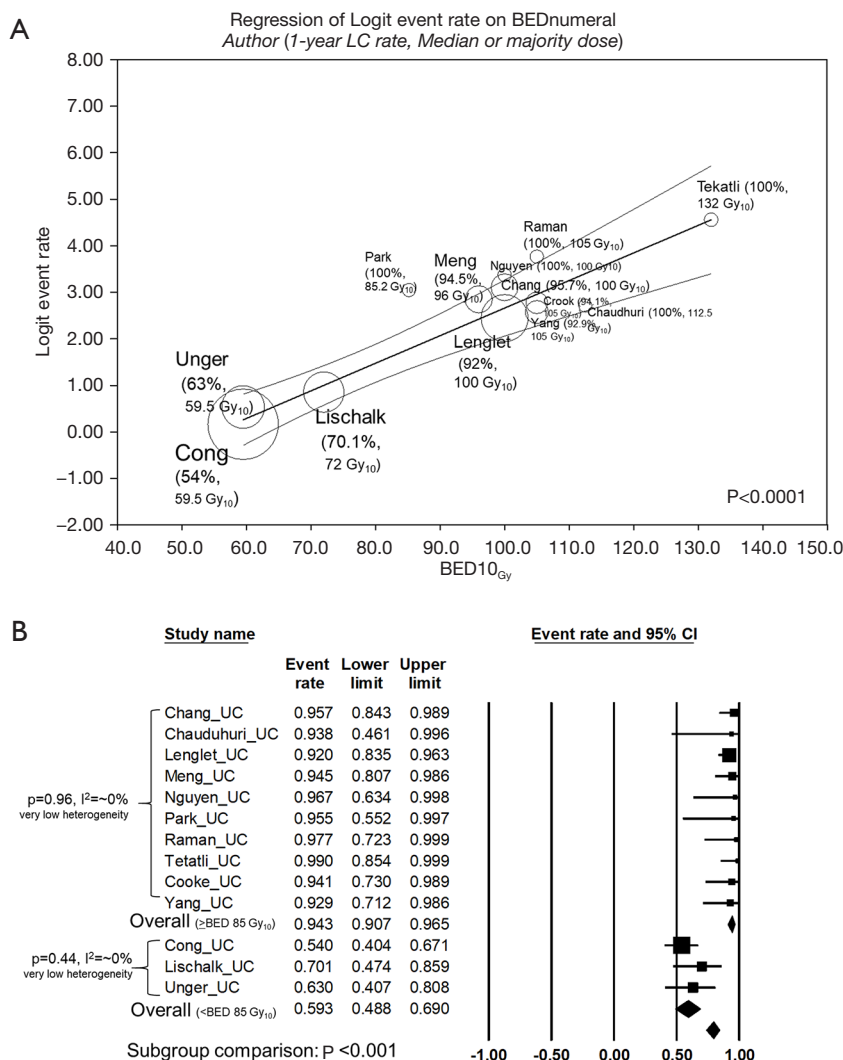
Figure 2 Dose-response relationship for local control in the scatterplot. (A) Meta-regression scatterplot for BED_{10Gy} and 1-year local control; (B) Forest plot of subgroup pooled analysis for 1-year local control with threshold of 85 Gy_{10}.

prescribed more than 100 Gy_{10}.

Grade 5 complication is the most significant factor determining the application of SBRT for UC tumors reluctant. Of note, most researchers reported factors that may have significantly influenced fatal toxicity. Tekatli *et al.* (11). reported 10 patients among 47 with UC tumors who experienced fatal toxicity, including 7 with hemorrhages. Anticoagulant use, squamous histology, excessive irradiation dose ($D_{Max} > 123\%$), and endobronchial involvement were the presumed causes of such toxicities. Haseltine *et al.* (12). reported fatal toxicities in 4 of their 18 patients with UC tumors (22.5%) and claimed that bevacizumab exposure might have caused fatal hemorrhagic

toxicities. Studies by Chang *et al.* (15), Meng *et al.* (17), Lenglet *et al.* (14), and Unger *et al.* (29). revealed much lower fatal toxicity rates (2–5%) than did the previous 2 studies, suggesting that underlying lung diseases such as interstitial lung disease and idiopathic pulmonary fibrosis might have been associated with fatal respiratory toxicities. Although none of the individual studies reported statistically significant differences in serious toxicities between patients with UC and central tumors (9,12,13,15,41), considering the small patient number of individual studies and borderline significance found in our subgroup comparisons, we support the notion that applying SBRT for UC tumors carries a greater risk of fatal toxicities than does applying

Table 5 Treatment-related complications in patients with UC tumors

First author	Patients (n)	SBRT dose	BED$_{10Gy}$	Grade ≥3 complication (%)	Grade 5 complication (%)	Possible risk factors for fatal or serious complications
Raman	UC, 26	60 Gy/8 F (76.9% of patients)	105 (76.9%)	0	0	–
	C, 180	60 Gy/8 F (50.6%) 48 Gy/4 F (32.3%)	105 or 105.6 (82.3%)	1.7% (3 patients, including 2 pneumonitis and 1 esophagitis)	0	
Comparisons					Grade ≥2 complications: UC 7.7% vs. C 9% (P=0.89)	
Lenglet	UC, 77	M50 [40–60] in M5F [3–8]	M100 [72–180]	7.8% (6 patients, 3 pneumonitis, 1 MI, 1 bronchial stricture)	5.2% (4 patients, 3 pneumonitis and 1 MI)	Suspicious for ILD and heart-contacting location
	C, 60			6.7% (4 patients, 2 MI, 1 pneumonitis, 1 bronchial stricture)	3.3% (2 patients, 1 pneumonitis and 1 MI)	–
Comparisons				NS in grade 3~5 (UC vs. C: P=0.7)		
Meng	UC, 37	M56 Gy [48–60]/7F [5–10]	M96.0 (81.3–132.0)	0	0	–
	C, 43	M60 Gy [48–60]/6 [4–8] F	M120.0 (83.3–150.0)	2.3% (1 patient, pneumonitis)	2.3% (1 patient, pneumonitis)	Chronic ILD for 15 years, tumor size 6.3×3.1 cm
Comparisons				Not performed		
Chang	UC, 46	Mostly 50 Gy/5 F	≥100 in 71.7%	8.7% (4 patients, bronchial stenosis or fistula)	2.2% (1 patient, pneumonia sequential to bronchial stenosis)	Of 3 fatalities, 1 had IPF, 1 was on nivolumab; having a lymph node target meant a longer length of PBT exposure, and was related to grade ≥3 toxicity
	C, 61		≥100 in 91.8%	3.3% (2 patients, bronchial stenosis and pneumonitis)	3.3% (2 patients, bronchial stenosis and pneumonitis)	
Comparison				NS in grade 3~5 (P=0.23) and grade 5 (P=0.76)		
Haseltine	UC, 18	M45 Gy/5 F	85.5	24.8%	22.2% (4 patients, 2 hemorrhages, 1 bacterial pneumonia, 1 respiratory failure,)	Two patients with fatal hemorrhage had a history of bevacizumab exposure
	C, 90			7.0%	0	
Comparison				NS for grade ≥3 toxicity free survival (P=0.11)		
Chaudhuri	UC, 7	50 Gy/4 F	112.5	0	0	–
	C, 21	50 Gy/5 F	100	4.7% (1 patient)	0	–
Comparison				NS for grade ≥2 complication (P=0.31)		

Table 5 (*continued*)

Table 5 (*continued*)

First author	Patients (n)	SBRT dose	BED$_{10Gy}$	Grade ≥3 complication (%)	Grade 5 complication (%)	Possible risk factors for fatal or serious complications
Nguyen	UC, 14	M50 [40–60] in M5 F [4–8]	M83.3	14.3% (2 patients, obstructive pneumoniae and respiratory failure)	7.2% (a respiratory failure)	–
	C, 39			2.6% (1 patient)	–	
Comparison				Not performed		
Cooke	UC, 22	60 Gy/8 F	105	0	0	–
	C, 6			0	0	
Comparison				Not performed		
Tekatil	UC, 47	60 Gy/5 F	132	38% (18 patients, 9 hemorrhage and 5 pneumonitis)	21.2% (10 patients: hemorrhage [7], respiratory failure [3])	Use of anticoagulant, squamous histology, endobronchial involvement, excessive Dmax (≥123% of prescribed in all patients)
Cong	UC, 51	M35 Gy/5 F	M59.5	9.8% (5 patients, 3 pneumonitis and 2 cardiac death)	3.9% (2 patients of cardiac death)	Two deceased patients had heart disease before SBRT
Lischalk	UC, 20	M40 Gy/5 F	M72	15% (3 patients, 1 pneumonitis and 2 atelectasis)	0	Prescription dose (P=0.031) and point dose to main bronchus (P=0.029) were both related to grade ≥2 late atelectasis
Unger	UC, 20	M35 Gy/5 F	M59.5	10% (dyspnea and bronchus fistula)	5% (patients with a bronchus fistula)	A patient with dyspnea had serious underlying COPD
						A deceased patient had a 324 cm^3 mainstem endobronchial tumor
Yang	UC, 21	60 Gy/8 F	105	0	0	–
Park	UC, 10	M55 Gy/10 F	M85.2	0	0	

An uppercase M prefix refers to the median value. BED, biologically equivalent dose; C, central; COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; interstitial lung disease; MI, myocardial infarction; NS, nonsignificant; PBT, proximal bronchial tree; SBRT, stereotactic body radiotherapy; UC, ultracentral.

it for central tumors. Hence, all risk factors suggested by previous investigators should be taken into consideration before treatment.

Limitations of the present meta-analysis include the non-randomized and retrospective design, and the clinical heterogeneity of the patients. Meta-analyses of observational studies are controversial because innate heterogeneity among studies might affect the pooled estimates (43). SBRT for UC tumors was contraindicated until recently when the indication was updated following pioneering research. As UC tumors are commonly inoperable or else require extensive surgeries, assessment of other curative modalities such as SBRT is crucial. In such situations, meta-analyses of observational studies can be one of the few options that provide helpful information for clinical practice (43). Short follow-up periods are another limitation in recent studies; we did not perform pooled analyses of the 2-year outcome rates in all UC cohorts because the available data were limited and follow-up periods in UC case series were too short. It should be considered that reporting of late toxicity events depends on follow-up and that risks of fatal toxicities may be higher. The heterogeneity of definitions for UC tumors is another drawback that ought to be resolved. The assessment of the feasibility or efficacy of treatment for UC tumors might be difficult if the definition of the target disease is unclear. We suggest that future studies use agreeable definitions and terminology regarding UC tumors.

Conclusions

The oncologic outcomes of SBRT for patients with UC and central tumors were comparable, although patients treated for UC tumors are more prone to serious toxicities. Nevertheless, SBRT for UC tumors is feasible considering the moderate rate of toxicities and the clinical need for a non-invasive curative modality. Considering the dose-response relationship, a dose of at least 85 Gy_{10} is recommended to be prescribed, and doses near or moderately higher than 100 Gy_{10} can be considered with cautious monitoring for risk factors of complications. Studies with longer follow-up which enable assessments of higher dose for sustained LC are warranted. The identified causes of fatal toxicities should be avoided in clinical practice as much as possible.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at http://dx. doi. org/10. 21037/tlcr-20-503

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx. doi. org/10. 21037/tlcr-20-503). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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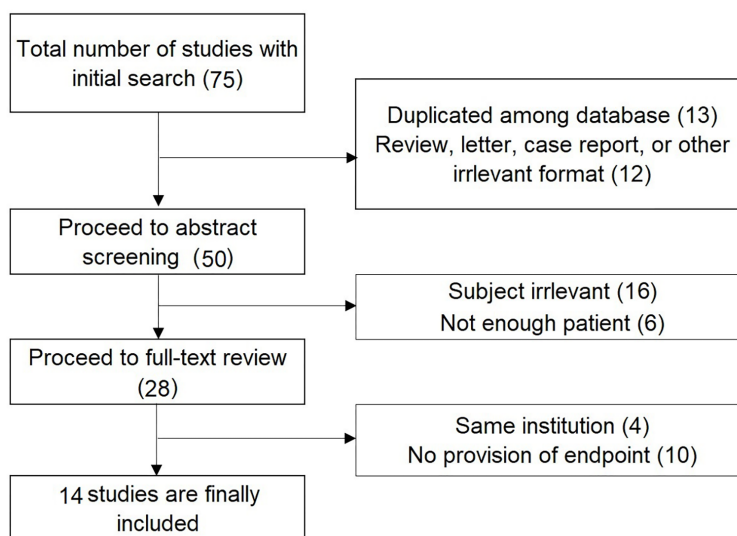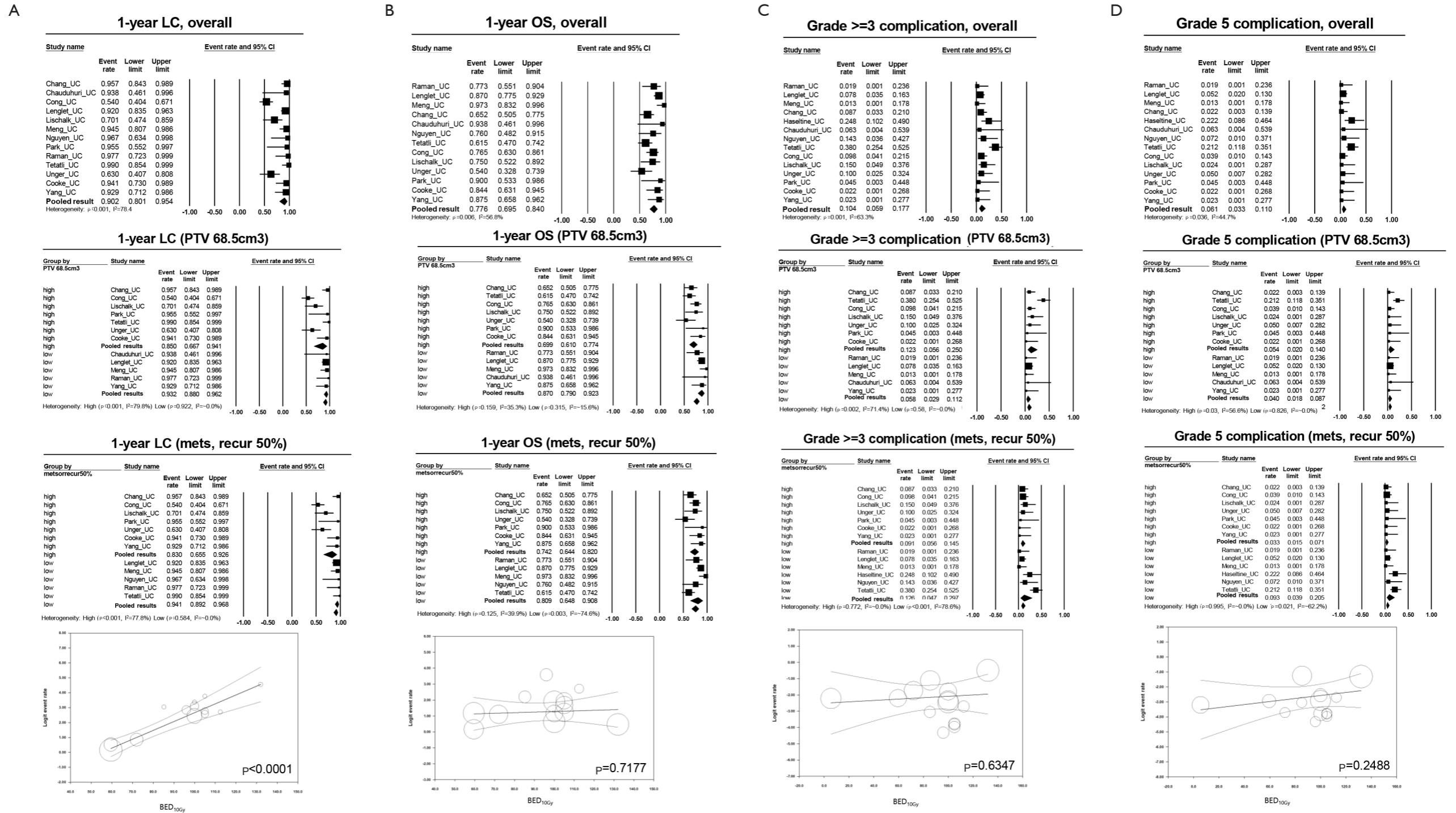
Figure S1 Study inclusion plot.

Figure S2 Forest plots and scatter plots of pooled analyses among all ultracentral cohorts. (A) 1-year local control rate (top to bottom: all cohort; subgroup comparison according to planning target volume; subgroup comparison according to the proportion of metastases or recurrence; scatterplot of meta-regression according to biologically equivalent dose); (B) 1-year overall survival rate (top to bottom: same order with above); (C) grade ≥3 complication rate (top to bottom: same order with above); (D) grade 5 complication rate (top to bottom: same order with above).