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Efficacy and safety of percutaneous ultrasound guided radiofrequency ablation for treating cervical metastatic lymph nodes from papillary thyroid carcinoma

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Abstract

Purpose The aim of this study was to assess the effectiveness and safety of ultrasound guided percutaneous radiofrequency ablation (RFA) of cervical metastatic lymph nodes (LNs) from papillary thyroid carcinoma.

Methods 54 metastatic LNs confirmed by percutaneous biopsy in 33 patients with previous total thyroidectomy and radioiodine therapy were enrolled in this retrospective study. US and contrast-enhanced ultrasound (CEUS) examinations were performed before ablation. Follow-up consisted of conventional US, CEUS, thyroglobulin (Tg) level at 1, 3, 6, and 12 months and every 6 months thereafter. In 3 months after ablation, US-guided core needle biopsy (CNB) was performed in the center, at the edge of the ablation area to exclude recurrence.

Results Technical success was obtained in all 54 lymph nodes (100%) without immediate or later major

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¹ Department of Ultrasound, Chinese PLA General Hospital, No.28 Fuxing Road, Haidian District, Beijing 100853, China complications occurred. With a mean follow-up of 21 ± 4 months (range 12-24 months), there were no evidence of recurrence at ablated sites. After RFA, 33 metastatic LNs completely disappeared (33/54, 61.1%) and 21 metastatic lymph nodes remained as small scarlike lesions (21/54, 38.9%) at the last follow-up visit. The mean volume reduction ratio (VRR) was $32.7 \pm 8.6\%$ (range 21.2-59.3%), $46.8 \pm 9.7\%$ (range 33.6–68.1%), $62.5 \pm 12.1\%$ (range 42.5– 95.4%), $77.1 \pm 10.6\%$ (range 54.3-100.0%), $89.2 \pm 8.3\%$ (range 68.7–100.0%) and $94.9 \pm 5.3\%$ (range 78.2–100.0%) at 1, 3, 6, 12, 18 and 24 months after RFA respectively. Significant differences in the VRR were found between every two follow-up visits (P < 0.001). At the last follow-up visit, the mean serum Tg level decreased from 10.2 ± 5.1 ng/ ml (range 0.8–16.2 ng/ml) to 1.1 ± 0.8 ng/ml (range 0.2– 3.1 ng/ml (P < 0.001).

Conclusions Ultrasound guided percutaneous RFA for cervical metastatic LNs from papillary thyroid carcinoma is a feasible, effective and safe therapy. This procedure shows a nonsurgical therapeutic option that can eradicate the lesions with a very low complication rate.

Keywords Ultrasound · Radiofrequency ablation (RFA) · Metastatic lymph node · Papillary thyroid carcinoma

Introduction

Papillary thyroid carcinoma is the most common subtype (about 85%) of thyroid carcinoma (Aschebrook-Kilfoy et al. 2011). Once a papillary thyroid carcinoma is diagnosed, treatment is based on surgery, with or without lymph node dissection, followed by radioiodine ablation in order to destroy any occult microcarcinoma foci (McLeod 2010; Gharib et al. 2010; Fallahi et al. 2012). After initial

treatment, most papillary thyroid carcinomas are cured, but loco-regional recurrences may occur in up to 20-30% of patients with during follow-up (Johnson et al. 2008; DeGroot et al. 1990; Burman 2012). Repeated neck surgery is required when nodal metastases are diagnosed by ultrasound (US) (Frasoldati et al. 2003), but reoperations increase risks of surgical complications (Burman 2012). Thus, finding alternatives less invasive than repeated surgery and radioidineablation may be extremely helpful. In these cases, a minimal-invasive approach for local control of foci of thyroid malignancy may be desirable as part of a multimodality treatment. Percutaneous ultrasound guided radiofrequency ablation (RFA) are nowadays considered as a safe and effective alternative to surgery in several different situations (Monchick et al. 2006; Dupuy et al. 2001; Park et al. 2011; Baek et al. 2011) and might represent a less invasive yet promising alternative to repeated surgery for the treatment of metastatic LNs from papillary thyroid carcinoma.

The aim of our work was to assess the feasibility, effectiveness and safety of percutaneous ultrasound guided RFA for the nonsurgical treatment of metastatic LNs from papillary thyroid carcinoma with particular attention placed upon contrast-enhanced ultrasound (CEUS) findings in a large clinical series with longer follow-up.

Materials and methods

Study design

We conducted a retrospective study of our previously collected RFA data. This study was approved by the ethics committee in our hospital, and written informed consents were obtained from all patients prior to US-guided core needle biopsy (CNB) and RFA. US and CEUS examinations before and after RFA, as well as during follow-up were performed using a Siemens Acuson Sequoia 512 Ultrasound System (Siemens, Mountain View, CA, USA) with a 15L8W linear array transducer or a Philips iU22 Ultrasound System (Philips Healthcare, Bothell, WA) with a L12-5 linear array transducer or a Mindray M9 Ultrasound System (Mindray, Shenzhen, China) with a L12-4 linear array transducer. US-guided RFA and CNB were all performed using a Siemens Acuson Sequoia 512 Ultrasound System with a 6L3 linear array transducer.

Study subjects

Patients enrolled in the study should fulfill the following criterias: (a) patients underwent total thyroidectomy for papillary thyroid carcinoma and at least one subsequent neck dissection; (b) patients with new metastatic LNs (maximum three) confirmed by US-guided biopsy in an area treated with surgical neck dissection; (c) patients who had medical contraindications for surgery or refused surgery, or refused to undergo further surgical resection and absent radioiodine uptake at post-therapeutic ¹³¹I whole-body scan; (d) patients with lymph node volume less than 2000 mm³, and (e) no evidence of distant metastases.

Exclusion criteria: (a) patients with metastatic LNs close to the "danger triangle" (within 5 mm distance from the trachea-esophageal groove); (b) pregnant women; (c) patients with severe heart failure/respiratory failure/ liver failure or renal failure; (d) coagulation disorder with severe bleeding tendency; (e) conscious disturbance or neck extension disorder that could not tolerate RFA; (f) cardiac pacemaker implantation; (g) contra-lateral vocal cord paralysis.

Between July 2013 and August 2014, 54 metastatic LNs in 33 patients (11 males, 22 females; mean age, 43.7 years; range 22–67 years) were treated with US-guided RFA in our department.

Pre-ablation assessment

For each metastatic LN, levels of situated (Som et al. 1999) and the three orthogonal diameters (the largest diameter and two perpendicular diameters) were recorded. The volume of LN was calculated with the equations $V = \pi abc/6$ (where V is volume; a, the largest diameter; b and c are the other two perpendicular diameters) (Baek et al. 2010).

CEUS was used to describe the blood supply region of the lesion before and after ablation. Sulphur hexafluoride (SonoVueR, Bracco. International, Milan, Italy) was used as ultrasound contrast agent. CEUS was performed after bolus injection of SonoVue (2.4 ml) using MI from 0.19 to 0.24, followed by a 5 ml of normal saline flush. In the meantime, the timer on the US machine was started, and the imaging plane was kept as stable as possible. Each contrast imaging acquisition lasted at least 3 min after bolus injection. The video clip was digitally recorded and further analyzed.

All examinations were performed by an experienced US physician in order to exclude a bias introduced by different operators. The US imaging data were independently analyzed by two other off-site investigators, who had not performed the US and CEUS examinations, were blinded to the histological finding of CNB samples, and imaging findings. When they did not reach agreement, the tumor was evaluated by another experienced investigator. Each investigator clarified the reasons for making the diagnoses, and a consensus was reached in cases of discrepancies.

Ablation procedure

All RFA procedures were performed by an experienced US physician with more than 20 years experience in thyroid US and interventional US. A bipolar RFA generator (CelonLabPOWER, Olympus Surgical Technologies Europe, Hamburg, Germany) and a 9-gauge/15-gauge bipolar RF applicator with 9/15 mm active tip was used (CelonProSurge micro 100-T09, Olympus Surgical Technologies Europe, Hamburg, Germany) in our study. During the application of RF energy the generator continuously measures the electric impedance of the tissue between the two electrodes at the tip of the RF applicator. The power output is automatically adjusted based on the change of tissue impedance.

Patients were supine with the neck extended during the procedure. An iv line was introduced via the antecubital vein. Before RFA, carefully evaluating the relationship between metastatic LNs and cervical critical structures such as trachea, vessels, esophagus and recurrent laryngeal nerves was performed by the operator in order to design the best insertion way. Local anesthesia with 1% lidocaine was injected at the subcutaneous puncture site and the periphery of metastatic LNs. If the distance between the metastatic LNs and critical cervical structures (including trachea, cervical artery, jugular vein, esophagus and recurrent laryngeal nerve) was less than 5 mm, normal saline was injected using another needle (23 gauge) to form at least 1 cm distance between the tumor and the critical structure in order to prevent thermal injury. RFA was performed using the moving-shot technique (Jeong et al. 2008; Kim et al. 2006) The RFA power was 3 W, if a transient hyperechoic zone did not form at the electrode tip within 5-10 s, the radiofrequency power was increased to 5 W. The RFA extent exceeded the LNs edge to prevent marginal residue and recurrence. The ablation was terminated when all portions of the target ablation area had changed to transient hyperechoic zones. During the procedure, we gave special attention to the preservation of critical cervical structures in order to prevent significant complications such as hematoma or nerve injury. After ablation, each patient was observed for 1-2 h in the hospital while any complication occurring during and immediately after ablation was carefully evaluated according to the clinical signs and symptoms.

Post-ablation assessment

Clinical follow-up consisted of Conventional US, CEUS, and thyroglobulin (Tg) levels at 1, 3, 6, and 12 months and every 6 months thereafter. The ablation area was evaluated by CEUS to screen for completeness and recurrence: Lack of enhancement was deemed to indicate complete

ablation and no evidence of local progression, while residual enhancement or appearance of the foci of enhancement in the lymph node that was previously considered to be completely ablated was deemed to indicate incomplete ablation or local progression, respectively (Hiraki et al. 2005). The serum Tg levels and the development of new metastatic tumors should be carefully assessed as well. In 3 months after ablation, US-guided CNB were performed in the center, and at the edge of the ablation area to evaluate the completeness of radiofrequency ablation. A biopsy specimen of any suspicious new lesion after RFA was also obtained. Follow-up of conventional US and CEUS were performed by two physicians with more than 5 years experience in thyroid US and CEUS; they were blinded to the previously obtained findings. If their results were inconsistent, another physician with more than 15 years experience of thyroid US and CEUS was asked for consultation. CNB were performed by the US physician who performed the RFA treatment. The percentage volume reduction ratio was calculated as followed: VRR = ([initial volume - final volume] \times 100)/initial volume (Baek et al. 2010).

Statistical analysis

Descriptive data were expressed as mean \pm SD (range). Statistical analysis was performed using SPSS statistical software (Version 17.0). The Wilcoxon signed rank tests were used to compare changes in the VRR between every two follow-up visits and the serum Tg levels before RFA and at the last follow-up visit. A difference with P < 0.05 was considered as statistically significant.

Results

Baseline demographic characteristics of the study subjects

A total of 54 metastatic LNs were confirmed by percutaneous biopsy. Ultrasound guided RFA was performed for all confirmed metastatic LNs. The mean number of treated metastatic LNs perpatient was 1.6 (range 1–3). Metastatic LNs were situated at levels I, II, III, IV, V, and VI respectively, in 2, 14, 19, 8, 2, and 9 cases. The mean largest diameter of the initial LNs was 12.2 ± 5.1 mm (range 4-28 mm), and the mean volume was 405.8 ± 440.3 mm³ (range 25.1–1905.3 mm³). The demographic and clinical characteristics before RFA are summarized in Table 1.

Treatment response of RFA

In all cases, it was possible to target the metastatic LNs correctly and to perform the ablation as planned. A power of
 Table 1
 Clinical characteristics

 regarding 33 patients treated
 with RFA of 54 cervical

 metastatic LNs from thyroid
 carcinoma

Parameter	Characteristics	Result	
Sex of patients $(n=33)$	M/F	11/22 ^a	
Age of patients $(n=33)$		$43.7 \pm 10.7 (22-67)^{b}$	
No. of LNs $(n=33)$			
	1	16 (48.5) ^c	
	2	14 (42.4) ^c	
	3	3 (9.1) ^c	
Side of LNs $(n=54)$	L/R	31/23 (57.4/42.6) ^d	
Level of LNs $(n=54)$			
	Ι	$2(3.7)^{d}$	
	II	$14(25.9)^{d}$	
	III	$19(35.2)^{d}$	
	IV	8 (14.8) ^d	
	V	$2(3.7)^{d}$	
	VI	9 (16.7) ^d	
Largest diameter of LNs $(n=54)$ (mm)	$12.2 \pm 5.1 (4 - 28)^{b}$		
Volume of LNs before RFA $(n=54)$ (mm ³)		$405.8 \pm 440.3 (25.1 - 1905.3)^{b}$	

LNs lymph nodes, RFA radiofrequency ablation, No. number

^aNumber of patients

^bMeans \pm standard deviations, with range in parentheses

^cNumber of patients, with percentages in parentheses

^dNumber of LNs, with percentages in parentheses

3 W was used in 51 LNs, and 5 W was used in 3 LNs. The mean RFA time was 140.7 ± 88.4 s (range 25–447 s), the mean total energy was 426.7 ± 279.8 J (range 70–1320 J). The procedures were well tolerated in all patients. No immediate or later major complications occurred. Only one patient had a sense of discomfort in the neck after the procedure and the symptom was relieved after stopping the ablation for several seconds.

In 5 metastatic LNs (9.3%), CEUS showed residual enhancement after the first ablation, and a second application of radiofrequency energy was applied. The complete absence of enhancement at CEUS was finally achieved in all cases at the end of the operative session (technical success: 100%).

Multivariable analysis of follow-up

The last follow-up obtained for the overall study population was at 21 ± 4 months (range 12–24 months). Post-RFA CEUS showed no regrowth of the previous successfully treated lesions in the follow-up. In the 12-month followup, US examination revealed that one patient had another metastatic LN, but there was no evidence of recurrence at the initial treatment site. The patient had successfully undergone a second RFA treatment, and the newly occured metastatic LN in the neck was also enrolled for further observation.

After RFA, 33 metastatic LNs completely disappeared (33/54, 61.1%) and 21 metastatic LNs remained as small scarlike lesions (21/54, 38.9%) at the last follow-up visit. Representative findings at percutaneous RFA treatment and at follow-up of a cervical metastatic LN case are shown in Fig. 1. The mean VRR was $32.7 \pm 8.6\%$ (range 21.2-59.3%), $46.8 \pm 9.7\%$ (range 33.6-68.1%), $62.5 \pm 12.1\%$ (range 42.5-95.4%), $77.1 \pm 10.6\%$ (range 54.3-100.0%), $89.2\pm8.3\%$ (range 68.7-100.0%) and $94.9 \pm 5.3\%$ (range 78.2–100.0%) at 1, 3, 6, 12, 18 and 24 months after RFA respectively (Table 2; Fig. 2). Significant differences in the VRR were found between every two follow-up visits (P < 0.001). At the last follow-up visit, the mean serum Tg level decreased from 10.2 ± 5.1 ng/ ml (range 0.8–16.2 ng/ml) to 1.1 ± 0.8 ng/ml (range 0.2-3.1 ng/ml (P < 0.001).

Discussion

Treatment of metastatic LNs is one of the major challenges in the management of patients with papillary thyroid carcinoma. When cervical metastatic LNs detected, treatment is based on repeat surgery followed by radioactive iodine ablation and/or thyroid hormone therapy. Repeating surgery in a previously operated patient is sometimes very challenging even for an experienced surgeon due to severe fibrosis and distortion of the normal

Fig. 1 Images of RFA treatment of a metastatic LN at left cervical level III in a 58-yearold woman previously underwent total thyroidectomy, two subsequent neck dissection and one subsequent ¹³¹I ablation for papillary thyroid carcinoma. a Conventional ultrasound image shows a hypoechoic LN with no lymphatic hilus (white arrows). **b** CEUS shows an irregular enhancement (white arrows) in the metastatic LN with unenhancement foci (arrowheads). c During RFA, ultrasound monitoring of the procedure shows gas formation in the metastatic LN which covered by a hyperechoic ablation area (white arrows). d CEUS performed immediately after RFA shows a complete lack of enhancement in the treated area (white arrows). e One month after RFA, CEUS shows the treated area shrunk and that complete lack of enhancement (white arrows). f Six month after RFA, CEUS shows complete lack of enhancement in the treated area, remained as a small scarlike lesion (*white arrows*)



tissue by scar formation and a higher rate of complications (LiVolsi 2011; Ito et al. 2007; Mazzaferri et al. 1994). Moreover, the current therapy of radioiodine ablation may not be effective, particularly in the patients who do not have adequate radioiodine uptake. Thus, finding less invasive alternatives than repeated surgery is extremely helpful and important. Several different techniques are now available for percutaneous treatments, such as ethanol injection, cryoablation, radiofrequency, laser and microwaves ablation (Pacella et al. 2009, 2004; Papini et al. 2013; Livraghi et al. 2012; Shyn et al. 2012). Ultrasound guided percutaneous RFA is a minimally invasive local therapy that has been shown with promising results for local tumor control in a variety Table 2Changes in 54 cervicalmetastatic LNs volume andvolume reduction ratio afterRFA at each follow-up

Time after RFA	Volume (mm ³)		Volume reduction ratio (%)	
	Mean ± SD	Range	Mean \pm SD	Range
1 month after RFA	270.5 ± 283.1	17.8–1105.1	32.7 ± 8.6	21.2-59.3
3 months after RFA	221.4 ± 224.5	15.1-845.4	46.8 ± 9.7	33.6-68.1
6 months after RFA	148.4 ± 158.7	11.3-643.3	62.5 ± 12.1	42.5-95.4
12 months after RFA	84.6 ± 96.9	0.0-404.3	77.1 ± 10.6	54.3-100.0
18 months after RFA 40.2 ± 54.3		0.0-296.8	89.2 ± 8.3	68.7-100.0
24 months after RFA	16.7 ± 25.2	0.0-131.9	94.9 ± 5.3	78.2-100.0



Fig. 2 Changes in Volume Reduction Ratio at Each Follow-up

of organs (Gervais et al. 2003; Selli et al. 2001; Fornage et al. 2004). Recently, in addition, RFA has also been reported to have feasibility and reproducibility in the treatment of recurrent thyroid carcinoma (Monchik et al. 2006; Lim et al. 2015; Suh et al. 2016). Up to recently, surgery is the gold standard for treatment for recurrent thyroid carcinoma; it seems that the effectiveness and safety of ultrasound guided percutaneous RFA for the disease are still controversial.

The present paper was designed to explore the feasibility, effectiveness and safety of ultrasound guided percutaneous RFA for cervical metastatic LNs from papillary thyroid carcinoma. In this paper, we share our own detailed procedure technique for the treatment of cervical metastatic LNs, which were rarely mentioned in other published literatures. Studies have been performed on the feasibility and reproducibility of laser ablation in the treatment of metastatic LNs from papillary thyroid carcinoma when the patients refuse surgery or if they have medical contraindications for undergoing surgery (Mauri et al. 2013, 2016). But RFA treatment has lower temperature (60–100 $^{\circ}$ C), which is less likely to cause thermal injury compared to laser ablation. In addition, we used the moving-shot technique, which allows precise controlling of the ablation area including both the tumor and the surrounding soft tissues. If the distance between the tumor and critical cervical structures was very close (less than 5 mm), normal saline was injected to form a distance of at least 1 cm in order to prevent thermal injury. Our results show that RFA is a viable treatment for patients with limited metastatic LNs from papillary thyroid carcinoma, as in our series we were able to successfully perform the ablation in all cases. The best methodology for evaluating tumor response after thermal ablation may still need further discussion. CEUS can provides good visualisation of vascular modifications after thermal ablation. CEUS in percutaneous ablative treatment and in surgery has been reported as an effective utility for assessing local control of tumor, and the utility is particularly helpful in monitoring the immediate result of the ablation procedure (Toshikuni et al. 2013). In our practice, we applied CEUS as an important mean to evaluate the effectiveness of RFA immediately after the procedure and during the follow-up period which were not reported in previous studies (Park et al. 2011; Baek et al. 2011; Lim et al. 2015). However, CEUS results suggest no residual tumor in the ablation area. In a series of studies (Shin et al. 2013; Jeon et al. 2009), the serum Tg levels had been proven to be an effective indicator to predict a successful control of recurrent thyroid carcinoma in the majority of patients, the patients in which local control was not achieved or who developed disease progression had elevated serum levels of Tg, whereas all patients with negative serum levels of Tg were found to have local control, which has been proven in our study also.

Our results show that RFA is feasible, effective and safe for the treatment of cervical metastatic LNs from papillary thyroid carcinoma and this technique can potentially reduce the number of radical neck dissections in specific patients. Furthermore, there are several key advantages of percutaneous treatments over standard therapy for treating patients with cervical metastatic LNs: percutaneous treatments are minimally invasive, can be performed without general anesthesia, require shorter hospitalization time, and are generally less expensive than open surgery. Moreover, percutaneous treatments can be performed several times without increased technical difficulties due to the previous treatments. In our study, there were no major complications. Nevertheless, only one patient had a sense of discomfort in the neck after the procedure and the symptom was relieved after stopping the ablation for several seconds. Our low complication rate may be due to the fact that we using low power and prolonging the time of the procedure, to have a better control of the energy deployment (31).

Limitation of our study should be taken into account. This study does not provide comparison with repeat surgical management or other treatment alternatives. Further study comparing different modalities needs to done to better understand which technology could be the best for performing thermal ablations in the neck.

In conclusion, RFA represents a new effective option to eliminate metastatic LNs in the neck from papillary thyroid carcinoma with a very low complication rate (1/54 = 1.85%). This procedure appears to be feasible, effective and safe that can eradicate the lesions or avoid unnecessary surgery in a greater number of patients.

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Compliance with ethical standards

Conflict of interest All authors of this manuscript declare that they have no conflict of interest.

Human and animal rights statement This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

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