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An Investigation of Popping During Radiofrequency Ablation After Lenvatinib Administration for Hepatocellular Carcinoma

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Abstract. *Background/Aim: Lenvatinib is available as a molecular target agent for hepatocellular carcinoma (HCC). In this study, we investigated the popping phenomena in patients with HCC who underwent radiofrequency ablation (RFA) after taking lenvatinib. Patients and Methods: Fifty-nine patients with HCC between 21-30 mm in diameter and no history of systemic treatment were enrolled in the study. The patients underwent RFA using a VIVA RFA SYSTEM with an ablation tip of 30 mm in length. For the initial lenvatinib administration, 16 patients had an adequate course of treatment and were treated with RFA as add-on therapy (combination group). The other 43 patients were treated by RFA monotherapy (monotherapy group). The popping frequency during RFA was recorded and compared. Results: Popping frequency in the combination group (RFA combined with lenvatinib) was significantly higher than that in the monotherapy group. There was no significant difference between the combination group and the monotherapy group in ablation time, maximum output level, tumour temperature after ablation, or initial resistance value. Conclusion: Popping frequency was significantly higher in the combination group. It is possible that the intra-tumour temperature increased rapidly during RFA in the combination group due to the inhibitory effect of lenvatinib on tumour angiogenesis, leading to the occurrence of popping. Further studies are needed to investigate popping after RFA, and precise protocols need to be developed.*

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Key Words: Hepatocellular carcinoma, radiofrequency ablation, popping phenomenon, MTA, molecular target agent.

Sorafenib was the first molecular target agent (MTA) that was approved as first-line treatment for unresectable/advanced disease (1, 2). Subsequently the REFLECT trial, which involved patients with unresectable hepatocellular carcinoma (HCC), demonstrated that lenvatinib, another MTA, was not inferior to sorafenib as a first-line treatment (3). This finding has been confirmed by several real-world evidence studies (4-6). Conversely, ablation therapy, including radiofrequency ablation (RFA), is attracting attention as a conversion therapy with pharmacotherapies, including MTAs.

In addition to a study by Park *et al*. that reported the effectiveness of ablation therapy performed post-sorafenib monotherapy, Wang *et al*. reported that a combination therapy of lenvatinib and ablation was more effective than lenvatinib monotherapy (7, 8). Lenvatinib is a potent inhibitor of angiogenesis. Its relatively early efficacy in comparison to other medications across different cancer types acts as an advantage for its use in conversion surgery. Therefore, lenvatinib-ablation therapy is expected to be an ideal form of conversion therapy. However, the time point for administration of lenvatinib as part of the ablation protocol is not clear.

Popping refers to a form of explosive tissue disruption caused by a rapid elevation in intra-tissue pressure. The occurrence of the 'popping' phenomenon during combination therapy of RFA and pharmacotherapy has not been adequately investigated. Therefore, we aimed to investigate the popping phenomenon in patients who had undergone RFA combined with lenvatinib.

Patients and Methods

Patients involved in the study. The study involved 59 patients (42 males and 17 females) with HCC between 21-30 mm in diameter. They were treated between March 2018 and March 2019.

Table I. *Patient and lesion characteristics at the time of enrollment.*

Baseline characteristics	Combination (n=16)	Monotherapy (n=43)	*p*-Value
Age (years)	80.4±8.5	72.4±9.2	0.052
Sex ratio (Male: Female)	12:4	30:13	0.693
Tumor diameter (mm)	29.7±1.3	27.0±5.7	0.083
Etiology (HBV/HCV/Non HBV/HCV)	3/11/2	2/27/14	0.104
Location (S1/S2/S3/S4/S5/S6/S7/S8)	1/0/1/0/2/2/5/5	1/3/1/6/8/8/7/9	0.457

HBV: Hepatitis B virus; HCV: hepatitis C virus; Non HBVHCV: non-HBV non-HCV; S: segment.

Inclusion criteria were as follows: 1) age >18 years old; 2) a Child-Pugh class A liver function score; and 3) no imaging evidence of vascular invasion or extrahepatic metastasis. Exclusion criteria were as follows: 1) patients who had been treated with previous systemic treatments; 2) patients with hepatic dysfunction or renal impairment; 3) patients with other malignancies besides HCC; and 4) patients with hepatic encephalopathy, refractory ascites, oesophageal variceal bleeding, or other serious complications. This study was approved by the Institutional Review Board of Saiseikai Niigata Hospital (No. E18-18) and conducted in accordance with the principles of the Declaration of Helsinki (as revised in 2013). Before participating in this study, written informed consent was provided by all patients.

Performance of RFA. RFA was performed percutaneously under ultrasonographic guidance. The protocol detailed the execution of the stepwise ablation approach. The procedure was initially performed at 40 Watt and increased by 10 Watt at every 60-s interval. A 480-kHz generator (VIVA RF generator; STARmed, Gyeonggi, Republic of Korea) and a 17-gauge internally cooled, adjustable radiofrequency electrode (VIVA; STARmed, Gyeonggi, Republic of Korea) were used. The length of the electrode active tips applied in this study was 30 mm. Every procedure aimed to obtain an ablative margin of ≥5 mm around the treated lesions. A post-operative contrast-enhanced ultrasound examination was performed to evaluate the adequacy of the ablation. Complete ablation was defined as no perfusion of the contrast agent into the ablative area (which completely covered the lesion area), showing a completely black appearance with a distinct boundary.

Popping phenomenon. In our study, the popping phenomenon was defined as an audible popping sound that suddenly occurs during the RFA session. The popping frequency during RFA was measured and compared using the chi square test.

Comparison between two study groups. Within the 59-patient population, we compared 16 patients with HCC who underwent RFA after taking lenvatinib (combination group) and 43 patients with HCC who underwent RFA without taking lenvatinib during the same period (monotherapy group). Ablation time, energy, maximum output, resistance, and final temperature were compared using the Mann-Whitney test.

Statistical analysis. Categorical variables are expressed as whole numbers. Two-tailed, unpaired *t*-tests were performed to compare the continuous variables that were normally distributed. Non-normally distributed data was compared using the Mann-Whitney *U*-test. The differences in distribution of categorical variables between the two groups were analysed using Pearson's Chi square test or Fisher's exact test.

Statistical significance was defined as $p<0.05$. All statistical analyses were performed using EZR (Saitama Medical Centre, Jichi Medical University, Shimotsuke, Japan), a graphical user interface for R version 3.2.2 (The R Foundation for Statistical Computing, Vienna, Austria) (9).

Results

No significant differences in baseline characteristics of patients. Fifty-nine patients with HCC with lesion diameters between 20.0 and 30.0 mm were screened. Among them, 16 were assigned to the combination group (RFA combined with lenvatinib) and the remaining 43 to the monotherapy group (RFA without lenvatinib). The baseline values of the combination and monotherapy groups are summarized in Table I. The baseline characteristics between the two groups were not significantly different (Table I).

No significant differences in RFA-related factors post-procedure. Between the two groups, no significant differences were seen in background liver factors or in the ablation time, maximum output level, tumour temperature after ablation, and initial resistance value (Figure 1).

Popping frequency in the combination group was significantly higher. We observed and recorded the popping phenomenon that occurred during RFA. Popping frequency was significantly higher in the combination group compared to that in the monotherapy group. Popping occurred in 8 of 16 nodes in the combination group and 8 of 43 nodes in the monotherapy group ($p=0.016$) (Table II).

Although there was a significant difference in popping frequency, no difference was seen in popping-related side effects or other adverse events due to RFA between the two groups.

Discussion

In this study, we investigated the popping rate in patients who underwent RFA after taking lenvatinib and showed that

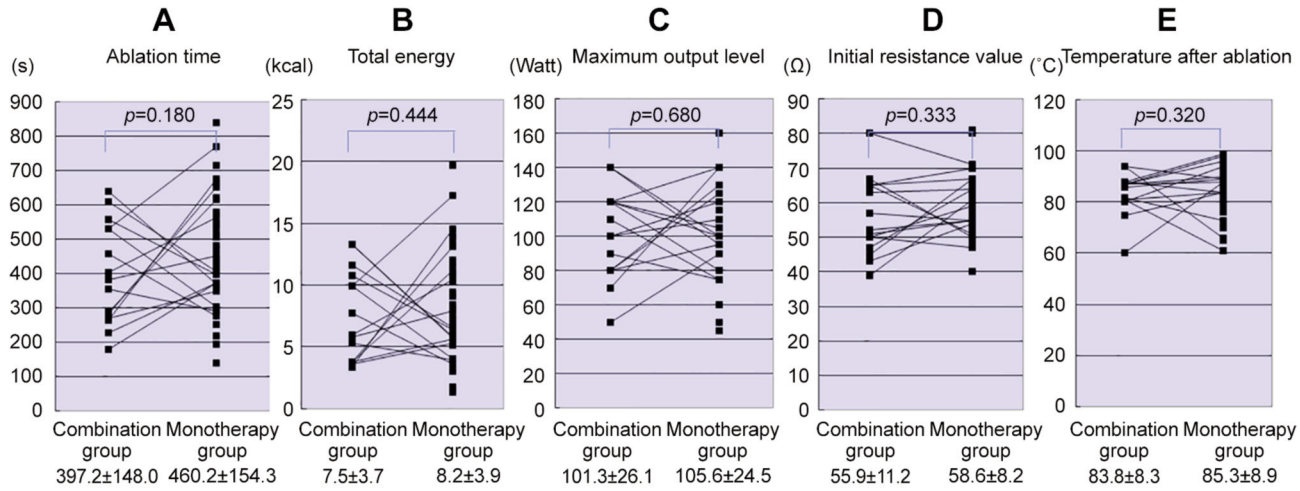

Figure 1. *Comparisons of the radiofrequency ablation (RFA) procedure between the combination group (RFA combined with lenvatinib) and monotherapy group (RFA without lenvatinib) post ablation. (A) Ablation time, (B) Total energy, (C) Maximum output level, (D) Initial resistance value, and (E) Temperature after ablation.*

it was significantly higher in the combination group than that in the monotherapy group.

In addition, no significant difference was seen in background liver factors, nor in the ablation time, maximum output level, tumour temperature after ablation, or initial resistance value between the groups. We speculated that the intra-tumoral temperature increased rapidly during RFA in the combination group due to the tumour-shrinking effect and marked inhibitory effect on tumour angiogenesis induced by lenvatinib, which led to the popping. In 2009, sorafenib (1) was developed as an initial first-line MTA. Thereafter, lenvatinib was developed as an oral multi-kinase inhibitor that targets vascular endothelial growth factor receptors 1-3, fibroblast growth factor receptors 1-4, platelet derived growth factor receptor α, RET receptor, and KIT receptor (10-12).

A preclinical study demonstrated that lenvatinib's antitumor activity against HCC tumour cells occurs by inhibiting fibroblast growth factor signalling pathways and tumour angiogenesis (13).

Furthermore, a global Phase III REFLECT trial in patients with advanced HCC demonstrated that lenvatinib was not inferior to sorafenib in terms of overall survival (median, 13.6 *vs*. 12.3 months, respectively), with secondary endpoints (*e.g*., progression-free survival and objective response) favouring lenvatinib over sorafenib (3). Lenvatinib's high response rate may allow patients with unresectable HCC to opt for the more curative conversion surgery, and it is expected to be important in the field of ablation.

RFA is performed as standard therapy with regards to percutaneous local therapy for HCC. However, there are some reports of rapid progression or disease recurrence after RFA (14-19). Therefore, careful judgment is required for its application. The exact mechanism of rapid progression remains unclear. However, the popping phenomenon, in which tumour cells are scattered or dispersed around the resection zone, may contribute to rapid progression. This may be the result of a rapid increase in the internal pressure of the tumour tissue due to RFA. To minimize the occurrence of popping, modified ablation techniques using low-output or multi-step radiofrequency power may be used. The popping phenomenon during RFA can cause complications, such as bleeding and tumour dissemination, because of water vaporization and increased internal pressure.

Table II. *Comparison of the popping rate between the combination group and the monotherapy group.*

	Combination	Monotherapy	*p*-Value
Popping rate	8/16 (50.0%)	8/43 (18.60%)	0.016

Our study has several limitations. First, the present study was conducted at a single institution with a small sample size, and therefore, a multicentre prospective randomized trial is needed to validate the results of this study. Second, patients and tumours may have different characteristics in different countries. Larger studies or meta-analyses in different regions may be required to demonstrate the efficacy of lenvatinib combined with ablation for treating unresectable HCC patients.

Lastly, we did not include a group of HCC patients who received trans-arterial chemoembolization (TACE) as the local therapy. Therefore, further comparative studies are

needed to elucidate the clinical efficacy and safety of these combination therapies in the treatment of unresectable HCC.

Future investigations should include more patients to verify our findings. The influence of lenvatinib on popping needs to be considered, and a new protocol for the concurrent use of lenvatinib and concise ablation needs to be established.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

Conceptualization: Toru Ishikawa; Data curation: Toru Ishikawa, Iori Hasegawa, Hiroshi Hirosawa, Tsubasa Honmou, Nobuyuki Sakai; Formal analysis: Toru Ishikawa; Investigation: Toru Ishikawa, Iori Hasegawa, Hiroshi Hirosawa, Tsubasa Honmou, Nobuyuki Sakai, Takanori Igarashi, Shun Yamazaki, Takamasa Kobayashi, Toshifumi Sato, Akito Iwanaga, Tomoe Sano, Junji Yokoyama, Terasu Honma; Methodology: Toru Ishikawa; Project administration: Toru Ishikawa; Resources: Toru Ishikawa; Software: Toru Ishikawa, Visualization: Toru Ishikawa, Writing – original draft: Toru Ishikawa, Writing – review & editing: Iori Hasegawa, Hiroshi Hirosawa, Tsubasa Honmou, Nobuyuki Sakai, Takanori Igarashi, Shun Yamazaki, Takamasa Kobayashi, Toshifumi Sato, Akito Iwanaga, Tomoe Sano, Junji Yokoyama, Terasu Honma.

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