research article

A population-based study of the effectiveness of stereotactic ablative radiotherapy versus conventional fractionated radiotherapy for clinical stage I non-small cell lung cancer patients

Chih-Yen Tu[1,5,#], Te-Chun Hsia[1,6,#], Hsin-Yuan Fang[2,#], Ji-An Liang[3,#], Su-Tso Yang[4,7,#], Chia-Chin Li[3], Chun-Ru Chien[3,5]

[1] Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, China Medical University Hospital, Taiwan
[2] Department of Chest Surgery, China Medical University Hospital, Taiwan
[3] Department of Radiation Oncology, China Medical University Hospital, Taiwan
[4] Department of Radiology, China Medical University Hospital, Taiwan
[5] School of Medicine, College of Medicine, China Medical University, Taiwan
[6] Department of Respiratory Therapy, College of Health Care, China Medical University, Taiwan
[7] School of Chinese Medicine, China Medical University, Taiwan

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Correspondence to: Chun-Ru Chien, M.D., Ph.D., School of Medicine, College of Medicine, China Medical University, No.91 Hsueh-Shih Road, North District, Taichung 40402, Taiwan. Phone: +886 4 22052121 7450; Fax: +886 4 22052121 7460; E-mail: d16181@gmail.com

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[#] The authors contributed equally to this work.

Background. Stereotactic ablative radiotherapy (SABR) is a promising option for non-operated early-stage non-small cell lung cancer (NSCLC) compared to conventional fractionated radiotherapy (CFRT). However, results from conclusive randomized controlled trials are not yet available. The aim of our study was to explore the effectiveness of SABR *vs.* CFRT for non-operated early-stage NSCLC.

Patients and methods. We used a comprehensive population-based database to identify clinical stage I non-operated NSCLC patients in Taiwan diagnosed from 2007 to 2013 who were treated with either SABR or CFRT. We used inverse probability weighting and the propensity score as the primary form of analysis to address the nonrandomization of treatment. In the supplementary analyses, we constructed subgroups based on propensity score matching to compare survival between patients treated with SABR *vs.* CFRT.

Results. We identified 238 patients in our primary analysis. A good balance of covariates was achieved using the propensity score weighting. Overall survival (OS) was not significantly different between those treated with SABR *vs.* CFRT (SABR *vs.* CFRT: probability weighting adjusted hazard ratio [HR] 0.586, 95% confidence interval 0.264–1.101, p = 0.102). However, SABR was significantly favored in supplementary analyses.

Conclusions. In this population-based propensity-score adjusted analysis, we found that OS was not significantly different between those treated with SABR *vs.* CFRT in the primary analysis, although significance was observed in the supplementary analyses. Our results should be interpreted with caution given the database (i.e., nonrandomized) approach used in our study. Overall, further studies are required to explore these issues.

Keywords: stereotactic ablative radiotherapy; conventional fractionated radiotherapy; non-small cell lung cancer

Introduction

Surgery is the cornerstone for treating early-stage non-small cell lung cancer (NSCLC), although radical radiotherapy may be used for medically inoperable cases.[1,2] In recent years, stereotactic ablative radiotherapy (SABR, or so-called stereotactic body radiotherapy) has been used to deliver radiothera-

py instead of conventional fractionated radiotherapy (CFRT).[2-5] Promising results have been reported for medically inoperable and operable cases and even other cancers.[6-9]

However, a recent randomized phase II study (the SPACE trial) challenged the general belief that SABR is superior to CFRT, as also mentioned in a 2017 systematic review.[5,10] It showed that disease control and overall survival were similar for SABR and CFRT, although SABR was better considering some side effects and quality of life. However, this study had limited power (67%), and a larger randomized controlled trial (RCT) is required.[10]

Statement of general knowledge

PubMed for published reports using the keywords ([*stereotactic radiotherapy*] OR [*stereotactic body radiotherapy*] OR [*stereotactic ablative radiotherapy*] OR [*SBRT*] OR [*SABR*]) AND ([*non-small cell lung cancer*] OR [*NSCLC*]) AND ([*survival*] OR [*OS*]) was searched on Sep 2nd 2017, for evidence regarding the efficacy of SABR *vs.* CFRT. In addition to the aforementioned SPACE trial, we identified another small (n = 50) randomized study showing better treatment efficacy for SABR compared to CFRT in peripheral NSCLC.[11] However, patients of various stages (stages I–IV) were included in the study, and the results of stage I patients were not reported. We also found a meta-analysis (published in 2010) that reported better overall survival (OS) for SABR compared to CFRT, but all of the included studies were nonrandomized.[12] In addition, none of the included studies directly compared SABR and CFRT.[12] We also found four subsequent single institutional nonrandomized studies from Europe or North America and two subsequent population-based studies from North America.[13-18] However, to the best of our knowledge, no population-based study from Asia has compared SABR *vs.* CFRT for treating early-stage NSCLC.

Study aim

Given the relatively limited evidence on this topic, we investigated the effectiveness of SABR *vs.* CFRT

TABLE 1. Patient characteristics for the whole study population

		SABR		CFRT		Standardized difference (rounded)*	
		Number or mean (sd)*	(%)*	Number or mean (sd)*	(%)*	Before IPW	After IPW
Age		77.81 (7.85)		75.40 (9.96)		0.27	0.24
Sex	Female	20	(29)	44	(26)	0.07	0.07
	Male	49	(71)	125	(74)		
Residency	Non-north	32	(46)	93	(55)	0.17	0.19
	North	37	(54)	76	(45)		
Comorbidity	Without	9	(13)	43	(25)	0.32	0.25
	With†	60	(87)	126	(75)		
Histology	Adenocarcinoma	40	(58)	82	(49)	0.19	0.24
	Non-adenocarcinoma	29	(42)	87	(51)		
T stage	T1	38	(55)	49	(29)	0.55	0.08
	T2	31	(45)	120	(71)		
Period	2007–2009	15	(22)	65	(38)	0.37	0.22
	2010–2013	54	(78)	104	(62)		
Use of PET	Yes	37	(54)	55	(33)	0.44	0.09
	No	32	(46)	114	(67)		
Use of systemic therapy	Yes	10	(14)	73	(43)	0.67	0.17
	No	59	(86)	96	(57)		
Previous cancer	Yes	9	(13)	16	(9)	0.11	0.06
	No	60	(87)	153	(91)		

CFRT = conventional fractionated radiotherapy; IPW = inverse probability weighting; PET = positron emission tomography; SABR = stereotactic ablative radiotherapy; sd = standard deviation; †modified Carlson comorbidity score ≥ 1; *rounded at the second

for non-operated early-stage NSCLC in a population-based sample from Taiwan.

Patients and methods

Data source

The Health and Welfare Data Science Center (HWDC) database is a set of databases providing complete information regarding the Taiwan cancer registry, death registry, and reimbursement data for the whole Taiwanese population provided by the Bureau of National Health Insurance (NHI).[19] The high quality of this cancer registry has been reported.[20] NHI is a single-payer, compulsory social insurance program that provides insurance coverage to the majority of citizens in Taiwan.[21] All of the above data were included in the HWDC with deidentified personal identifiers.

Identification of study cases and study design

A flowchart showing the identification of study cases appears in Figure 1 as suggested by the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline.[22] Briefly, we identified stage I histology-documented NSCLC patients diagnosed from 2007 to 2013 who received either CFRT or SABR without surgery. We used the date of diagnosis as the index date. We determined the explanatory variable of interest (CFRT *vs.* SABR) based on the record in the cancer registry using the dose/fractionation recommended by the National Comprehensive Cancer Network (NCCN) NSCLC guideline (CFRT: 60–70 Gy in 1.8–2 Gy/fraction; SABR: 25–34 Gy/1 fraction, or 45–60 Gy/3 fractions, or 48–50 Gy/4 fractions, or 50–55 Gy/5 fractions, or 60–70 Gy/8–10 fractions).[1] We also collected other covariate and outcome data from the HWDC. We decided on covariates (age, sex, residency, comorbidity, histology, T stage, period, use of positron emission tomography [PET], use of systemic therapy, and previous cancer) based on our clinical and HWDC-related research experiences as well as previous reports.[23-25] The covariates were defined as follows. Patient residency was classified as northern Taiwan or elsewhere. We included this covariable because geographic practice variation had been report in the literature[26] and we felt it might influence treatment choice in our clinical and research experiences.[24] Comorbidity was defined as with or without a modified Carlson comorbidity score ≥1, as used in our previous

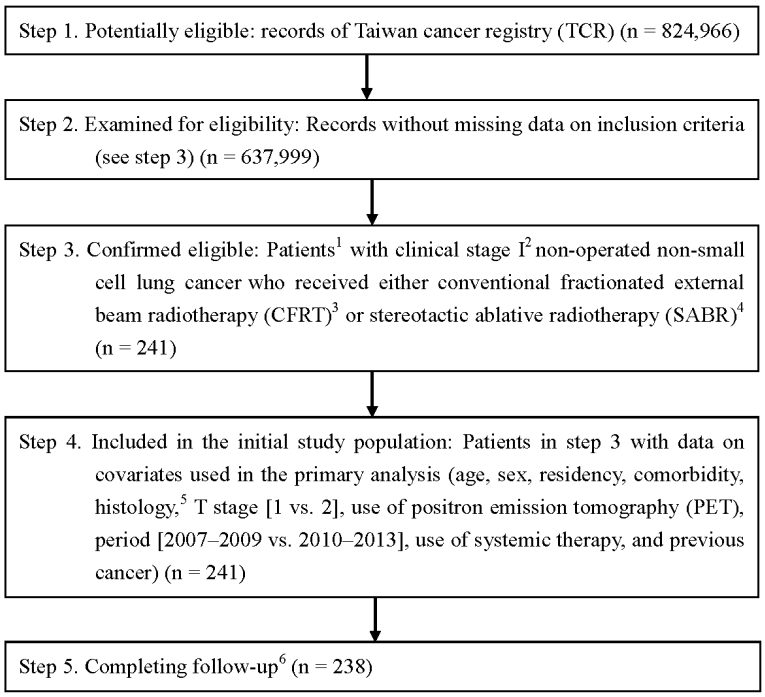

FIGURE 1. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) study flowchart and the number of individuals at each stage of the study.

[1] We only included those treated (class 1–2) at a single institution to ensure data consistency. [2] Sixth (2007–2009) or Seventh (2010–2013) American Joint Committee on Cancer. [3] 60–70 Gy in 1.8–2 Gy/fraction, ±10% in dose. [4] Dose/fraction compatible with National Comprehensive Cancer Network non-small cell lung cancer guideline 2017 v8 (i.e., 25–34 Gy/1 fraction, or 45–60 Gy/3 fractions, or 48–50 Gy/4 fractions, or 50–55 Gy/5 fractions, or 60–70 Gy/8–10 fractions), ±10% in dose. [5] Adenocarcinoma or non-adenocarcinoma. [6] Without missing information in the Taiwan cancer registry and death registry.

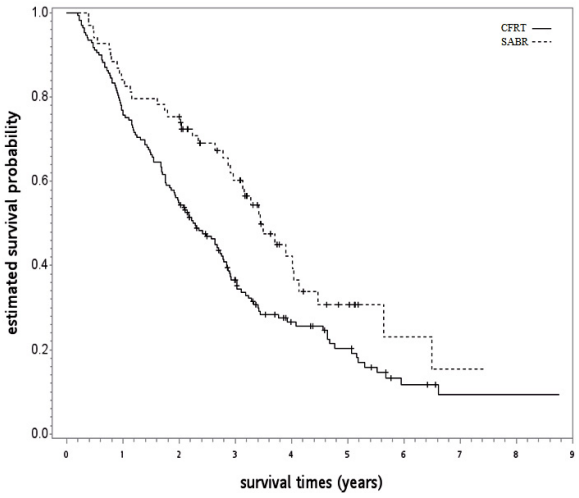

FIGURE 2. Kaplan-Meier survival curve for the whole study population.

CFRT = conventional fractionated radiotherapy; SABRT = stereotactic ablative radiotherapy

NHI cancer study.[24] Histology was classified as adenocarcinoma or non-adenocarcinoma. T stage was classified as T1 *vs.* T2. Period was classified as 2007–2009 or 2010–2013 because staging was changed since 2010. Use of PET, systemic therapy, and previous cancer was classified as yes or no. We used the national death registry to determine survival status and used OS as our endpoint, as initially completed in the SPACE trial.[10] This study was approved by the Research ethics committee at our institute (CMUH104-REC-002).

Statistical analysis

We used the Kaplan-Meier method and log-rank test to compare crude OS between patients treated with SABR *vs.* CFRT. We further used inverse probability weighting (IPW) based on the propensity score (PS) as the primary means of analysis to address the nonrandomization of treatment.[27] We modeled the use of SABR *vs*. CFRT as the dependent variable and the above covariates as independent variables and used logistic regression to model the probability of receiving SABR. Then we used the logit of the probability as the PS, as described previously.[27] Tabulation and standardized differences were used to assess the balance of covariates between treatment groups.[27,28] We used a weighted Cox model to compare OS between treatment groups for the entire follow-up period (censored on December 31, 2015).[27,29] We used bootstrap analysis to obtain confidence intervals and p-values, as described previously.[30] For OS results with statistical significance, we further calculated the E-factor to evaluate the robustness of our finding regarding potential unmeasured confounder[s] as suggested in the recent literature.[31]

Supplementary analyses

In the first supplementary analysis (SA-1), we constructed a subgroup based on PS matching and used a robust variance estimator to compare OS and lung cancer-specific survival of patients treated with SABR *vs.* CFRT. We also used cause of death to obtain lung cancer-specific survival (LCSS). In the second supplementary analysis (SA-2), we constructed another subgroup by PS matching limited to cases from 2011 to 2013 to use the additional covariate (performance status, classified as Eastern Cooperative Oncology Group [ECOG] 0–2 *vs.* 3–4) in PS modeling to compare the survival of patients treated with SABR *vs.* CFRT. We limited to this period [2011–2013] because performance information was available in Taiwan cancer registry since 2011. SAS 9.4 (SAS Institute, Cary, NC) was used for all analyses.

Results

Identification of study cases

As shown in Figure 1, we found 238 clinical stage I NSCLC patients who received either SABR or CFRT from 2007 to 2013 were included in our primary analysis. The characteristics of these patients are described in Table 1. Although an imbalance in covariate distribution was observed before PS weighting such as higher percentage of patients with comorbidity received SABR [32%] than those without comorbidity [17%], a good balance of covariates and small standardized differences (≤ 0.25) were observed for all covariates after we adjusted for PS weighting.[28,32]

Primary analysis

After a median follow-up of 28 months (range 2–105), 171 patients were found to have died (40 SABR and 131 CFRT). We found that SABR led to higher crude OS compared to CFRT, as shown in Figure 2. The 5-year OS rates for SABR and CFRT were 31% and 20%, respectively (log-rank test, p = 0.0008). After IPW, OS was not significantly different between those treated with SABR *vs.* CFRT (SABR *vs*. CFRT: IPW adjusted hazard ratio [HR] 0.586, 95% confidence interval 0.264–1.101, p = 0.102).

Supplementary analyses

In SA-1, a good balance of covariates was observed with small standardized differences (≤ 0.25) for the PS-matched subgroup (n = 120; see Table 2). Compared to CFRT, the OS (HR 0.672, p = 0.039) and LCSS (HR 0.529, p = 0.007) of patients receiving SABR were superior. The observed HR 0.672 for OS could be explained away by an unmeasured confounder that was associated with both selections of SABR/CFRT and live/death by a risk ratio of 1.96 fold each, but weaker confounding could not do so. The OS curve is shown in Figure 3. In SA-2, well-balanced covariates were observed with small standardized differences (≤ 0.25) when cases were limited to 2011 to 2013 with an available performance status (n = 52; see Table 3), although there were some imbalances before matching such as those with poor performance status [ECOG 3~4] were more likely to

TABLE 2. Patient characteristics in the first supplementary analysis

		SABR		CFRT		Standardized difference (rounded)*
		Number or mean (sd)*	(%)*	Number or mean (sd)*	(%)*	
Age		77.47 (8.26)		77.75 (9.79)		0.03
Sex	Female	18	(30)	24	(40)	0.21
	Male	42	(70)	36	(60)	
Residency	Non-north	29	(48)	30	(50)	0.03
	North	31	(52)	30	(50)	
Comorbidity	Without	9	(15)	8	(13)	0.05
	With†	51	(85)	52	(87)	
Histology	Adenocarcinoma	37	(62)	41	(68)	0.14
	Non-adenocarcinoma	23	(38)	19	(32)	
T stage	T1	30	(50)	31	(52)	0.03
	T2	30	(50)	29	(48)	
Period	2007–2009	15	(25)	15	(25)	0.00
	2010–2013	45	(75)	45	(75)	
Use of PET	Yes	30	(50)	31	(52)	0.03
	No	30	(50)	29	(48)	
Use of systemic therapy	Yes	10	(17)	13	(22)	0.13
	No	50	(83)	47	(78)	
Previous cancer	Yes	8	(13)	7	(12)	0.05
	No	52	(87)	53	(88)	

CFRT = conventional fractionated radiotherapy; PET = positron emission tomography; SABR = stereotactic ablative radiotherapy; sd = standard deviation; † modified Carlson comorbidity score ≥ 1; * rounded at the second

receive SABR [60%] than those with acceptable performance status [33%]. We found SABR was associated with further improvement in hazard for death (HR 0.381, p = 0.016) compared to CFRT, as seen in Figure 4. The observed HR 0.381 for OS could be explained away by an unmeasured confounder that was associated with both selections of SABR/CFRT and live/death by a risk ratio of 3.29 fold each, but weaker confounding could not do so.

Discussion

In this population-based PS-adjusted analysis, we provide the first empirical evidence from Asia regarding non-operated early-stage NSCLC patients treated with either SABR or CFRT. We found that OS was not significantly different between those treated with SABR *vs.* CFRT in the primary analysis, although statistical significance was observed in the supplementary analyses.

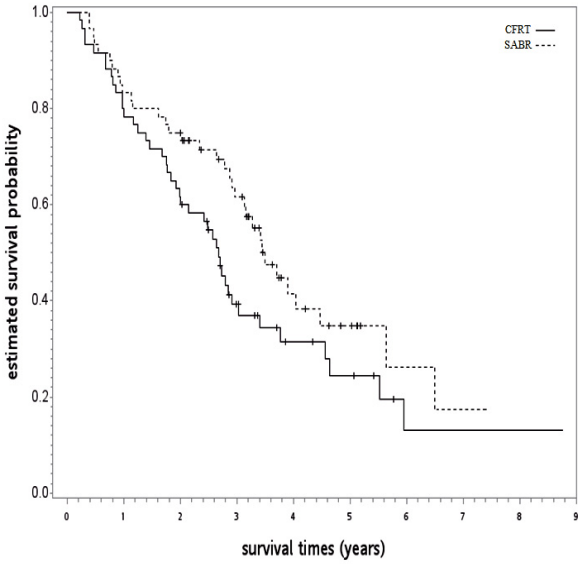

FIGURE 3. Kaplan-Meier survival curve for the first supplementary analysis.

CFRT = conventional fractionated radiotherapy; SABRT = stereotactic ablative radiotherapy

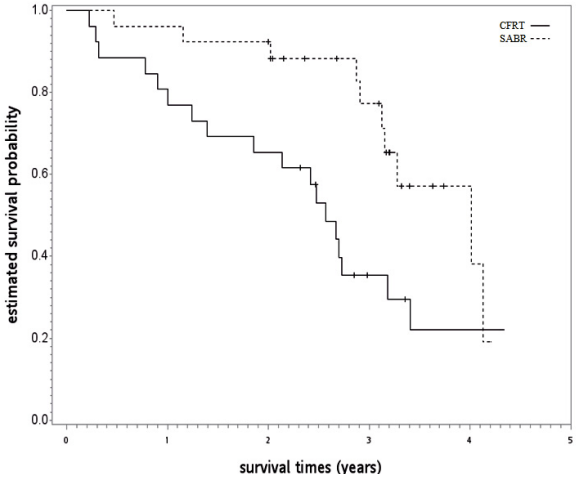

FIGURE 4. Kaplan-Meier survival curve for the second supplementary analysis.

CFRT = conventional fractionated radiotherapy; SABRT = stereotactic ablative radiotherapy

Our results may be interpreted as compatible with the SPACE trial in that OS was not significantly different between those treated with SABR *vs.* CFRT. On the contrary, because the point estimate of HR for death was around 0.6, SABR may lead to better OS, but the statistical significance was limited by the moderate sample size. The statistical significance found in our SA supported this hypothesis, as reported in other studies from Europe and North America, and indirect comparison in a previous meta-analysis showed that SABR led to better survival.[12-18] Therefore, our results should not be interpreted as conclusive.

Our study provides additional evidence for practitioners considering SABR in addition to conventional CFRT for non-operated early-stage NSCLC.[33] Although the available randomized data did not support the superior efficacy of SABR compared to CFRT, the power of that study was limited and is not compatible with previous retrospective data.[10] Although the results of our primary analysis were not significant, the trend was in favor of SABR (HR 0.59), and similar trends with statistical significance were observed in SA. Furthermore, we observed that patients with comorbidity or poor performance status were more likely to receive SABR in the pre-matched population (i.e., SABR patients were possibly prone to die from competing death), so it is possible that SABR had improved LCSS [HR 0.529] but OS benefit was less obvious [HR 0.72] as seen in our SA-1. Therefore, our study may be used by practitioners to select treatment for non-operated early-stage NSCLC while awaiting results from ongoing RCTs (such as NCT01968941 or NCT01014130).

There are some limitations to our study. First, the sample size was moderate, particularly in both supplementary analyses, which severely limits statistical power [around 0.5 ~ 0.8 in the setting of our SA]. Second, identification of the study population may be inhomogeneous because a higher dose may be more effective, although we used the NCCN criteria to classify SABR *vs.* CFRT.[34] Third, treatment selection was not random or specified. The reason for choosing radiotherapy but not surgery was not available due to data limitation. In addition, the reason for choosing SABR or CFRT remains unclear. Unobservable bias is possible in retrospective studies, and results of the aforementioned ongoing trials are required. For example, the location of the primary tumor (central *vs.* peripheral) or lung function test results were not known and could have been unbalanced, even after we matched for observable covariates.[35] Epidermal growth factor receptor (EGFR) status may also have been unbalanced. Population variation in treatment response is an emerging issue, and highly prevalent EGFR mutations in Asia (including Taiwan) is a well-known example.[36] Adjuvant EGFR-directed treatment may even improve the outcomes of resected NSCLC.[37] However, we found our result was somehow robust [E-factor 3.29] to potential unmeasured confounder(s). Fourth, other endpoints such as local control were not available due to data limitation, although no difference in local control was reported in the SPACE trial.[10]

Conclusions

In this population-based PS-adjusted analysis, we provide the first empirical evidence from Asia regarding non-operated early-stage NSCLC patients treated with either SABR or CFRT. We found that OS was not significantly different in the primary analysis between those treated with SABR *vs.* CFRT, although statistical significance was observed in supplementary analyses. Thus, the results of ongoing randomized controlled studies are required.

Acknowledgements

The data analyzed in this study was provided by the Health and Welfare Data Science Center, Ministry of Health and Welfare, Taiwan. This

TABLE 3. Patient characteristics in the second supplementary analysis

		SABR		CFRT		Standardized difference (rounded)*
		Number or mean (sd)*	(%)*	Number or mean (sd)*	(%)*	
Age		76.92 (8.84)		77.73 (9.19)		0.09
Sex	Female	8	(31)	7	(27)	0.09
	Male	18	(69)	19	(73)	
Residency	Non-north	16	(62)	18	(69)	0.16
	North	10	(38)	8	(31)	
Comorbidity	Without	#		#		0.13
	With†	#		#		
Histology	Adenocarcinoma	14	(54)	15	(58)	0.08
	Non-adenocarcinoma	12	(46)	11	(42)	
T stage	T1	11	(42)	11	(42)	0.00
	T2	15	(58)	15	(58)	
Use of PET	Yes	13	(50)	12	(46)	0.08
	No	13	(50)	14	(54)	
Use of systemic therapy	Yes	#		#		0.13
	No	#		#		
Previous cancer	Yes	3	(12)	3	(12)	0.00
	No	23	(88)	23	(88)	
Performance status	ECOG (0–2)	#		#		0.00
	ECOG (3–4)	#		#		

CFRT = conventional fractionated radiotherapy; ECOG = Eastern Cooperative Oncology Group; PET = positron emission tomography; SABR = stereotactic ablative radiotherapy; sd = standard deviation; † modified Carlson comorbidity score ≥ 1; * rounded at the second; # Exact numbers are not reported because the Health and Welfare Data Science Center (HWDC) database center policy is to avoid numbers in single cells ≤ 2

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