



# Can “no-touch” radiofrequency ablation for hepatocellular carcinoma improve local tumor control? Systematic review and meta-analysis

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## Abstract

**Objectives** Percutaneous radiofrequency ablation (RFA) is one of the curative treatments for hepatocellular carcinoma (HCC), but local tumor progression (LTP) has been a main limitation of RFA. This study aims to evaluate the LTP of percutaneous no-touch RFA (NtRFA) for HCC  $\leq 5$  cm and compare with conventional RFA (intratumoral puncture) through a systematic review and meta-analysis.

**Methods** MEDLINE, EMBASE, and Cochrane Library were searched for studies on percutaneous NtRFA for HCC  $\leq 5$  cm. The pooled proportions of the overall and cumulative incidence rates at 1, 2, and 3 years for LTP after NtRFA were assessed using a random-effects model. For studies comparing NtRFA with conventional RFA, relative risks (RR) and hazard ratios (HR) were meta-analytically pooled with LTP as the outcome.

**Results** Twelve studies with 900 patients were included. The pooled overall rate of LTP after NtRFA was 6% (95% CI, 4–8%). The pooled 1-, 2-, and 3-year cumulative incidence rates of LTP were 3% (95% CI, 2–5%), 5% (95% CI, 3–9%), and 8% (95% CI, 6–11%), respectively. Compared to conventional RFA, the pooled RR and HR of LTP were 0.26 (95% CI, 0.16–0.41) and 0.28 (95% CI, 0.11–0.70), respectively (both  $p < 0.01$ ). Subgroup analysis including only randomized controlled studies also showed better local tumor control of NtRFA with HR of 0.13 (95% CI, 0.14–0.42).

**Conclusions** Percutaneous NtRFA is an effective treatment for HCC  $\leq 5$  cm with an overall LTP rate of 6% and provides lower LTP compared with conventional RFA.

## Key Points

- The pooled 1-, 2-, and 3-year cumulative incidence rates of local tumor progression after no-touch radiofrequency ablation for HCC  $\leq 5$  cm were 3% (95% CI, 2–5%), 5% (95% CI, 3–9%), and 8% (95% CI, 6–11%).
- No-touch radiofrequency ablation had significantly lower rates of local tumor progression compared to conventional radiofrequency ablation (hazard ratio, 0.28; 95% CI, 0.11–0.70; relative risk, 0.26; 95% CI, 0.16–0.41;  $p < 0.01$ , respectively).

**Keywords** Carcinoma, hepatocellular · Radiofrequency ablation · Neoplasm recurrence, local

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## Abbreviations

CIs	Confidence intervals
HCC	Hepatocellular carcinoma
HR	Hazard ratio
LTP	Local tumor progression
NtRFA	No-touch radiofrequency ablation
QUIPS	Quality in prognostic studies tool
RFA	Radiofrequency ablation
RR	Risk ratio

## Introduction

Percutaneous radiofrequency ablation (RFA) is one of the curative treatment options for early-stage hepatocellular carcinoma (HCC), providing comparable overall survival with the potential benefits obtained from repeat RFA and less aggressive deterioration on liver function compared to hepatic resection [1–3]. Conventional RFA has been performed by placing RF electrodes intratumorally to maximize thermal energy delivery to the target tumor. However, local tumor progression (LTP) has been one of the main limitations of conventional RFA with reported risk factors such as satellite nodules [4] or microvascular invasion [5], which may be untreated by insufficient ablative margins [6], track seeding along the electrode insertion route [7], increased intratumoral pressure during ablation which may facilitate tumor spread [8], or decrease of RFA temperature when a tumor is located in the vicinity of blood flow (so-called heat-sink effect) [9]. In fact, the 3-year and 5-year cumulative incidence rates of LTP after conventional RFA for single HCC smaller than 3 cm were 28.5% and 32.1%, respectively [10]. Although subsequent interventions in patients with LTP provide comparable overall survival outcome to those without LTP, there is still a clinically unmet need to reduce LTP [3].

In this regard, no-touch RFA (NtRFA) has recently been introduced and investigated in clinical practice, to improve local tumor control. NtRFA is performed by inserting multiple electrodes outside the tumors to achieve ablation with sufficient margins and to avoid violation of the tumor itself to prevent track seeding or intratumoral pressure increase. Previously, the proof of concept of better local tumor control of NtRFA compared to conventional RFA was substantiated in both *in vivo* [11] and histopathological study [12]. Several clinical studies with NtRFA with multi-bipolar electrodes have been published providing LTP rates as low as 4% at 3 years [13–16] and lower LTP rates [17–19] compared to conventional RFA with monopolar electrodes. Two recent studies using the same RFA system and electrodes also showed similar trends of lower LTP in NtRFA than in conventional RFA [20, 21]. In addition, another retrospective study by Kawamura et al [19] reported that NtRFA showed significantly lower intra-subsegmental recurrence than conventional RFA, although the cumulative LTP rates were not significantly different between ablation procedures.

The clinical application of NtRFA has been slow despite satisfactory local tumor control rates in the literature [13–24]. This is partly because of the heterogeneous study population, different RF energy delivery modes (i.e., multi-bipolar or monopolar), and the small number of patients in prior studies. Therefore, this study aimed to systematically review the literature and perform a meta-analysis of LTP after percutaneous NtRFA for HCC equal to or less than 5 cm, and to compare it with conventional RFA.

## Materials and methods

We performed this meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines [25]. This study was not registered on PROSPERO (International Prospective Register of Systematic Reviews).

### Literature search

We conducted systematic search in MEDLINE, EMBASE, and Cochrane Library databases up to May 9, 2022, to find relevant original articles reporting on per-patient or per-lesion LTP after NtRFA for HCC. The following keywords and their synonyms were included in the search terms: (“no touch” OR nontouch OR bipolar OR multipolar) AND (“radiofrequency ablation” OR RFA) AND recurrence AND (“hepatocellular carcinoma” OR “hepatic cancer” OR hepatoma OR HCC). The references of the included articles were screened to identify other eligible studies.

### Inclusion criteria

The inclusion criteria according to the Population, Intervention, Comparison, Outcomes and Study criteria for studies in the meta-analysis were as follows [26]: (1) studies comprising patients (P) diagnosed with HCC (either by pathology or by non-invasive imaging criteria)  $\leq 5$  cm who underwent percutaneous NtRFA for curative purposes; (2) studies with NtRFA as an index test (I); (3) studies with conventional RFA as comparison (C) if available; (4) studies with outcome (O) as the overall or cumulative incidence rates of LTP; and (5) studies with study type (S) as an original article.

### Exclusion criteria

The exclusion criteria were as follows: (1) studies with sample size less than 10 patients; (2) studies with publication type other than original articles; (3) studies with insufficient data for evaluating the overall or cumulative incidence rates for LTP after NtRFA; and (4) studies with complete population and data overlap. One author (T.H.K.) performed the literature search and study selection, which was double-checked by another author (J.M.L.).

### Data extraction and quality assessment

Data from the included studies regarding demographic and clinical characteristics, overall rates, and cumulative incidence rates at years 1, 2, and 3 of LTP after NtRFA were retrieved using a standardized form. If studies provided comparison data of LTP rates between conventional RFA and NtRFA, the data were also recorded for further analysis.

Two reviewers independently assessed the methodological quality of the selected studies by using the Quality in Prognostic Studies (QUIPS) tool [27]. Disagreements were resolved by consensus from the two reviewers.

## Data synthesis and analyses

The primary outcome for the current meta-analysis was pooled proportions of the overall and cumulative incidence rates at years 1, 2, and 3 of the LTP after NtRFA. We separately calculated per-lesion and per-patient LTP rates, and combined both to synthesize the overall LTP rates. The pooled proportions and 95% confidence intervals (CIs) were calculated using the DerSimonian-Laird random-effects model, and weights were determined using the inverse variance method [28].

The second outcome was to compare the LTP rates between conventional RFA and NtRFA based on the risk ratios (RR) and hazard ratios (HR) with 95% CIs extracted, respectively. For studies that only provided the Kaplan-Meier curves without HR from univariate Cox regression analysis, their HRs and 95% CIs were indirectly calculated using Engauge Digitizer (version 10.4; <http://markumitchell.github.io/engauge-digitizer/>), based on the methodology proposed by Guyot et al [29]. Heterogeneity among studies was assessed using Higgins  $I^2$ , which describes the percentage of variation across studies that is due to heterogeneity rather than chance, with significant heterogeneity considered present when  $I^2$  was > 50% [30]. For the pooled proportions, publication bias was visually assessed by using funnel plots, and statistical significance was evaluated using the Egger test [31]. A meta-regression analysis using the following covariates was performed to identify the sources of heterogeneity: study design (retrospective vs. prospective), mean or median HCC size ( $\leq 2$  cm vs.  $> 2$  cm), HCC number (single vs. multiple), inclusion of recurrent HCC (vs. only including treatment-naive HCC), continent (Asia vs. Western), and RFA mode (multi-bipolar vs. multiple monopolar).

All statistical analyses were performed using the “meta” and “metafor” packages of the R statistical software (version 3.6.0, The R Foundation for Statistical Computing).

## Results

### Literature search

The initial systematic search identified 295 studies. After the removal of 100 duplicates, 195 articles were screened based on their titles and abstracts. Subsequent full-text review of 23 potentially eligible studies excluded 11 studies. Ultimately, 12 studies evaluating LTP after NtRFA in HCC  $\leq 5$  cm were

included [13–24]. The study selection process is illustrated in Fig. 1.

### Characteristics of included studies

The patient, study, and RFA characteristics are summarized in Table 1. The number of patients and HCC treated with NtRFA ranged from 15 to 181 and 17 to 132, respectively. In total, 900 patients and 639 HCC treated with NtRFA were included in our meta-analysis, reflecting two studies only reported the number of patients and not the number of treated HCC [18, 22]. Initial HCC diagnosis was based on pathology in one study [14], non-invasive imaging criteria in six studies [13, 16, 17, 21–23], or both in five studies [15, 18–20, 24]. Six studies included single HCC [14, 16, 17, 19, 23, 24], and the other six studies included multiple HCC, with maximum number up to 3 [13, 15, 18, 20–22]. The median or mean size of HCC was less than 2 cm in six studies [17, 19–23] and larger than 2 cm in six studies [13–16, 18, 24]. Seven studies included only patients with treatment-naive HCC [13–18, 24], whereas five studies also included patients' recurrent HCC from previous treatments [19–23]. Seven studies were retrospective [13–15, 17–19, 24], three prospective [16, 22, 23], and two randomized controlled trials [20, 21]. Regarding the NtRFA mode, three studies utilized multiple switching monopolar [14, 20, 23], whereas the other nine studies used multi-bipolar [13, 15–19, 21, 22, 24]. Six studies compared LTP with conventional RFA [17–22]. Operator numbers and experience varied across the studies.

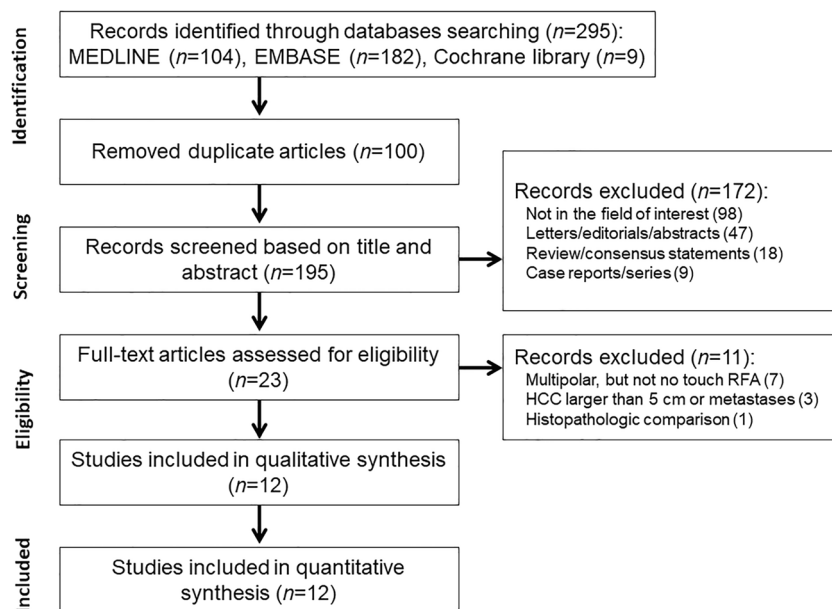
### Quality assessment

The risk of bias evaluation using the QUIPS tool is summarized in Fig. 2. For the study participant domain, four studies showed a moderate risk as they shared a partial overlapping population [13, 15, 18, 24]. A low risk of bias was observed in all studies for the study attrition and study confounding domains. Regarding the prognostic factor measurement domain, high risk of bias was present in one study as it included two patients who underwent NtRFA under laparoscopic approach [24]. For the outcome measurement domain, all studies showed a moderate risk of bias because LTP was determined by knowing that patients underwent NtRFA. For the statistical analysis and reporting domain, two studies showed a moderate risk of bias as they included both LTP and primary RFA failure in the cumulative incidence calculation [13, 18].

### Local tumor progression

The definition of LTP was almost identical throughout the 12 studies, 11 studies [13, 15–24] defining recurrence abutting the ablation zone and one study [14] additionally including recurrence within 2 cm from the ablation zone. The pooled

Fig. 1 Study inclusion



proportion of LTP is summarized in Fig. 3A. The LTP rate was available as per-lesion analysis in nine studies, and as per-patient analysis in three studies, ranging from 2 to 11%. The pooled proportion of LTP was 6% (95% CI, 4–9%), 5% (95% CI, 2–9%), and 6% (95% CI 4–8%) in per-lesion, per-patient, and overall analysis, respectively. In the funnel plots and the Egger test, significant publication bias was observed ( $p < 0.01$ ) (Supplementary Figure 1). The pooled 1-, 2-, and 3-year cumulative incidence rates of LTP were 3% (95% CI, 2–5%), 5% (95% CI, 3–9%), and 8% (95% CI, 6–11%), respectively (Fig. 3B). Heterogeneity among studies was not observed in the pooled proportions of the overall rate and the 1- and 3-year cumulative incidence rates ( $I^2$ , 15–29%) and were moderate only in the 2-year cumulative incidence rate ( $I^2 = 51\%$ ).

The results of the meta-regression analysis performed to explore the possible sources of heterogeneity are summarized in Table 2. The analysis revealed that studies with prospective design showed significantly lower rates of LTP (2.4%; 95% CI, 1.1–5.1%) than those with retrospective design (6.9%; 95% CI, 5.1–9.5%;  $p = 0.01$ ). Other covariates, including HCC characteristics (mean/median size cutoff of 2 cm, number of HCC, or inclusion of recurrent HCC), study population (Asia vs. Western), and RFA mode (multi-bipolar vs. multiple monopolar) did not differ significantly across the studies.

### Local tumor progression comparison between no-touch radiofrequency ablation and conventional radiofrequency ablation

Figure 4 summarizes the pooled analysis for LTP comparison between NtRFA and conventional RFA from studies which provided relevant data [17–22]. NtRFA had significantly

lower rates of LTP compared to conventional RFA (HR, 0.28; 95% CI, 0.11–0.70; RR, 0.26; 95% CI, 0.16–0.41;  $p < 0.01$  respectively). Subgroup analysis including only studies with randomized controlled design also showed better local tumor control of NtRFA with HR of 0.13 [95% CI, 0.04–0.42] (Fig. 4C) [20, 21].

## Discussion

This is the first meta-analysis focusing on local tumor control of NtRFA for HCC  $\leq 5$  cm, which proved to be effective with an overall LTP rate of 6% and cumulative incidence LTP rates of 3%, 5%, and 8% at 1, 2, and 3 years, respectively. Furthermore, NtRFA showed better control of LTP than conventional RFA, with four times more likelihood of LTP occurring in conventional RFA than in NtRFA. Based on our study results, NtRFA is an effective treatment for achieving satisfactory LTP for HCC and may be preferentially used for better local tumor control than conventional RFA.

The efficacy of local tumor control in conventional RFA has been investigated in numerous studies. For instance, in a large-scale retrospective study with 1305 patients with 1502 early-stage HCC over 12 years of enrollment period [2], the incidence rate of LTP was 19.4% with 1- and 3-year cumulative rates of 9.7% and 27.0%, respectively. Another retrospective study of 301 patients with solitary HCC less than 3 cm over 15 years of enrollment period [32] reported overall LTP rates of 16.6% and 20.1% in HCC  $> 2$  cm. The reported results from conventional RFA were approximately three times higher than the pooled overall rates and cumulative incidence rates of LTP after NtRFA from our meta-analysis. Furthermore, we reidentified the better local tumor control

**Table 1** Patient, study, and RFA characteristics

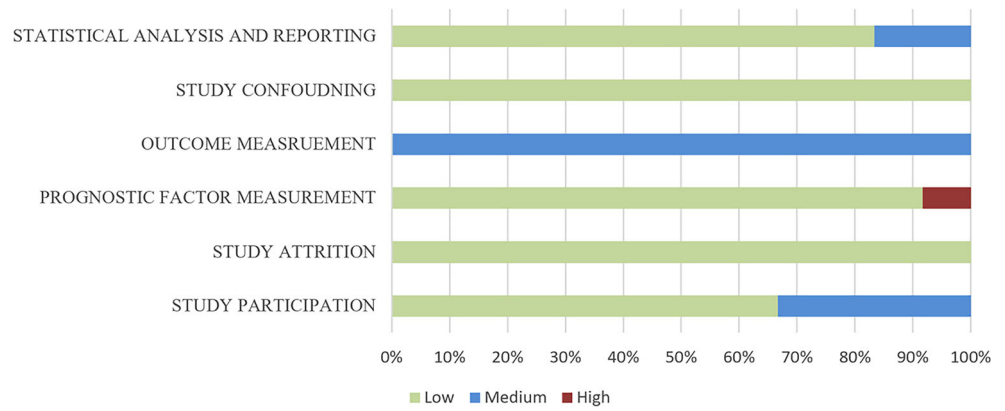
First author	Patient characteristics				Study and RFA characteristics						
	No. of patients	No. of HCC	Inclusion criteria	HCC size (cm) Median (range)	Previous HCC treatment	Follow-up duration (months) Median (range)	Study design	Country	nRFA mode	Conventional RFA mode	Operator number and experience (years)
Chai	46	46	Single ≤ 3 cm	1.9* (1.5–2.2)	No	Up to 24 months (NA)	Retrospective/single center	China	Multi bipolar	Monopolar	One, 10
Hirooka	110	NA	Single < 4 cm, or maximum 2 lesions < 3 cm	1.8 (IQR 1.2–2.3)	Yes	25.3 (IQR 15.9–35.2)	Prospective/single center	Japan	Multi bipolar	Monopolar	NA
Hocquelet	181	NA	Single ≤ 5 cm, or maximum 2 lesions < 3 cm	2.5* (NA)	No	36 (IQR 18.8–55.5)	Retrospective/multi center	France	Multi bipolar	Monopolar	Eight, at least 5
Kawamura	35	35	Single ≤ 3 cm	1.6 (0.8–2.4)	Yes	32.7* (4.9–40.7)	Retrospective/single center	Japan	Multi bipolar	Monopolar	NA
Lee	128	128	Single ≤ 2.5 cm	1.7* (NA)	Yes	18 (3–31)	Prospective/multi center	Korea	Multiple switching monopolar	NA	Six, at least 5
Mohkam	72	72	Single 2–5 cm	3.0 (IQR 2.5–4.0)	No	NA	Retrospective/single center	France	Multi bipolar	NA	Three, at least 4
Partk	58	60	Maximum of 2 lesions, each ≤ 2.5 cm	1.6* (NA)	Yes	24.6* (NA)	Randomized controlled study/single center	Korea	Multiple switching monopolar	Multiple switching monopolar	Four, at least 12
Petit	58	59	Maximum of 3 lesions, each ≤ 5 cm	2.5 (1.0–5.0)	No	30.5 (1–97)	Retrospective/single center	France	Multi bipolar	NA	One, more than 10
Qu	56	56	Single ≤ 3 cm	2.6 (1.8–2.8)	No	Up to 24 months	Retrospective/single center	China	Multiple monopolar	NA	One, more than 15
Suh	33	34	Maximum of 2 lesions, each ≤ 2.5 cm	1.7* (NA)	Yes	33.2 (NA)	Randomized controlled study/single center	Korea	Multi bipolar	Multi bipolar	One, more than 20
Seror	108	132	Single ≤ 5 cm, or maximum 3 lesions ≤ 3 cm	2.5 (IQR 2.0–4.5)	No	40.5* (2–84)	Retrospective/single center	France	Multi bipolar	NA	One, more than 10
Wu	15	17	Maximum of 2 lesions, each ≤ 3 cm	2.6* (NA)	No	10* (3–21.5)	Prospective/single center	Taiwan	Multi bipolar	NA	One, 4

HCC hepatocellular carcinoma, IQR interquartile range, NA not available, RFA radiofrequency ablation

\*Mean



Fig. 2 QUIPS



of NtRFA compared to conventional RFA in our meta-analysis, with pooled HR and RR of 0.28 and 0.26, respectively. It is noteworthy that subgroup analysis including only studies with randomized controlled design showed a similar trend of better local tumor control of NtRFA with HR of 0.13. The lower incidence of LTP after NtRFA may be explained by several factors. First, during NtRFA, multiple electrodes inserted outside the tumor margins initiate ablation from the periphery to centripetally to the target tumor, which enables sufficient ablation margins to be achieved. Second, coagulation of tumor feeding and draining vessels in the periphery of the target tumor occur in the early period of ablation, which may block the dispersal of tumor cells into the drainage bloodstream. Furthermore, contrary to conventional RFA, NtRFA does not violate the tumor capsule or elevate intratumoral pressure during ablation which are well-known leading factors for recurrence in surgery and conventional RFA, respectively [33, 34]. In line with this, lower rates of intra-subsegmental

recurrence of NtRFA have also been highlighted ranging from 2.9 to 5.5% [15, 19], compared to 13.2 to 19.2 % for conventional RFA [19, 35]. Finally, as more than one electrode are used in NtRFA, in treating HCC located near large vessels where the heat-sink effect precludes efficient treatment, one of the electrodes can be placed at the abutting vessels to deliver optimal energy to maximize the local efficacy [15, 18].

In the meta-regression analysis, studies stratified by the cutoff of 2 cm for the mean or median tumor size did not show significant difference in overall LTP rates ( $p = 0.13$ ). Although not all studies in the current meta-analysis targeted HCC larger than 3 cm, the high efficacy of NtRFA even in larger tumors between 3 and 5 cm may be attributed to this insignificance. For instance, in the retrospective study by Seror et al [15], which included HCC  $\leq 5$  cm treated by NtRFA, tumor larger than 3 cm was not a predictive factor for LTP. Furthermore, a lower rate of LTP of 9.3% after NtRFA compared to 20% after conventional RFA for HCC

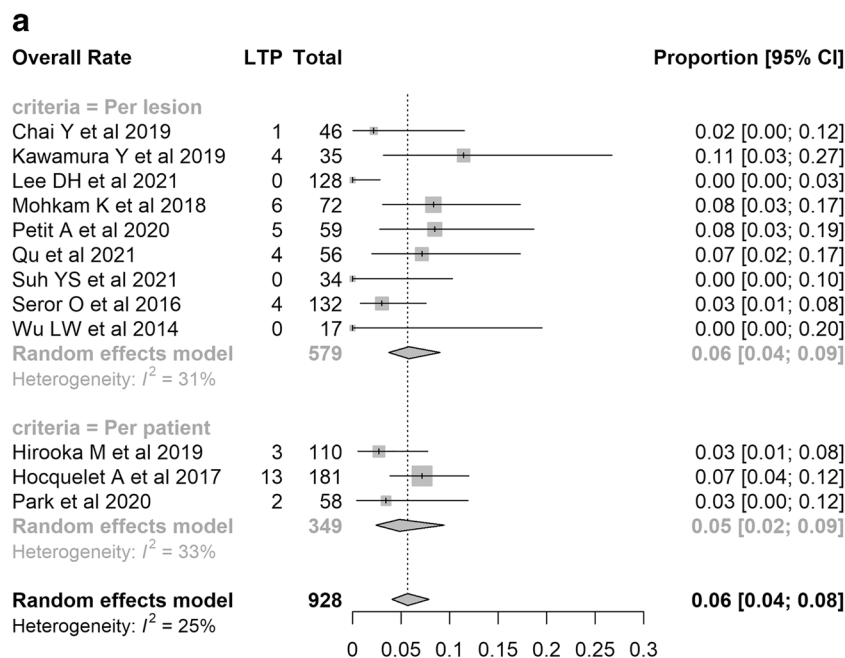


Fig. 3 Overall and cumulative local tumor progression after no-touch radiofrequency ablation. a Overall rate. b Cumulative rates at 1, 2, and 3 years

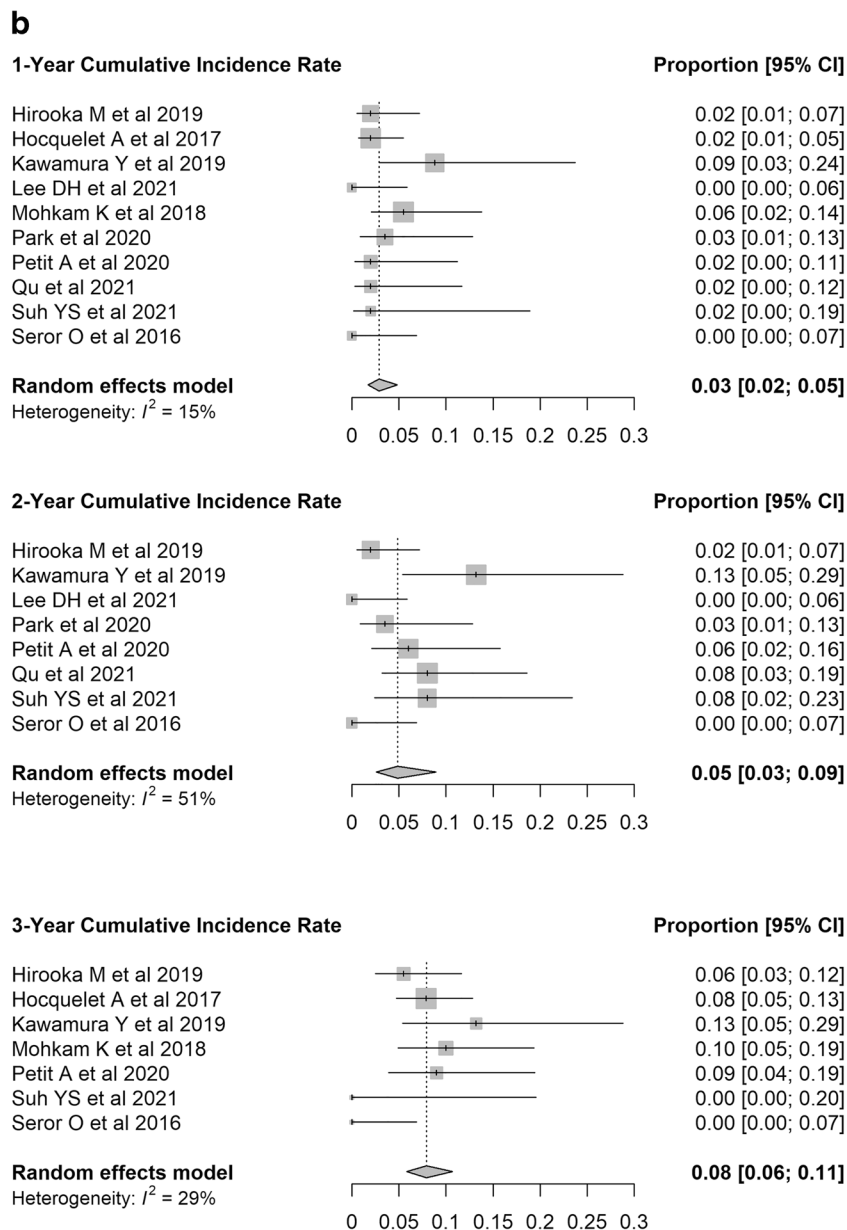


Fig. 3 (continued)

larger than 3 cm may substantiate the capacity of NtRFA to successfully treat HCC larger than 2 cm [18, 36]. At the same time, albeit without statistical significance, given that overall LTPs after NtRFA for HCC larger than 2 cm are twice as high as those for HCC less than 2 cm (6.7% vs. 3.3%) and technical difficulty in performing NtRFA for HCC larger than 3 cm, we may not have reached a statistical significance from a small number of included studies. Second, the, RFA mode (i.e., multi-bipolar vs. multiple monopolar) in NtRFA was not a significant factor for LTP. Although multi-bipolar has been reported to induce a larger ablation volume compared to multiple monopolar [37], the mode may not affect as in the real clinical situation as operators manipulate to achieve optimal

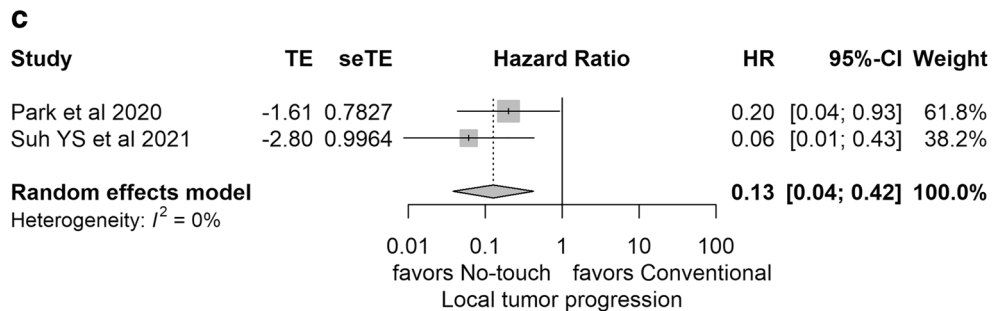
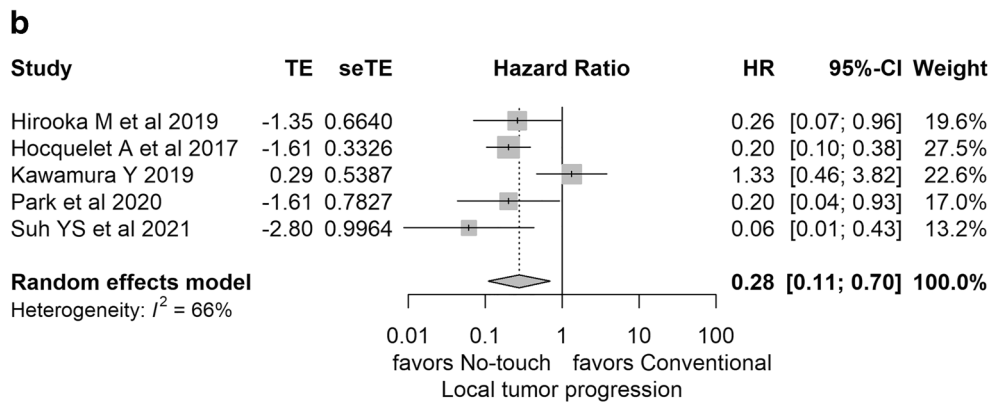
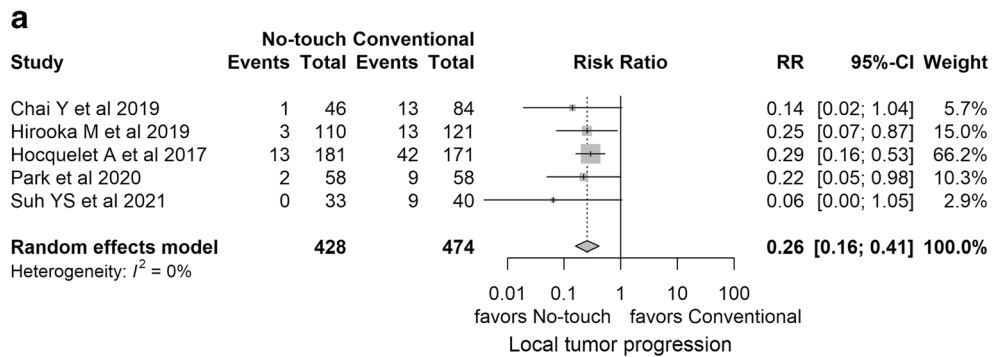
ablation. Lastly, prospective studies showed a lower overall LTP rate than retrospective studies (2.4% vs. 6.9%). We speculate that at least in part, predetermined focus with strict eligibility criteria to achieve complete ablation in prospective design may have contributed to lower LTP.

This study has some limitations. First, the number of included studies was relatively small ( $n = 12$ ). This may stem from the fact that NtRFA was introduced recently in the last decade and has not been as extensively studied as conventional RFA. Caution is also warranted as publication bias was present in the funnel plot and Egger’s test. Second, although we performed subgroup analysis based on the tumor size with a cutoff of 2 cm, subgroup analysis based on the different

**Table 2** Result of meta-regression analysis

Covariate, subgroup	Number of studies	Meta-analytic summary of estimates for LTP	
		Pooled proportion, % (95% CI)	<i>p</i>
Study design			
Retrospective	7	6.9 (5.1–9.5)	0.01
Prospective	5	2.4 (1.1–5.1)	
Mean/median HCC size			
< 2 cm	6	3.3 (1.4–7.7)	0.13
> 2 cm	6	6.7 (4.8–9.3)	
HCC number			
Only single HCC	5	6.2 (3.0–12.4)	0.63
Included multiple HCC	7	5.1 (3.4–7.6)	
Inclusion of recurrent HCC			
Only including treatment-naïve HCC	7	6.5 (4.6–8.9)	0.22
Including recurrent HCC	5	3.4 (1.3–8.9)	
Continent			
Asia	8	4.1 (2.2–7.6)	0.20
Western	4	6.7 (4.5–9.8)	
RFA mode			
Multi-bipolar	9	5.9 (4.1–8.6)	0.41
Multiple monopolar	3	3.4 (1.0–11.5)	

**Fig. 4** Comparison between conventional radiofrequency ablation. **a** Risk ratio. **b** Hazard ratio. **c** Hazard ratio, only including randomized controlled studies





tumor sizes (i.e., < 3 cm versus 3–5 cm) or RFA characteristics that may influence the technical success and subsequent LTP rate such as visibility during the ablation, or application of adjuvant maneuvers such as artificial ascites or fusion imaging, was not feasible due to the unavailability of information in the included studies. Third, as we mainly focused on the LTP of NtRFA, clinical aspects of NtRFA, such as technical feasibility according to tumor location, learning curve to achieve satisfactory treatment efficacy, or postprocedural liver failure from larger ablation margins could not be dealt in depth.

In conclusion, NtRFA showed effective local tumor control in the treatment of HCC  $\leq$  5 cm, with lower LTP compared to conventional RFA. Therefore, NtRFA should be considered an effective therapeutic option with the intent to cure for HCC.

**Supplementary Information** The online version contains supplementary material available at <https://doi.org/10.1007/s00330-022-08991-1>.

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## Declarations

**Guarantor** The scientific guarantor of this publication is Jeong Min Lee.

**Conflict of interest** The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

**Statistics and biometry** Tae-Hyung Kim, one of the authors, has significant statistical expertise in meta-analysis.

**Informed consent** Written informed consent was waived by the Institutional Review Board.

**Ethical approval** Institutional Review Board approval is not required because the study design is systematic review and meta-analysis.

## Methodology

- retrospective
- not applicable
- multicenter study

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