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ABOUT COVER

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CASE REPORT

Residual tumor and central lymph node metastasis after thermal ablation of papillary thyroid carcinoma: A case report and review of literature

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Abstract

BACKGROUND

Debate exists regarding the use of thermal ablation (TA) to treat papillary thyroid carcinoma (PTC). Some studies have recommended TA as a new, efficient and safe technology for PTC. In this article, we report one case of a residual tumor and central lymph node metastasis (CLNM) after TA for PTC.

CASE SUMMARY

A 63-year-old female underwent bilateral ultrasound (US)-guided radiofrequency ablation for PTC. Three months later, she was diagnosed as thyroid cancer with suspected CLNM by US and contrast-enhanced computed tomography. The subsequent fine-needle aspiration (FNA) biopsies were negative. Due to her strong personal preference, she underwent total thyroidectomy and central lymph node dissection. Local tissue adhesion and a difficult dissection were noted during the operation. The pathology of the frozen sections during the operation was still negative. The final pathology results of paraffin-embedded sections revealed residual tumor cells at the edge of the PTC and CLNM.

CONCLUSION

TA may lead to a residual tumor in patients with PTC. Follow-up using US and FNA biopsy may not be adequate to evaluate the residual tumor. TA should be carefully considered in PTC treatment.

Key Words: Papillary thyroid carcinoma; Thermal ablation; Residual tumor; Central lymph node metastasis; Follow-up; Case report



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Core Tip: Thermal ablation may lead to a residual tumor in patients with papillary thyroid carcinoma. Follow-up using ultrasound and fine-needle-aspiration biopsy may not be adequate to evaluate the residual tumor. Therefore, thermal ablation of papillary thyroid carcinoma should be carefully considered.

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INTRODUCTION

Recently, thermal ablation (TA) has become an acceptable treatment for benign thyroid nodules, and it has also been used to treat distant metastasis and locoregional recurrence of thyroid cancer. TA was described as an alternative treatment for primary papillary thyroid carcinoma (PTC), particularly in patients who were unwilling or unable to undergo surgery[1-6], and TA was considered an efficacious and safe treatment with rare reports of residual tumor cells, recurrence, and metastasis. In this article, we report one patient with PTC who presented with a residual tumor and central lymph node metastasis (CLNM) after TA.

CASE PRESENTATION

Chief complaints

A 63-year-old female who presented with neck discomfort was admitted to our hospital.

History of present illness

She was diagnosed as bilateral PTC and received bilateral radiofrequency ablation (RFA) at another hospital on March 1, 2019. Prior to RFA, she received ultrasound (US) and fine-needle aspiration (FNA). US showed bilateral multiple thyroid nodules. The nodule in the left lobe was 4.2 mm × 5.2 mm × 4 mm in size, with irregular margins and calcification, and was classified as Thyroid Imaging Reporting and Data System (TI-RADS) 4a. The nodule in the right lobe, which was 11.6 mm × 6.4 mm × 9.3 mm in size, was classified as TI-RADS 3. No lymph node metastasis was detected. FNA biopsy revealed bilateral PTC. She was diagnosed as PTC $(T_1N_0M_0)$, and she subsequently received bilateral RFA.

History of past illness

No special history of past illness was recorded.

Personal and family history

The patient denied family history of thyroid disease or malignancy.

Physical examination

No obviously palpable thyroid nodules and suspected lymph nodes could be touched on physical examination.

Laboratory examinations

No abnormal Laboratory examinations, including thyroid function, were detected(.

Imaging examinations

Both US and contrast-enhanced computed tomography performed at our hospital showed bilateral suspected thyroid cancer with CLNM (Figure 1). The nodule in the



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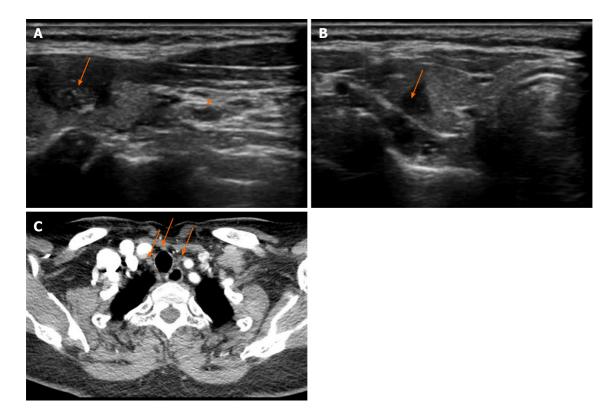


Figure 1 Ultrasound and contrast-enhanced computed tomography images obtained 3 mo after radiofrequency ablation for papillary thyroid carcinoma. A: The left thyroid nodule (arrow) (6 mm × 8 mm × 12 mm) with hypoechogenicity, unclear margins, and scattered small calcifications on ultrasound was classified as Thyroid Imaging Reporting and Data System stage 4c. Metastatic central lymph nodes (arrowhead) were also detected; B: The right thyroid nodule (5 mm × 5 mm × 7 mm) with hypoechogenicity and unclear margins on ultrasound was classified as Thyroid Imaging Reporting and Data System stage 4a; C: Central lymph node metastasis was detected using contrast-enhanced computed tomography.

left lobe (6 mm × 8 mm × 12 mm) with irregular margins and calcification was classified as TI-RADS 4c, and the nodule in the right lobe (5 mm × 5 mm × 7 mm) with unclear margins was classified as TI-RADS 4a by US.

Cytology

The patient underwent FNA biopsy again, but no PTC cells were detected.

Diagnosis procedure

Based on the patient's strong willingness to undergo a subsequent operation, she underwent total thyroidectomy with central lymph node dissection. In the operation, the thyroid tissue was extensively adhered to the surrounding tissue, and the thyroid tissue, parathyroid tissue, and recurrent laryngeal nerve were relatively difficult to be dissected. The pathology of frozen sections obtained during the operation still revealed no residual PTC cells.

FINAL DIAGNOSIS

The final pathology of paraffin-embedded sections revealed residual tumor cells along the edge of the tumor and CLNM (4/14+) (Figure 2). The patient was diagnosed as bilateral PTC with CLNM, stage I ($T_1N_1M_0$) after operation.

TREATMENT

The patient was treated with levothyroxine suppression therapy after surgery.

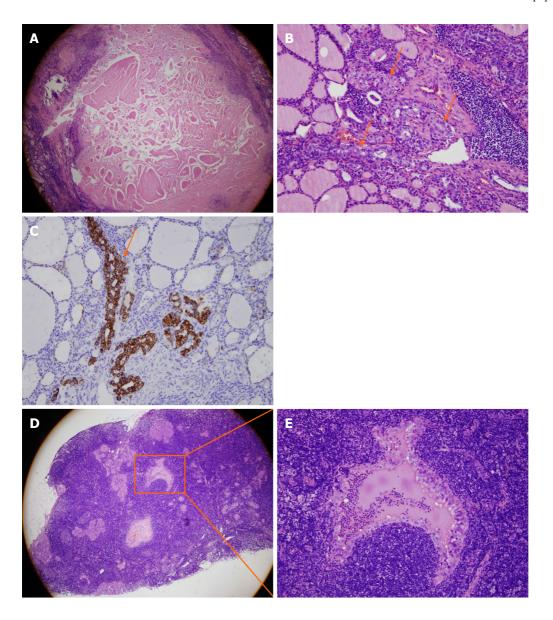


Figure 2 The images of pathological specimens showed residual papillary thyroid carcinoma and central lymph node metastasis. A: The middle part of the tumor was completely ablated, 50 × magnification; B: Residual tumor cells were detected at the edge of the tumor, 200 × magnification; C: Immunohistochemical staining showed residual tumor cells, 200 × magnification; D: Central lymph node metastasis, 50 × magnification. The boxed region is shown at higher magnification in E; E: Image of the box shown in D at 4 × magnification.

OUTCOME AND FOLLOW-UP

The patient was discharged from the hospital when her condition was stable. No recurrences or metastases were reported at the time of manuscript submission.

DISCUSSION

The Medline (PubMed) and Cochrane Library were searched using the following search terms: "Papillary thyroid carcinoma", "radiofrequency ablation", "thermal ablation", "laser ablation", "microwave ablation", and/or "residual tumor". This search was performed independently by two reviewers. Regions were not limited. The languages of reference were only English and Chinese, and the references published before April 1, 2020 were collected in this study.

Since the 1990s, TA, including RFA, laser ablation (LA), and microwave ablation (MWA), has been used to treat solid organ tumors, such as liver carcinoma^[7], renal cancer[8], lung cancer[9], and prostate cancer[10]. To date, TA has been adopted by National Comprehensive Cancer Network guidelines for some solid tumors. Regarding the use of ablation for thyroid tumors, Pacella et al^[11] first reported the use

of LA to treat two patients with autonomously functioning thyroid nodules in 2000. Dupuy et al^[12] used RFA to treat the regional recurrence of well-differentiated thyroid cancer in 2001. Kim et al^[13] first succeeded in using RFA to treat benign thyroid nodules in 2006. Jeong ${\it et~al}^{{\scriptscriptstyle [14]}}$ showed an 84.1% shrinkage in the average volume of benign thyroid nodules after RFA in 236 patients. Zhang et al[1] reported a prospective study of 98 papillary thyroid microcarcinomas (PTMCs) in 92 patients that explored the efficacy and safety of US-guided RFA for the treatment of low-risk PTMC. No residual tumors, recurrence, or metastasis was detected during the 18-mo follow-up using US, contrastenhanced US (CEUS), or core-needle biopsy (CNB).

The 2017 Thyroid Radiofrequency Ablation guidelines in Korea^[15] recommended the use of RFA for patients with benign thyroid nodules complaining of symptomatic or cosmetic problems, patients with recurrent thyroid cancer at high surgical risk or who refused surgery, and, alternatively, patients with primary thyroid cancer who refused surgery or were unable to undergo an operation. The Italian consensus statement on minimally invasive treatments for benign thyroid nodules[16] suggested that TA may be proposed as a first-line treatment for solid non-functioning thyroid nodules that are benign according to cytology when they cause symptoms. The 2015 American Thyroid Association guidelines^[17] proposed TA as a choice for patients with PTC presenting with metastatic disease and suggested that responsiveness to TA is associated with improved survival in patients with distant metastases to various organs; the guidelines also proposed that RFA shows high efficacy in treating individual distant metastases of advanced thyroid cancer with relatively few side effects. A 2018 Chinese expert consensus[18] recommended TA as a treatment for benign thyroid nodules, but the routine use of TA for papillary thyroid microcarcinoma has not been established due to insufficient medical evidence. China also permits TA to be conducted by experienced doctors with more than 2 years of experience performing TA in the thyroid. The preliminary common indications include the following: A thyroid nodule diameter less than 5 mm (or less than 10 mm without invasion of the capsule), PTC confirmed by FNA biopsy before surgery, no cervical lymph node metastasis or distant metastasis, no history of neck irradiation, and anxiety or a desire for minimally

Numerous studies have been conducted to explore the efficacy and safety of TA for PTC. The PubMed database was searched to identify publications on thermal ablation in treating PTC. The following search terms were used: [(papillary thyroid carcinoma) AND (radiofrequency ablation OR laser ablation OR microwave ablation OR thermal ablation)]. The detailed characteristics of the searched studies are shown in Table 1. Four of them are randomized controlled trials. Eight studies investigated RFA^[1,2,19-24], four explored LA^[25-28], and six studied MWA^[5,6,29-32]. The cohort sizes ranged from six to 421 patients, with the numbers of PTC nodules ranging from six to 440 total nodules. All TA-treated subjects included were ineligible for surgery or refused surgery, except in the study by Luo et al^[20] (the inclusion criteria were not mentioned). The main follow-up examinations included US, CEUS, computed tomography, and FNA biopsy or CNB. Yue et al[5] reported three cases of immediate thyroidectomy after MWA, and complete necrosis of the tumor was confirmed. The follow-up periods in these studies ranged from 2 mo to 104 mo. The results from eight studies[1,2,5,6,19,22,23,29] were satisfactory, with no residual cancer cells, recurrences, or metastases. Furthermore, comparisons of the efficacy and safety of RFA, LA, or MWA and surgery for the treatment of PTMC showed that the performance of TA was not inferior to surgery regarding the therapeutic effect, incidence of complications, recurrences, metastases, and disease-free survival^[28,29,31,33]. According to recently published reviews and metaanalyses, all types of TA had reasonable safety and efficacy profiles for the treatment of PTMC[34-38]. Choi et al[37] reported that LA was less effective than RFA at reducing the volume of PTMC. Cho et al[38] concluded that TA provides excellent local tumor control in low-risk patients with PTMC, but strict inclusion criteria and technical expertise are required to obtain favorable results. However, the limitations of these studies include an insufficient evidence level, inaccurate comparisons due to different baseline data of the enrolled patients, inconsistent parameters for US-guided ablation, short follow-up durations, and ambiguous clinical risk stratification of PTMC due to insufficient prognostic factors.

Few articles have reported problems after TA, such as a residual tumor, needle track seeding, incidental papillary microfoci, lymph node micrometastasis, and possible carcinogenic effects. Incomplete ablation was observed in one RFA study and three LA studies, and second ablations were conducted[21,25-27]. A biopsy confirmed that recurrences and cervical lymph node metastases occurred after the use of all three $techniques^{\underline{\scriptsize{[20,24,26-28,30-32]}}}. \ The \ shortest \ follow-up \ durations \ during \ which \ recurrence \ and$ cervical lymph node metastasis were detected were 1 mo^[30] and 6 mo^[31], respectively.

Table 1 Characteristics of selected studies

Technique	Ref.	No. of patients/tumors	Follow-up periods/mo, mean ± SD (range)	Follow-up examinations	No. of incomplete ablation	No. of recurrence/mo, post-TA	No. of cervical lymph node metastasis/mo, post-TA
RFA	Zhang et al ^[1] , 2016	92/98	7.8 ± 2.9 (3-18)	US, CEUS, and CNB	0	0	0
RFA	Kim et al ^[19] , 2017	6/6	48.5 ± 12.3 (36-65)	FNA and CNB	0	0	0
RFA	Luo et al ^[20] , 2017	421/440	N/A (12-36)	US, CEUS and biopsy	0	4 proven; 5 suspicious (N/A)	4 (N/A)
RFA	Jeong et al ^[21] , 2018	6/7	19.3 ± 3.5 (15-24)	US and CT	1	0	0
RFA	Zhang et al ^[22] , 2019	60/60	N/A (18-60)	US, CEUS, and CNB	0	0	0
RFA	Ding et al ^[23] , 2019	37/38	N/A (1-18)	CEUS and CT	0	0	0
RFA	Lim et al ^[2] , 2019	133/152	39 ± 25 (6-104)	US, CT, and biopsy	0	0	0
RFA ¹	Zhang et al ^[24] , 2020	94/94	64.2 ± 2.8 (median ± SD)	US, CEUS, CNB, CT, PET, and bone scan	0	1 (N/A)	0
LA	Zhou et al ^[25] , 2017	30/30	13.2 (12-24)	US, CEUS, chest X-ray or CT, and FNA	1	0	0
LA	Zhang et al ^[26] , 2018	64/64	25.7 ± 8.2 (12-42)	US, CEUS, and FNA	2	0	1 (30)
LA	Ji et al ^[27] , 2019	37/37	16.5 ± 6.9 (12-24)	US, CEUS, and chest radiographs or CT	8	0	1 (24)
LA ¹	Zhou et al ^[28] , 2019	36/36	49.2 ± 4.5 (30-54)	US, chest X-ray or CT, and FNA	0	1 (42)	1 (30)
MWA	Yue et al ^[5] , 2014	21/21	11 (3-22)	US, chest X-ray or CT, and biopsy	0	0	0
MWA ¹	Li et al ^[29] , 2018	46/46	42	US, CEUS, and biopsy	0	0	0
MWA	Teng et al ^[6] , 2018	15/21	N/A (36-48)	US, CT, and FNA	0	0	0
MWA	Teng et al ^[30] , 2019	185/206	20.7 ± 8.8 (12-36)	US and FNA	0	1 (1)	0
MWA ¹	Li et al ^[31] , 2019	168/168	25.1 ± 17.3 (2-60)	US and FNA	0	2 (36-44)	5 (6-44)
MWA	Yue et al ^[32] , 2020	119/119	37.2 ± 20.9 (12-101)	US, CEUS, CNB, and CT	0	0	1 (26)

 $^{^{1}} Randomized \ controlled \ trials. \ CEUS: Contrast-enhanced \ ultrasound; CNB: Core-needle \ biopsy; CT: Computed \ tomography; FNA: Fine-needle \ aspiration; CNB: Core-needle \ biopsy; CT: Computed \ tomography; FNA: Fine-needle \ aspiration; CNB: Core-needle \ biopsy; CT: Computed \ tomography; FNA: Fine-needle \ aspiration; CNB: CORE-needle \ biopsy; CT: Computed \ tomography; FNA: Fine-needle \ aspiration; CNB: CORE-needle \ biopsy; CT: CORE-nee$



LA: Laser ablation; MWA: Microwave ablation; N/A: Not available; PET: Positron emission tomography; RFA: Radiofrequency ablation; SD: Standard deviation; TA: Thermal ablation; US: Ultrasound.

> Notably, the 1 mo recurrence was another small nodule that had not been detected before MWA. Patients with recurrence or cervical lymph node metastases underwent a second RFA or surgery. Ma et al[39] reported 11 patients with PTC treated with RFA and one patient with PTC treated with MWA who were surgically confirmed to have residual PTC cells (12/12) and lymph node metastases (8/12). In the study by Kim et al[40], one patient underwent robotic thyroid surgery after incomplete RFA for PTC, but the patient had not been diagnosed before RFA. Lee et al[41] observed needle track PTC seeding after a second RFA for thyroid cancer that appeared benign. Ruzzenente et al[42] and Koda et al[43] also reported needle track seeding and rapid tumor progression after RFA for hepatocellular carcinoma. Valcavi et al^[4] found two cases of incidental papillary microfoci and one case of lymph node micrometastasis during immediate thyroidectomy surgery after LA for PTMC. Ergul et al[44] reported a rare case of mixed papillary and medullary thyroid carcinoma, which might have occurred due to LA for a benign thyroid nodule 2 years previously.

> In our case, tumor shrinkage of bilateral PTC was also detected on follow-up US, but the TI-RADS classifications of the bilateral nodules after TA were still 4. The pathology of the sample obtained through repeated FNA biopsy was negative. However, residual tumor cells were detected at the edge of the PTC. Therefore, we should consider whether US, CEUS, and biopsy are adequate to evaluate the thoroughness of TA. Actually, changes in the tumor size or disappearance on US should not be used to confirm the complete ablation of the tumor. Moreover, the middle portions of the bilateral tumors were completely ablated, while residual tumor cells were mainly located along the edges. In US-guided TA, doctors may generally focus on the middle portion of the nodules. This focus may explain why the pathology results of the FNA biopsy and frozen sections were negative. Metastatic lymph nodes were only detected 3 mo later and may be due to a missed diagnosis before TA or the progression of residual cancer cells after TA. The diagnostic accuracy of US for cervical lymph node metastases in patients with PTC, depending on the experience of the radiologist, was reported to range from 55.8% to 95.2% [45-50]. US showed worse performance in identifying CLNM than lateral lymph node metastases^[51]. Therefore, the use of US alone to determine the presence of lymph node metastasis before TA is not sufficient. In addition, because TA exacerbated the adhesion of the thyroid tissue to the surrounding tissue, the dissection of the thyroid tissue, parathyroid tissue, and recurrent laryngeal nerve was difficult. The complication rate might be relatively higher after thyroidectomy. In summary, the efficacy and safety of TA for PTC must be carefully considered. The use of US, CEUS, and CNB or FNA biopsy as follow-up assessments for the efficiency of TA may be insufficient. Additional prospective, multicenter, randomized controlled studies with large populations and longer follow-up periods are necessary in the future.

CONCLUSION

In conclusion, TA is unable to guarantee complete PTMC ablation or resolve cervical lymph node metastases, the current follow-up methods are not reliable, and subsequent surgery is more difficult after TA. Therefore, TA is not recommended as a routine treatment for PTMC.

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