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REVIEW ARTICLE

Efficacy and safety of radiofrequency ablation in the treatment of low-risk papillary thyroid carcinoma: a review

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Abstract

Ultrasound-guided radiofrequency ablation (RFA) has recently been used for the treatment of thyroid carcinomas. In this study, we aimed to evaluate the efficacy and safety of RFA for treating low-risk papillary thyroid carcinomas (PTCs). We searched the MEDLINE and the SCOPUS databases up to December 29, 2020, for studies assessing the efficacy and safety of RFA in the management of low-risk PTCs. Data on volume reduction ratio (VRR), complete disappearance, carcinoma recurrence, and complication frequency were collected. Thirteen studies with a total of 1389 patients and 1422 tumors were included in the synthesis of this study. Mean VRR varied between 47.8 and 100%, with most studies reporting a ratio of 98.5–100%. The ratio of complete disappearance ranged between 33.7 and 100%, although studies with a prolonged follow-up period reported a frequency of 56–100%. The tumor progression/recurrence frequency was 0–4.5%. Complications occurred in 45 patients (3.2%). Mild-moderate pain and cervical discomfort were the most common complications and no life-threatening complications were reported. Based on these data, we suggest that ultrasound-guided RFA can serve as an efficacious and safe alternative for the treatment of low-risk PTC in patients who are unable or unwilling to receive surgical therapy.

Keywords Thyroid · Cancer · Papillary carcinoma · Radiofrequency ablation

Introduction

Thyroid cancer is the most common malignant endocrine tumor and papillary thyroid carcinoma (PTC) is the most frequent type of thyroid malignancy. The incidence of PTC has risen over the last few decades, the increased incidence attributable to numerous factors, including the extensive use of diagnostic methods, such as ultrasonography (US) and fine needle aspiration (FNA), which are considered the most accountable for this increase [1, 2]. An example of how increased diagnosis influences the rise in thyroid cancer incidence is the case of Korea, where the implementation of a national screening program resulted in a 15-fold increase in thyroid cancer within 18 years [3]. The increased detection of asymptomatic low-risk carcinomas also contributes to the declining mortality rates of thyroid cancer.

Low-risk PTCs are small tumors localized inside the thyroid parenchyma with no apparent capsule invasion or extrathyroidal extension, as well as no lymph node or distant metastases [4]. Papillary thyroid microcarcinomas (PTMCs) are a subgroup of PTCs that are characterized by a diameter equal or less than 10mm and are considered very low-risk cancer. These tumors are associated with a favorable prognosis and current treatment guidelines support the effectiveness of less extensive surgical approaches, like lobectomy, for their management [5]. Non-surgical, minimally invasive treatment strategies have also been proposed for the management of low-risk PTCs. US-guided thermal ablation techniques, including radiofrequency, laser, and microwave ablation (MWA), as well as ethanol injection have shown promising results. Active surveillance with frequent imaging examinations is considered an alternative management option [6].

US-guided radiofrequency ablation (RFA) is a minimally invasive technique that has been used for the management of thyroid tumors, particularly benign thyroid adenomas [7–9] and recurrent thyroid carcinomas [10–12]. RFA uses an alternating electric current oscillating between 200 and 1200 kHz

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that induces vibration of the ions of the ablated tumor. Vibration is transformed into heat, with high-energy deposition within the tumor and low-energy deposition in the surrounding thyroid parenchyma, allowing for a focused treatment approach [13]. The electric current is created by a radiofrequency generator and is applied to the tumor via an electrode needle. Fourteen-gauge expandable multitined electrodes or 17-gauge straight needles with a 10-mm active tip were initially used. Thinner 18-gauge and 19-gauge electrodes with a 5-, 7-, 10-, 15-, or 20-mm active tip were later developed [14]. Smaller active tips are also available for the ablation of smaller nodules [15]. The patient is placed in a supine position with mild extension of the neck. Skin sterilization and local anesthetic injection precede the ablation. Two main ablative techniques have been used. The "fixed ablation" technique uses an expandable electrode with four hooks to create a spherical ablation zone. In contrast, in the more widely used "moving shot" technique, the thyroid nodule is divided into units and each unit is sequentially ablated by a continuously moving straight internally cooled electrode [14].

Compared to surgery, RFA offers advantages that include the avoidance of general anesthesia and the lack of a surgical scar. The possible advantages of US-guided RFA could offer an alternative to surgery for primary thyroid carcinomas, especially for more indolent malignant tumors, such as the low-risk PTCs. However, adequate effectiveness and low complication rates are essential for the wide utilization of this therapeutic approach. The aim of this study is to evaluate the efficacy and safety of US-guided RFA in the management of primary low-risk PTCs.

Materials and methods

Search strategy

We used the MEDLINE and the SCOPUS databases, with an initial search for articles with publication date up to May 29, 2020. We later updated our search to include articles published up to December 29, 2020. We used the following search strategies: 1. ((radiofrequency ablation [Title/Abstract]) OR (thermal ablation [Title/Abstract])) AND (thyroid [Title/Abstract]) in MEDLINE, and 2. radiofrequency ablation [Title/Abstract/Keywords] OR thermal ablation [Title/Abstract/Keywords] AND thyroid [Title/Abstract/Keywords] in SCOPUS.

Inclusion criteria

The inclusion criteria specified the following: (1) Patients with primary PTC diagnosed with US-guided FNA or core needle biopsy (CNB) with no evidence of thyroid capsule invasion, extrathyroidal extension, lymph node, or distant metastases on clinical exam and imaging studies, and who refused surgery, or for whom surgery was contraindicated; (2) treatment with US-guided RFA without any other co-intervention; (3) report of data concerning the efficacy and safety of US-guided RFA; (4) original article; and (5) full text article availability in English.

Data extraction

We collected data regarding the sample size, the patients' age and sex, the number of tumors per patient, tumor size, the RFA technique, the number of ablation sessions, the duration of each session and the power used, and the duration of follow-up period. The efficacy of US-guided RFA was assessed using data on the tumor volume reduction ratio (VRR), complete disappearance rates, and carcinoma recurrence rates. The safety of RFA was assessed with complication rates.

Quality assessment

The methodological quality and the subsequent risk of bias of the included studies were assessed using one of the following questionnaires, according to the study design:

- The NIH Quality Assessment Tool for Before-After (Pre-Post) Studies With No Control Group, for interventional studies without a control group [16].
- The Newcastle-Ottawa Scale, for interventional studies with a control group [17].

Results

Literature search

The literature search was conducted by one of the authors (S.N.) and produced 1357 results. After the removal of duplicates, 919 titles or abstracts were screened for relevance to the study subject. A total of 859 articles were excluded through the screening process due to irrelevance or insufficient information. Sixty full-text articles were assessed for eligibility. After application of the inclusion criteria, 46 articles were excluded. There were two studies with an overlapping sample and it was decided that the most recent one should be included. Thirteen articles were declared eligible and were included in the synthesis of this study. Our search strategy is presented in a flow diagram (Fig. 1).

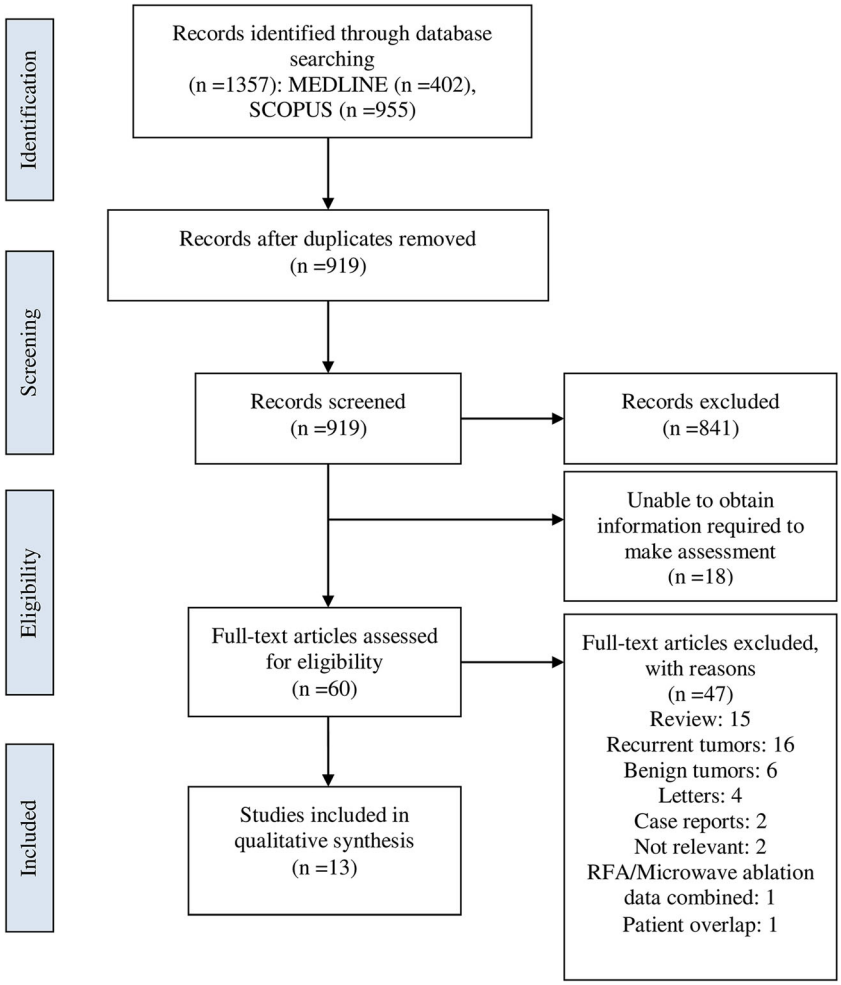

Fig. 1 Flow diagram of the literature search

Characteristics of the included studies

The characteristics of the included studies are summarized in Table 1. Eleven retrospective, one prospective, and one study of unclear design were included in this review. A total of 1389 patients and 1422 tumors treated with RFA were assessed in these studies. The smallest sample consisted of six patients in two studies and the largest sample included 414 patients, with six, seven, and 414 tumors, respectively. The mean age of the patients varied between 40.7 and 72 years. The majority of patients were female, with their percentage varying between 67 and 89%. Eight of the studies reported cases of PTMCs only and three studies specifically assessed patients with a tumor diameter between 1 and 2 cm. Two studies included both PTMCs and larger low-risk PTCs. Specifically, Jeong et al. [28] presented six cases of PTMC in five patients and one case of PTC separately due its much larger dimensions (diameter: 8 cm), while Kim et al. [29] presented data regarding six tumors with comparable size (diameter: 6–13 mm) in six patients. The mean tumor diameter ranged between 4 and 17.7 mm and the mean tumor volume varied between 20 and 18266 mm^3. The mean follow-up period after the RFA was 6–72 months. Five studies used a control group, of which two compared the efficacy of RFA in different categories of patients with PTC (patients with chronic lymphocytic thyroiditis (CLT) vs. patients without CLT and patients with PTC vs. patients with PTMC, respectively). Two studies compared RFA with surgery and one study compared RFA with MWA. The quality of the included studies was declared at least moderate-fair, using different quality control tools in relation to the presence or absence of a control group.

The mean duration, power, and energy of the procedure were reported to be between 151 and 479.4 s, 3–5 and 20 W, and 767.68 and 7950 J, respectively. One or two RFA sessions were needed for the treatment of each tumor. The post-RFA results were evaluated by both less experienced and highly experienced radiologists. The technical features of the RFA sessions of the included studies are summarized in Table 2.

Tumor volume reduction after RFA

The data concerning VRR as well as complete reduction, tumor recurrence, and complication frequency are summarized

Table 1 Characteristics of the included studies

Study	Country	Design	Number of patients	Number of tumors	Gender (percentage)		Age (years) (mean±SD)	Diagnostic method	Tumor diameter (mm) (mean±SD)	Tumor volume (mm^3) (mean±SD)	Follow-up (months) (mean ±SD)	Presence of other treatment group
					Male	Female						
Xiao [18]	China	Retrospective	91	91	21%	79%	40.7 ± 9.3	CNB	14 ± 2	730 ± 380	26.0 ± 10.3	Surgery (*n*=91)
Yan [19]	China	Retrospective	202	211	25%	75%	42.79 ± 10.13	CNB	5.35 ± 1.63	102.34 ± 93.84	24.42 ± 9.15	No
Yan [20]	China	Retrospective	414	414	22%	78%	43.56 ± 9.79	CNB	5.22 ± 1.59	92.74 ± 83.43	42.15 ± 11.88	No
Cao [21]	China	Retrospective	49	49	14%	86%	46 ± 14	CNB or FNA	13.2 ± 2.8	Not reported	22.1 ± 13.2	Microwave ablation (*n*=123)
Cho [22]	Korea	Retrospective	74	84	11%	89%	46±12	FNA	4±1.6	20±40	72±18	No
Zhang [23]	China	Retrospective	94	94	26%	74%	45.4±10.8	CNB	6.14±2.54	175.9±228.3	64.2±2.8	Surgery (*n*=80)
Xiao [24]	China	Retrospective	66	66	21%	79%	41.0±9.2	CNB	13 ±2	690±340	20.5±7.4	No
Wu [25]	China	Retrospective	198	204	29%	71%	42.5±9.5	CNB or FNA	6.34±1.8	99.42±84	25.9±4.5	No
Zhang [26]	China	Unclear	30 30	30 30	27% 13%	73% 87%	44.07±8.99 42.2±9.61	CNB	Not reported Not reported	110±170 100±130	Not reported Not reported	No
Ding [27]	China	Retrospective	37	38	22%	78%	45.14±12.96	FNA	7.36±4.13	120±100	6 mo (median)	No
Jeong [28]	Korea	Retrospective	6	7	33%	67%	59.5±17.6	CNB or FNA	80 (PTC)	126,900 (PTC)	5 (PTC)	No
									7.3±1.3 (PTMC)	160±80 (PTMC)	19.3±3.4 (PTMC)	No
Kim [29]	Korea	Retrospective	6	6	33%	67%	72±6.6	CNB or FNA	9.2±2.8	260±177	48.5±12.3	No
Zhang [30]	China	Prospective	92	98	25%	75%	44.7±10.7	CNB	5.8±2.2	118.8±106.9	7.8±2.9	No

CNB core needle biopsy, *FNA* fine needle aspiration, *PTC* papillary thyroid carcinomas, *PTMC* papillary thyroid microcarcinomas

Table 2 Technical features of RFA sessions

Study	Ablation time (s) (mean±SD)	Power (W) (mean±SD)	Energy (J) (mean±SD)	Operators' experience (years)
Xiao [18]	322.8 ± 117.6	Not reported	Not reported	20
Yan [19]	153.81 ± 88.11	4.55 ± 1.16	767.68 ± 461.78	>20
Yan [20]	217.29 ± 117.53	3.71 ± 0.91	803.84 ± 489.30	>20
Cao [21]	240 ± 129	Not reported	Not reported	>3
Cho [22]	151 (median)	20 (median)	3150 (median)	13
Zhang [23]	479.4±227.4	5	Not reported	>20
Xiao [24]	302.4±127.0	5.9±1.6	1789.4±801.1	>20
Wu [25]	257.5±131.4	3–5	910±590	>20
Zhang [26]	228±126 174±126	Not reported Not reported	900±500 700±500	Not reported
Ding [27]	Not reported	20	Not reported	>5
Jeong [28]	720 (PTC) 300±127 (PTMC)	30 (PTC) 16±5 (PTMC)	21,600 (PTC) 5675±3473 (PTMC)	10 and 18
Kim [29]	Not reported	Not reported	Not reported	1, 3 and 4
Zhang [30]	450.8±230.2	Not reported	1404.7±822.0	>20

PTC papillary thyroid carcinomas, *PTMC* papillary thyroid microcarcinomas

in Table 3. Most studies reported a VRR of 98.5–100% at the end of the follow-up period. VRR was estimated as follows: (initial volume − final volume) × 100/initial volume. One study [28] demonstrated a significantly lower VRR (47.8%) at the end of the follow-up of six PTMCs in five patients. Xiao et al. [24] and Zhang et al. [30] found a statistically significant ($p<0.01$) difference in VRR at every other follow-up assessment up to 18 months and 6 months, respectively. Xiao et al. [18] and Wu et al. [25] found a statistically significant difference ($p<0.001$) in VRR between every follow-up visit up to 18 months and 24 months after the ablation, respectively. The ablation zone volume was significantly different ($p<0.001$) compared to the initial tumor volume at every assessment in the study of Yan et al. [19].

Frequencies of complete disappearance and local recurrence after RFA

The frequency of complete disappearance ranged between 33.7 and 100%. The lowest disappearance frequencies were noted in studies with small sample sizes and/or short follow-up periods. Studies with large samples and mean follow-up periods exceeding 2 years reported a complete disappearance rate of 56–100%. Cao et al. [21] found no statistically significant difference in complete tumor disappearance rate ($p=0.15$) between RFA and MWA.

Eight studies reported local tumor progression/recurrence [18–25]. The local recurrence frequency was 0–4.5%. Seventeen new tumors in 16 patients and six regional lymph node metastases in six patients were collectively reported in all of the included studies. Additionally, residual malignant cells were detected on CNB at the edge of the ablation zone of nine tumors. No distant metastasis was found. Zhang et al. [23] found no significant difference in parenchymal recurrence ($p=0.363$) or recurrent lymph node metastasis ($p=0.460$) between US-guided RFA and surgery. In addition, no statistically significant difference ($p=0.682$) in local progression was found between the RFA (4.4%) and the surgery group (2.2%) in the study of Xiao et al. [18].

Frequencies of complications from RFA

Complications occurred in 0–33% of patients. The highest percentage was found in the study with the smallest sample size (six patients) [29]. The most common complication was mild-moderate pain and cervical discomfort (28 patients). Other complications were the following: transient hoarseness-voice change (12 patients), hematomas with immediate recovery (two patients), 1st degree burn (one patient), slight fever (one patient), and transient hypertension with mild headache (one patient). There was no report of a life-threatening complication or a complication with subsequent long-term disability. No significant difference was found between surgically and RFA-treated patients with respect to complication frequency in two studies ($p=0.682$ and $p=0.095$, respectively) [18, 23]. However, all the reported surgical complications were permanent (five cases of permanent hypoparathyroidism and two cases of permanent recurrent laryngeal nerve damage). In the study of Cao et al. [21], the difference in complication frequency between the RFA group ($n=49$) and the MWA group ($n=123$) was not statistically significant ($p=0.96$).

Table 3 Efficacy and safety of RFA

Study	Complete disappearance rate	Progression/ recurrence rate	Complications frequency	VRR (%) 1 month	3 months	6 months	12 months	18 months	24 months	>24 months
Xiao [18]	56%	4.4%	2.2%	−82.67 ± 131.27	9.04 ± 74.68	64.13 ± 37.14	85.42 ± 24.85	94.81 ± 11.53	96.18 ± 9.13	99.0 ± 3.44 (48 months)
Yan [19]	65.88%	1.5%	Not reported	−479.28 ± 478.53	-83.51 ± 178.54	34.00 ± 91.67	84.01 ± 34.91	97.81 ± 6.99	99.14 ± 4.18	Not reported
Yan [20]	88.41%	3.62%	3.9%	-586.87 ± 1072.61	− 132.98 ± 483.02	10.20 ± 215.94	86.78 ± 34.48	93.95 ± 31.44	97.53 ± 10.13	98.81 ± 6.41 (48 months)
Cao [21]	Not reported	2%	2%	Not reported						
Cho [22]	100%	4%	5.5%	Not reported	Not reported	−202 ± 787	54 ±138	Not reported	100	100 (60 months)
Zhang [23]	Not reported	1.1%	0%	Not reported						
Xiao [24]	57.6%	4.5%	3%	−92.32 ± 143.38	2.28 ± 83.23	63.83 ± 41.27	84.64 ± 28.64	92.42 ± 14.11	93.22 ± 12.33	99.11 ± 2.44 (30 months)
Wu [25]	Not reported	0.5%	4.5%	73.9 ± 13.7	90.5 ± 8.2	96.1 ± 5.9	98.8 ± 3.2	99.6 ± 1.9	99.8 ± 1.0	Not reported
Zhang [26]	100%	0%	6.7%	73 ± 15	95 ± 0.7	99 ± 03	99.9 ± 0.3	100	Not reported	Not reported
				70 ± 21	90 ± 11	97 ± 04	99.8 ± 0.7	100	Not reported	Not reported
Ding [27]	97.4%	0%	0%	23.09 ± 161.15	51.89 ± 160.10	97.31 ± 6.35	99.34 ± 3.49	Not reported	Not reported	Not reported
Jeong [28]	0%	0%	0%	99.4 (end of follow-up)						
	50%			47.8 (end of follow-up)						
Kim [29]	66.7%	0%	33.3%	98.5 ± 3.3 (end of follow-up)						
Zhang [30]	33.7%	0%	5.4%	52.6	81	92	96	100	Not reported	Not reported

Discussion

Our study determined that US-guided RFA is a promising therapeutic method with satisfactory results. The VRR of the tumors was 98.5–100% in studies with a mean follow-up period of 7.8–72 months. RFA resulted in complete disappearance of the ablated carcinomas in 33.7–100% of cases. The wide range that is noted in the complete disappearance rate may be explained by differences in the number of the recruited patients and the duration of the follow-up period of the included studies. Specifically, studies with large study samples and long follow-up periods reported a complete disappearance frequency of 56–100%. Six studies [18, 19, 24–26, 30] included US-guided CNB in the postoperative assessment and viable malignant cells were found in nine out of 718 patients. Consequently, the reported complete disappearance rate could have underestimated the therapeutic success of RFA. Additionally, early tumor progression or recurrence detection may be benefited by the addition of routinely performed CNB to post-ablation follow-up, along with imaging studies (including US and contrast-enhanced US) and a clinical exam.

Local PTC progression/recurrence was observed in 0–4.5% of cases. No distant metastasis was noted. Only two of the included studies [22, 23] had mean follow-up periods longer than 5 years and both reported tumor recurrence, suggesting that studies with long-term follow-up of patients are needed for an accurate recurrence rate estimation. Recurrent tumors can be successfully treated with RFA [10–12, 18–22, 24, 25]. As far as RFA complications are concerned, 45 out of the 1389 assessed patients (3.2%) suffered a complication and no patients developed long-term disabilities as a result of treatment.

Some of the cited studies were conducted by the same author groups and had overlapping data collection periods. Therefore, there is a concern that some of the studies could have overlapping cohorts. Specifically, the study of Xiao et al. [18] could be reporting on the same cohort as a previous study of the same group [24], with the addition of more recently treated patients. Additionally, some of the PTMC cases that were reported in the studies of Jeong et al. [28] and Kim et al. [29] may be included in the study of Cho et al. [22]. Finally, there is a potential overlap among the samples of some of the other included studies [19, 20, 23, 25, 26, 30].

RFA can offer an additional therapeutic approach to low-risk PTCs. Other thermal ablation techniques have also demonstrated efficacy in the treatment of thyroid carcinomas. Numerous studies have shown that microwave ablation [31–33] and laser ablation [34, 35] are highly effective in the management of localized thyroid cancer. A systematic review and meta-analysis by Shen et al. showed that thermal ablation of PTMCs was associated with significantly reduced complications, cost, and postoperative length of stay and similar recurrence rate and recurrence-free survival compared to

surgery [36]. However, other studies report that thermal ablation has a high risk of incomplete tumor absorption and consequently an increased risk of recurrence and metastasis [37, 38]. A recent systematic review and meta-analysis compared the three percutaneous ablation methods and found no statistically significant differences in volume reduction, complete disappearance, tumor recurrence, and complications after PTMC treatment, though RFA appeared to have the highest complete absorption ratio and the lowest recurrence ratio [39].

Although surgery is currently the recommended treatment for PTCs, the 2017 South Korean guidelines suggest that US-guided RFA is an alternative treatment option for patients who are unable or unwilling to undergo surgery [40]. Only two of the included studies compared the effectiveness of RFA and surgery [18, 23]. Xiao et al. assessed 182 patients (RFA group: 91 patients, surgery group: 91 patients) and found no significant difference between RFA and surgery in local progression and complication rates. RFA had a shorter duration ($p<0.001$) and a lower cost ($p<0.001$) [18]. In the study of Zhang et al. [23], 174 patients (RFA group: 94 patients, surgery group: 80 patients) were assessed. There was no statistically significant difference between the two methods in parenchymal ($p=0.363$) or regional lymph node recurrence ($p=0.460$). RFA was associated with shorter procedure duration, shorter hospitalization period, and decreased cost ($p<0.001$). Surgically treated patients had a lower post-treatment thyroid-related quality of life, but surgery offered the advantage of removing nine occult carcinomas and nine occult lymph node metastases that were identified with post-operative pathology. However, the clinical benefit of removing occult microcarcinomas and lymph node micrometastases with surgery has not to date been proven. In both studies, no disabling complications were reported in the RFA group [18, 23], in contrast to a total of seven cases of permanent complications (two patients with permanent recurrent laryngeal nerve injury and five patients with permanent hypoparathyroidism) in the surgery group.

Reports of the advantages of RFA compared to surgery can be found in studies that assess the effectiveness of these methods in the treatment of benign thyroid nodules. Che et al. [41] studied patients with nodular goiter and found that surgery was associated with higher rate of residual nodules ($p=0.004$), longer hospitalization ($p<0.001$), and more frequent complications ($p=0.002$). Yue et al. [42] found that RFA was associated with better health-related quality of life at 6-month follow-up, albeit this method was not considered cost-effective. Bernardi et al. [43] showed that RFA produced a more satisfactory cosmetic result ($p=0.001$), although satisfaction with resolution of nodule-related symptoms was higher in the surgery group. There was no difference between the groups in overall satisfaction. Further multicenter studies with long-term follow-up and large samples are needed in order to have more solid conclusions regarding the efficacy, safety, and cost-effectiveness of US-guided RFA in the treatment of localized PTCs in comparison to surgery.

Our study has specific limitations. First, the number of studies that were included is relatively small, as RFA has only recently been explored as a treatment option for thyroid cancer. Second, most studies had a small number of patients and a short follow-up period. Third, the retrospective design of most of the studies could have had a negative impact on the accuracy of their results. Finally, the literature search and data extraction were executed by a single researcher, which could have negatively affected the completeness of the provided information.

In conclusion, US-guided RFA appears to be an efficacious and safe method for the treatment of low-risk PTCs and can be considered for patients who refuse or are unable to undergo surgery.

Code availability Not applicable.

Author contribution Dimitrios Linos had the idea for the article. Spyridon Ntelis performed the literature search and data analysis, and wrote the first draft of the manuscript. Dimitrios Linos critically revised the work.

Data Availability Not applicable.

Declarations

Ethical approval Not applicable.

Informed consent Not applicable.

Conflict of interest The authors declare no competing interests.

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