



# Comparison of parallel and crossed placement of antennas in microwave ablation of 3–5 cm hepatocellular carcinoma

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## Abstract

**Purpose** To evaluate the effects of ablation strategies on local tumor progression (LTP) after microwave ablation (MWA) of hepatocellular carcinomas (HCCs) measuring 3–5 cm.

**Materials and methods** Between December 2011 and May 2017, 71 HCC patients with 71 nodules treated by ultrasound(US)-guided percutaneous MWA were divided into parallel (group A) and crossed (group B) antenna placement groups. All patients underwent MWA using two antennas with four insertions. LTP and overall survival (OS) rates were compared between the two groups.

**Results** The median follow-up time was 16.8 months. There was no significant difference in the complete ablation rate and treatment sessions between the two groups. LTP was diagnosed in 8 of 48 nodules (16.7%) in group A and 1 of 23 nodules (4.3%) in group B, with no significant difference between two groups ( $P=0.115$ ). The 1-, 2-, and 3-year OS rates were 88.5%, 79%, and 71.8% in group A and 93.8%, 87.5%, and 87.5% in group B, respectively ( $P=0.236$ ). Multivariate analysis showed that the tumor diameter ( $P=0.017$ ), the distance between the antennas ( $P=0.032$ ), and the total emission time ( $P=0.015$ ) were associated with LTP.

**Conclusions** There were trends with lower LTP and improved OS in group B, despite the lack of statistically significant differences between the two strategies at a level of  $P < 0.05$ . The increase of distance between antennas and total emission time will facilitate reductions in LTP rate.

**Keywords** Ablation strategy · Microwave ablation · Hepatocellular carcinoma

## Introduction

Percutaneous thermal ablation is one of several available curative treatment options for HCCs measuring  $\leq 3$  cm in diameter [1–3]. Compared with hepatic resection, it is

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associated with a lower rate of serious complications and has shorter recovery time owing to its advantage of minimal invasiveness [4]. As one of the most recent advances in the field of thermal ablative techniques, microwave ablation (MWA) has undergone considerable development for improving liver cancer therapy [5, 6]. Compared with most radiofrequency ablation (RFA) techniques, MWA is less affected by the heat-sink effect of local blood vessels and can involve multiple antennas working in concert, which can produce a larger ablation zone [7, 8]. These advantages have provided the foundation for the treatment of HCCs measuring  $> 3$  cm using MWA.

For the HCCs measuring  $< 3$  cm treated using MWA, a complete ablation rate of 88–98% and a local tumor progression (LTP) rate of 5–15.1% have been reported in previous studies [9–11]. Several researchers have attempted to apply MWA to HCCs measuring 3–5 cm based on the experience with tumors measuring  $< 3$  cm with complete ablation rates in the range of 83.3–92.6%, and LTP rates in the range of 10.5–22% [11–14]. According to previous studies [14–16], increased tumor size is the main challenge to complete necrosis of the tumor using MWA. For tumors  $> 3$  cm, MWA requires a combination of at least four ablation zones to overlap the entire tumor in three-dimensional (3D) space, which is different from small lesions ablation, which only requires the combination of 1–2 ablation zones [15, 17]. A combination of  $> 4$  antennas remains a significant challenge in terms of suitable placement, and requires more ablation experience for interventional physicians and operators.

With the development of MWA techniques and advances in technology, overlapping ablation was proposed to generate a confluent ablation zone by making two antennas act in concert [18, 19]. Most research studies have reported MWA

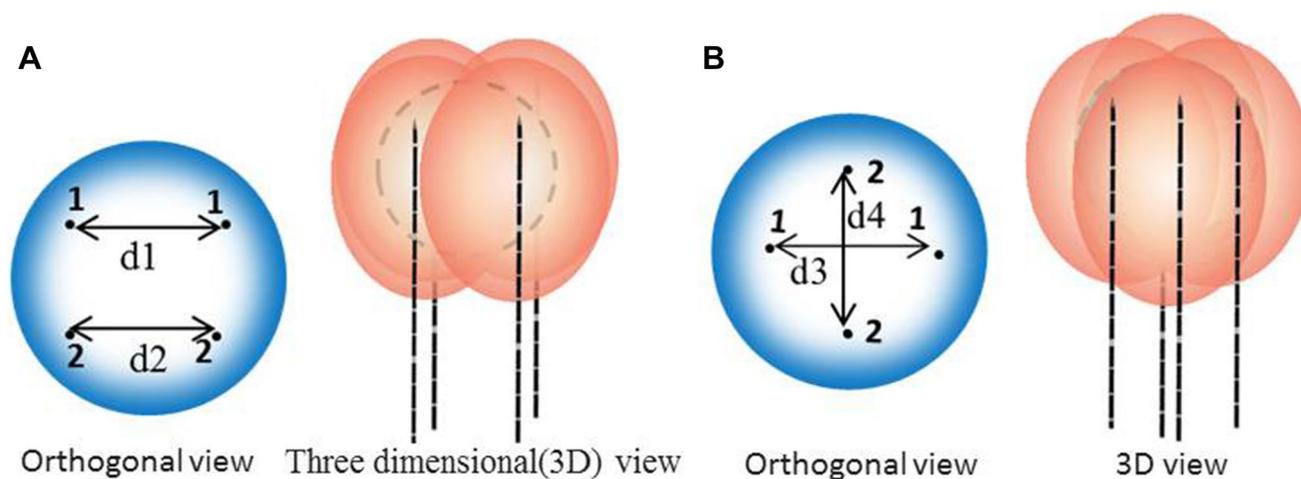
of tumors measuring  $> 3$  cm with preliminary results focusing on indexes of complete ablation and local recurrence. There are, however, very limited data regarding ablation strategies, including the number of antenna insertions, and the distance between antennas for tumors  $< 5$  cm that generally characterize early stage HCC.

This study aimed to compare the effectiveness of percutaneous MWA using the two different ablation strategies (parallel and crossed placement of antennas) in treating HCCs measuring 3–5 cm for analyzing differences in LTP and overall survival (OS) rates of the two ablation strategies and to evaluate related risk factors for LTP.

## Materials and methods

### Patients

Between December 2011 and May 2017, 71 HCC patients with 71 nodules, who were treated at interventional ultrasound department in Chinese PLA General Hospital using ultrasound (US)-guided percutaneous MWA with four insertions, were included in this retrospective study. In our center, for tumors measuring 3–5 cm, two ablation strategies were applied to generate overlapping ablations depending on the operators' discretion. The first is that two antennas were inserted simultaneously in the upper part of the tumor, and then, the other two were inserted simultaneously in the lower part of the tumor (group A). The second is that two antennas were inserted in the middle part of the tumor first, and then, the other two were inserted in the upper and lower part simultaneously (group B) (Fig. 1). All antennas were inserted roughly



**Fig. 1** Two antenna placement strategies of MWA with four antenna insertions. **a** The protocol for group A shown in orthogonal view and 3D view. **b** The protocol for group B shown in orthogonal view and

3D view. 1 and 2 represent the first and second procedure of overlapping ablations with two antennas acting in the concert, respectively. d1, d2, d3, d4: the distances between the two antennas

in parallel. Written informed consent was obtained from each patient before treatment, and the protocol was approved by the ethics committee of our hospital.

Among the 71 nodules, 48 in group A and 23 in group B underwent MWA. Information for each patient was obtained including demographics, longest diameter of lesions, number of lesions, liver function status, alpha fetoprotein level, and treatment variables (including distance between antennas, power of each generator, and microwave emission time of each antenna), treatment session, technique effectiveness, date and site of recurrence or metastasis, and date and status at last follow-up.

The inclusion criteria were as follows: liver function status Child-Pugh category A or B;  $\leq 3$  lesions with a maximum nodule diameter 3–5 cm; absence of portal vein thrombosis; prothrombin time  $< 25$  s, prothrombin activity  $> 40\%$ , and platelet count  $> 40$  cells  $\times 10^9/L$ ; and unsuitable for or refused partial hepatectomy.

### MWA procedure

Ablation was performed using a clinical MWA system (KY-2000, Canyon Medical Inc, Nanjing, Jiangsu, China). The device consists of two independent microwave generators operating at a frequency of 2450 MHz and a power output of 1 to 100 W, which can drive two antennas simultaneously, and two flexible coaxial cables with 15-gage (1.9 cm) cooled-shaft antennas, which are used to deliver microwave energy into liver tissue.

All ablative procedures were performed percutaneously under US-guidance by three operators (L.P., X.L.Y., and Z.G.C., with 20, 20, 9 years of experience in MWA, respectively). General anesthesia (propofol, 6–12 mg/kg/h; ketamine, 1–2 mg/kg) was induced before MWA. The operators chose one of the two ablation strategies at their discretion. MWA was performed at 50–60 W using two antennas simultaneously with four insertions (according to the protocol for group A or B), with a distance between them of no more than 2.5 cm. Microwave energy emission was not stopped until the hyperechoic area overlapped the area of the tumor with a surrounding 5 mm [20, 21] safety margin according to real-time US. At the end of the procedure, the needle tracks were cauterized to avoid tumor seeding and bleeding. Treatment was considered to be complete if the tumor was covered by ablation zone completely according to contrast-enhanced US or contrast-enhanced MRI. Microwave energy emission time, the power of each generator, and the distance between antennas were recorded. The average distance between the antennas in the two procedures was recorded and analyzed as a factor in the comparative analysis.

### Follow-up

Tumor responses to therapy were initially assessed within 3 days after ablation, then at 1 month, then at every 3 months for 1 year, and every 6 months thereafter, using contrast-enhanced US and contrast-enhanced CT/MRI. Complete ablation was considered to have been achieved if the tumor was covered completely, and there was no enhancement adjacent the ablation zone confirmed on follow-up imaging performed 1 month after treatment. In case of incomplete ablation, an additional MWA was performed. LTP was defined as the appearance of irregular peripheral enhancement in a scattered, nodular, or eccentric pattern on contrast-enhanced images around the ablation zone [18]. After complete ablation was performed, the rate of LTP was assessed during follow-up. If LTP was confirmed on follow-up imaging, further MWA was performed.

### Statistical analysis

Continuous variables are expressed as mean  $\pm$  standard deviation (SD). The independent sample *t*-test was used to compare the means between the two groups. For qualitative variables, the Chi-square test or Fisher's exact probability test was performed. LTP and OS rates were estimated using the Kaplan-Meier method, and differences between groups were compared using the log-rank test. Multivariate Cox proportional hazards regressions were performed to predict risk factors for LTP. The level of statistical significance was set at  $P < 0.05$ . All statistical analyses were performed using SPSS (IBM Corporation, Armonk, NY, USA) for Windows.

## Results

### Comparison of treatment parameters

The follow-up time was 5.8–74.7 months (median, 16 months) in group A, and 5.8–68.1 months (median, 15.1 months) in group B. All patients were treated successfully. Complete ablation was achieved in 62 patients after initial treatment and 9 patients after additional treatment as confirmed by follow-up imaging. Physical characteristics of the patients and tumor characteristics are presented in Table 1. The mean tumor diameter was comparable between the two groups ( $P = 0.11$ ,  $3.8 \pm 0.55$  VS  $3.6 \pm 0.51$ ). There was no significant difference in the complete ablation rate performed with one session ( $P = 1.0$ , [87.5%, 42/48 vs. 87.0%, 20/23]). In the two groups, there was no significant difference in mean total emission time ( $P = 0.98$ ).

**Table 1** Baseline characteristics and treatment parameters of 71 patients treated by two strategies with four antenna insertions

Characteristic	Group A	Group B	P value
Mean age (year) $\pm$ SD	61.8 $\pm$ 11.7 (37–88)	61.4 $\pm$ 9.5 (42–76)	0.89
Sex			
Male	38	20	0.53
Female	10	3	
Cirrhosis	40/48	21/23	0.48
Hepatitis HBsAg/ HCVAb	19/6	18/3	0.31
Tumor characteristics			
Mean tumor diameter (cm) $\pm$ SD	3.8 $\pm$ 0.55 (3.0–4.9)	3.6 $\pm$ 0.51 (3.1–4.9)	0.11
Tumor number	1.4 $\pm$ 0.61 (1–3)	1.5 $\pm$ 0.73 (1–3)	0.72
Child-Pugh class A/B	48/0	23/1	0.32
AFP > 200 ng/ml	10/48	3/23	0.74
Distance between antennas (cm) $\pm$ SD	1.6 $\pm$ 0.33 (1.1–2.5)	1.5 $\pm$ 0.21 (1.1–1.9)	0.05
3.0–4.0 cm	1.6 $\pm$ 0.34	1.5 $\pm$ 0.21	0.09
4.1–5.0 cm	1.6 $\pm$ 0.33	1.6 $\pm$ 0.21	0.67
Session	1.1 $\pm$ 0.33 (1–2)	1.1 $\pm$ 0.34 (1–2)	0.95
3.0–4.0 cm	1.1 $\pm$ 0.35	1.1 $\pm$ 0.32	0.83
4.1–5.0 cm	1.1 $\pm$ 0.32	1.2 $\pm$ 0.45	0.62
Mean total emission time (min) $\pm$ SD	27.3 $\pm$ 6.29 (15–44)	27.4 $\pm$ 4.25 (20–36)	0.98
3.0–4.0 cm	26.4 $\pm$ 6.99	27.1 $\pm$ 1.09	0.68
4.1–5.0 cm	28.83 $\pm$ 4.73	28.4 $\pm$ 5.18	0.86
Major complications	2/48	2/23	0.59
LTP	8/48	1/23	0.12*
3.0–4.0 cm	3/30	0/18	0.17*
4.1–5.0 cm	5/18	1/5	0.63*

SD standard deviation, HBsAg hepatitis B surface antigen, HCVAb hepatitis C virus antibody, LTP local tumor progression

## Treatment effectiveness

LTP was diagnosed in 8 of 48 patients (16.7%) in group A and 1 of 23 (4.3%) in group B on follow-up contrast-enhanced imaging. The 1-, 2-, and 3-year LTP-free rates were 89.4%, 81.1%, 64.9%, respectively, in group A, and 95.7%, 95.7%, and 95.7%, respectively, in group B, with no statistically significant difference between the two groups ( $P=0.115$ ) (Fig. 2a).

Ten (20.8%) and two (8.7%) patients died in groups A and B, respectively, during follow-up. Four of the ten patients in group A died of HCC progression, three of gastrointestinal bleeding, one of liver failure, one of heart failure, and one of hepatic encephalopathy. One of the two patients in group B died of HCC progression and the other of liver failure. The 1-, 2-, and 3-year OS rates were 88.5%, 79%, and 71.8% in group A and 93.8%, 87.5%, and 87.5% in group B, respectively, with no significant difference between the two groups ( $P=0.236$ ) (Fig. 2b).

Tumors were divided into nine parts based on the four needle insertion points, and regions were numbered in a clockwise manner (Fig. 3). The sites of recurrence were recorded according to region number. Treatment parameters

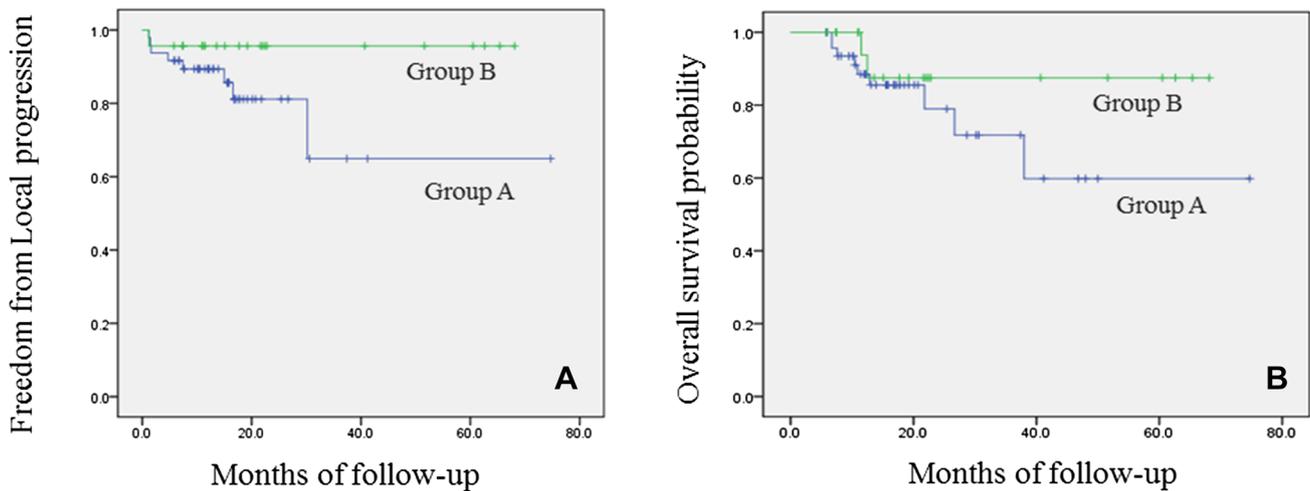
of the nine patients who exhibited LTP are summarized in Table 2. Six of the nine (66.7%) exhibited LTP occurring at the border between two thermal fields (region 2,4,6,8,9) and three at the outer edge of a single thermal field (region 1,3,5,7).

## Risk factor analysis

The influences of patient, tumor-, and treatment-related factors on LTP are shown in Table 3. Multivariate Cox proportional hazards regression analysis was performed to predict risk factors for LTP. Multivariate analysis (Table 4) revealed three factors that were related to LTP rate and exhibited a significant hazard tendency: tumor diameter ( $P=0.017$ ); distance between the antennas ( $P=0.032$ ); and total emission time ( $P=0.015$ ).

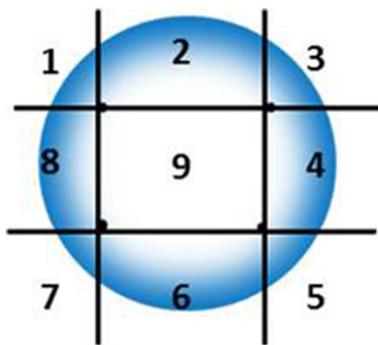
## Discussion

MWA and RFA have been regarded to be curative methods in the treatment of small liver cancer, especially for those less than 3 cm in diameter in many clinical practice guidelines



**Fig. 2** **a** Graph showing LTP-free curves after MWA of HCC by different ablation strategies. The 1-, 2-, and 3-year LTP-free rates were 89.4%, 81.1%, 64.9%, respectively, in group A, and 95.7%, 95.7%, and 95.7%, respectively, in group B, with no statistically significant differences between the two groups ( $P=0.115$ ). **b** Graph showing

cumulative OS rates of the two groups. The 1-, 2-, and 3-year OS rates were 88.5%, 79%, and 71.8% in group A and 93.8%, 87.5%, and 87.5% in group B, respectively, with no significant difference between the two groups ( $P=0.236$ )



**Fig. 3** Tumors divided into nine parts in two dimensions based on the four needle insertion points, and regions numbered in a clockwise manner. Parts 2,4,6, and 8 and nine represent the junction of two thermal fields, and parts 1,3,5, and 7 represent the boundary of a single thermal field according to the protocol for groups A and B

on HCC management [2, 3]. Compared with RFA, MWA affords a more predictable ablation zone, permits simultaneous treatment of multiple lesions, and achieves larger ablation zones in a shorter procedural time [22, 23]. For tumors > 3 cm in diameter, the challenge for ablation is complete tumor necrosis. Ablation zones created using simultaneous activation of multiple antennas are larger, more confluent, and achieve greater peripheral temperatures than do ablations created by single antenna acting alone [24, 25]. It provides us with a promising method for the percutaneous ablation of large HCCs. A clinical study from Thamtorawat et al. [26] showed that the LTP rate for tumors measuring 3–5 cm ablated by this promising method was 14.5%,

with no significant difference to tumors  $\leq 3$  cm. The LTP rate (12.7%, 9/71) in the present study was lower than that reported by Liu et al. [14], who described LTP in 14% of the patients with HCCs measuring 3–5 cm. In another study, Yin et al. [13] reported that local recurrence occurred in 22% of 109 patients with HCCs measuring 3–7 cm treated by MWA and with a median time of 4.6 months. Most published research studies have reported the association between tumor characteristics and patient survival; however, to date, few have focused on the relationship between ablation strategy and OS for tumors > 3 cm.

In our study, we assessed two types of ablation strategies for MWA of tumors measuring 3–5 cm and analyzed the effects of the two strategies on LTP. LTP and OS rates in group A were comparable to those in group B. The hazard ratio for LTP was higher for patients with larger nodules, less ablation time, and less distance between the antennas.

The crossed placement strategy used to ablate the maximum plane of the tumor initially, achieved a decrease in LTP rate (4.3% vs. 16.7%), which may be because most tumors are not perfect sphere. Moreover, initial ablation at the maximum plane of the tumor facilitates coverage of the remaining upper and lower part of the tumor.

The mean size of the ablation zone is 2.8 × 3.6 cm (50 W, 10 min) for 2450 MHz cooled-shaft antenna in ex vivo porcine livers [27]. Therefore, retreating antennas along the long axis of a tumor during ablation is inevitable for tumors measuring > 3 cm. There were 3 patients who experienced LTP occurring adjacent to the liver surface in our study, which was probably because the depth of antenna insertion or the retreated distance was insufficient.

**Table 2** Information of LTP occurring in 9 patients after MWA

No.	Group	Diameter (cm)	Site of recurrence (according to Fig. 3)	Distance between antennas (cm)	Total emission time (min)	Time after ablation (Mon)	Site of tumor
1	A	3	Part 4	1.3	38	4.9	Segment VII, adjacent to liver surface
2	A	3.6	Part 2	1.2	30	16.6	Segment VII
3	A	3.9	Part 4 and 8	1.5	28	4.7	Segment V
4	A	4.1	Part 1	2.3	28	1.6	Segment VIII, adjacent to liver surface
5	A	4.2	Part 3	1.5	28	30.2	Segment VI, adjacent to liver surface and kidney
6	A	4.2	Part 2	1.5	28	7.4	Segment V
7	A	4.5	Part 4 and 6	1.7	36	15	Segment VI
8	A	5	Part 1,7 and 5	1.6	32	1.5	Junction of Segment IV and V
9	B	4.9	Part 2	1.5	24	17.2	Junction of Segment VI and VII

**Table 3** Univariate analysis of risk factors for LTP

Variable	No. of patients	No. of LTP	<i>P</i> value
Men	58	7	0.67
Women	13	2	
Age			0.29
< 60 years	29	2	
≥ 60 years	42	7	
Tumor diameter			0.05
3.0–4.0 cm	48	3	
4.1–5.0 cm	23	6	
AFP > 200 ng/ml	13	2	0.67
Distance between antennas			1.0
1–1.5 cm	50	6	
> 1.5 cm	21	3	
Ablation strategy			0.12 <sup>a</sup>
Group A	48	8	
Group B	23	1	
Session			0.08
1	62	6	
> 1	9	3	
Total emission time			0.15
≤ 28 min	47	8	
> 28 min	24	1	

LTP local tumor progression, AFP alpha fetoprotein

<sup>a</sup>Univariate Kaplan-Meier analysis

There were 6 patients (6/9, 66.7%) with LTP occurring at the border between the two thermal fields and 3 with LTP occurring at the outer edge of a single thermal field, which was probably caused by further distance with less

emission time during the MWA procedure. According to the results of the present study, the distances between the antennas and total emission time—both of which have a direct effect on the volume of the ablation zone—were the two independent risk factors for LTP. The further distance with less emission time was likely to give rise to a cleft in the border between two thermal fields, which would lead to a reduced ablation margin. Teng et al. [28] reported that ablative margins < 5 mm were associated with higher rates of LTP in HCC after thermal ablation and the risk decreased by 46% for each 5-mm increase in minimal margin size [29]. However, if the distance is too close, it will result in low utilization of the thermal field and an increase in the number of antenna insertion. Therefore, preoperative planning in 3D may be a useful tool for the ablation of tumors > 3 cm [30, 31].

This study had some limitations, mainly due to its retrospective design, and relatively small sample size, which may have reduced statistical power in the comparative analysis, thus precluding detection of some associations. In addition, the retreated distance of antennas was not taken into consideration, which may have led to deviations in the results of multivariate analysis of tumor recurrence. Finally, LTP was not reconstructed in 3D space by follow-up CT/MRI imaging; consequently, we were unable to accurately locate the site of the LTP.

In conclusion, there were trends that were observed with lower LTP and improved OS in group B despite the lack of statistically significant differences between the two strategies at a level of  $P < 0.05$ . Nevertheless, initial ablation at the maximum plane of the tumor with sufficient ablation time and a suitable distance between antennas will facilitate reductions in LTP rate.

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**Table 4** Independent risk factors associated with LTP with cox proportional hazards model

Variable	B level	SE	Wald	df	Sig.	Exp(B) (95% CI)
Age	− 1.362	1.234	1.220	1	.269	.256 (0.023, 2.873)
Tumor diameter	<b>3.830</b>	<b>1.609</b>	<b>5.667</b>	<b>1</b>	<b>.017</b>	<b>46.044 (1.967, 1077.596)</b>
Sex	.142	1.164	.015	1	.903	1.153 (0.118, 11.276)
Total emission time	− <b>.009</b>	<b>.004</b>	<b>5.919</b>	<b>1</b>	<b>.015</b>	<b>.991 (0.984, 0.998)</b>
AFP	− 2.524	1.346	3.518	1	.061	.080 (0.006, 1.120)
The number of sessions	− 2.174	1.191	3.334	1	.068	.114 (0.11, 1.173)
Ablation strategy	2.218	1.866	1.412	1	.235	9.186 (0.237, 356.283)
Antenna distance	− <b>2.959</b>	<b>1.382</b>	<b>4.580</b>	<b>1</b>	<b>.032</b>	<b>.052 (0.003, 0.780)</b>

According to multivariate analysis, the three risk factors of LTP that in bold presented significant hazard tendency because the *P* value was less than 0.05

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### Compliance with ethical standards

**Conflict of interest** All the authors declare no conflict of interest.

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