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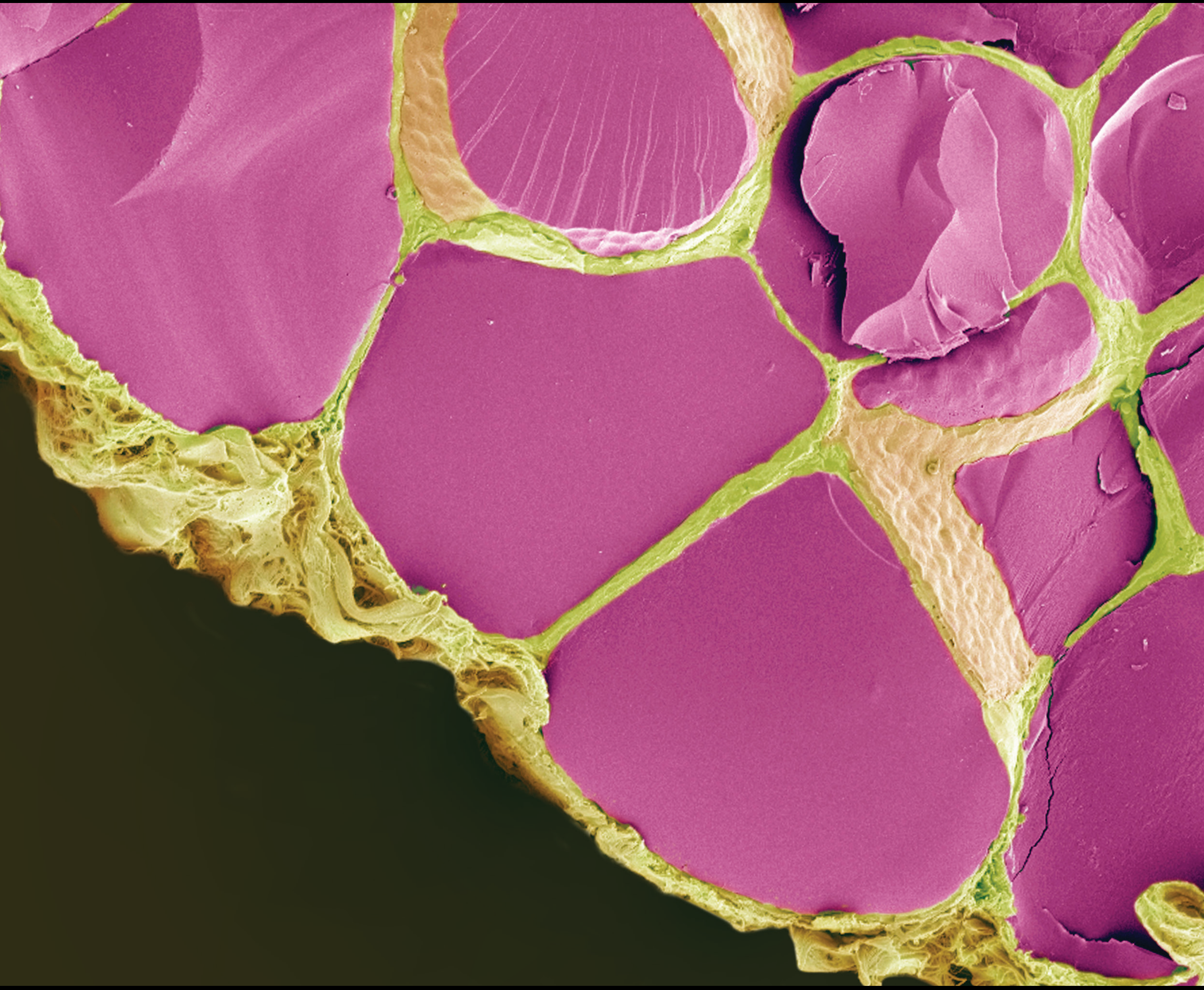

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Research Article

A Single-Center Retrospective Study of the Impact of Thyroid Cancer on the Malignant Risk of Contralateral TI-RADS 3 and 4 Nodules

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Background. The incidence of thyroid nodules increases in the general population. Similarly, we have also seen a dramatic increase in the number of thyroid surgeries. However, the mortality rate of thyroid cancer remained stable or even decreased. The purpose of our study was to investigate whether thyroid cancer affects the malignant risk of the contralateral TI-RADS 3 and 4 nodules. *Methods*. We conducted a retrospective cohort study in our institution for all thyroid procedures due to nodules from December 2018 to December 2019. All eligible patients were divided into the experimental group (bilateral nodules) and the control group (unilateral nodules) to assess whether the proportion of malignant nodules was different between the two groups. Multivariate logistic regression analysis was used to control potential confounding factors to investigate whether their differences were statistically significant. *Results*. A total of 330 patients underwent thyroid surgery, of whom 137 were eligible, including 84 in the experimental group and 53 in the control group. The proportion of malignant nodules was significantly different between the experimental group and the control group (29.8% versus 58.5%, unadjusted OR 0.30, 95% CI: 0.17–0.82, $p = 0.001$). However, after controlling for potential confounding factors, including age ($p = 0.004$), gender ($p = 0.775$), and TI-RADS classification ($p \leq 0.001$), we found that the difference was not significant (adjusted OR 1.08, 95% CI: 0.39–3.01, $p = 0.886$). *Conclusion*. There is no evidence that thyroid cancer affects the malignant risk of the contralateral TI-RADS 3 and 4 nodules. This study has been registered with the Chinese Clinical Trial Registry (clinical trial registration number: ChiCTR2000038611, registration time: September 26, 2020).

1. Introduction

Thyroid nodules are defined as discrete lesions within the thyroid, which are radiologically different from the surrounding thyroid parenchyma [1]. It is extremely common in the general population, reaching 4%–7% and 30%–67% in palpation and Imaging examination, respectively [2]. Currently, more thyroid nodules are identified by occasional imaging studies, rather than thyroid-related symptoms or palpation. Moreover, these occasional thyroid nodules are asymptomatic and small [3]. The incidence of occult thyroid nodules in the general population is as high as 68% [2], and many imaging studies are beneficial to identify these thyroid nodules. Just as previous studies have shown the incidence of thyroid nodules in ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI), 18-fluorodeoxyglucose positron emission tomography (PET) is 65%, 15%, and 1%–2%, respectively [4]. Among them, ultrasound is the most common imaging examination for thyroid nodules, and it is recommended by the British, American, and European Thyroid Association (BTA, ATA, and ETA, respectively) as the preferred imaging method to evaluate thyroid nodules [1, 5, 6]. Thyroid ultrasound can accurately identify malignant thyroid nodules and may even be better than fine-needle aspiration biopsy (FNAB) [7, 8].

Thyroid nodules include benign and malignant ones, and the incidence of malignant nodules varies from 4% to 12%, including incidental thyroid nodules [7, 9–16]. Thyroid cancer currently ranks fifth among female cancers, but it is estimated that thyroid cancer will rank second and ninth among female and male cancers by 2030 [17]. However, not all thyroid nodules require surgery or even biopsy. More than 90% of thyroid nodules are of no clinical significance because there are no malignant ultrasound features or pathologically proven benign [18]. The emergence of the Thyroid Imaging Report and Data System (TI-RADS) [19], developed by the American College of Radiology (ACR), allows clinicians to stratify the risk of thyroid nodules and take appropriate management strategies. This is conducive to timely treatment of clinically significant thyroid cancer and can also reduce costs and risks due to biopsy and surgery for benign thyroid lesions and indolent thyroid cancer. Previous studies reported that the malignant risk in TI-RADS1-5 is significantly different, which are <2%, <2%, 5%, 5%–20%, and ≥20%, respectively.

We have noted an interesting phenomenon that the incidence of thyroid nodules is increasing; however, the absolute mortality of thyroid cancer has remained stable or even decreased. This may be caused by the current more aggressive management strategy for thyroid nodules, which is not only reflected in the number of procedures, but also reflected in its scope (preferably total thyroidectomy), even for the low-to-medium risk thyroid cancer [20]. Based on the 2017 ACR Thyroid Guidelines and many subsequent studies including prospective and retrospective clinical trials, there is almost no controversy regarding the treatment of TI-RADS 1 and 2 nodules because almost all are benign. Similarly, the treatment of TI-RADS 5 nodules is also not controversial due to the extremely high risk of malignancy. However, the treatment of TI-RADS 3 and 4 is still controversial. Moreover, thyroid nodules are characterized by bilateral ones, which makes the surgeon confused about whether bilateral thyroid requires surgery and what its scope is. Therefore, this leads to more complicated and confusing treatments for bilateral nodules, especially TI-RADS 3 and 4, which vary based on surgeons' preferences and institutional experience. Because of the relatively independent anatomical characteristics of bilateral thyroid, we consider whether thyroid cancer will affect the malignant risk of the contralateral thyroid nodule, and whether this may also be an influencing factor in the treatment of bilateral thyroid nodules. However, there are few related studies.

Therefore, we regarded bilateral thyroid glands as two independent parts to investigate whether thyroid cancer affects the malignant risk of the contralateral TI-RADS 3 and 4 nodules.

2. Materials and Methods

2.1. Population and Data Collection. This study was a single-center retrospective cohort study. We reviewed patients with thyroid nodules in our hospital from December 1, 2018, to December 31, 2019, through the electronic case system. The data included demographic characteristics (including age and gender), medical history, thyroid ultrasound results, surgical procedures, and postoperative pathology. All thyroid ultrasound examinations were completed by 5 experienced sonographers within 3 days after admission or in the clinic and reviewed by chief physicians with more than 25 years of experience. The thyroid ultrasound reports included the number, size, location, grade of the thyroid nodules, and cervical lymph nodes. The thyroid nodule grading was based on the 2017 ACR Thyroid Imaging Report and Data System (TI-RADS) guidelines.

2.2. Research Objects and Groups. All eligible patients were divided into the experimental group and the control group as follows. To facilitate the subsequent statistical analysis, we had a special definition for bilateral thyroid nodules. For bilateral thyroid nodules, the side with higher TI-RADS grade or more advanced pathology was the b-side, while the contralateral was the a-side. For example, the side with anaplastic or medullary cancer was the b-side, and the contralateral papillary carcinoma was the a-side. When both thyroid cancers were papillary cancers, the side with higher TI-RADS grade was the b-side. In our study, statistical analysis was performed on the a-side of the experimental group and the control group.

The inclusion criteria of the experimental group were as follows: (1) bilateral thyroid nodules, (2) bilateral thyroid nodules that were surgically removed, and (3) bilateral thyroid nodules that had postoperative pathology. Exclusion criteria of the experimental group were as follows: (1) bilateral benign nodules, (2) history of malignant tumors in other tissues or organs (except thyroid), (3) history of thyroid procedures due to thyroid nodules or other thyroid diseases, and (4) the a-side thyroid with TI-RADS 1, 2, and 5 nodules.

The inclusion criteria of the control group were as follows: (1) unilateral thyroid nodules, (2) unilateral nodules that were surgically removed, and (3) unilateral thyroid nodules that had postoperative pathology. Exclusion criteria of the control group were as follows: (1) history of malignant tumors in other tissues or organs (except thyroid), (2) history of thyroid procedures due to thyroid nodules or other thyroid diseases, and (3) patients with TI-RADS 1, 2, and 5 nodules.

2.3. Statistics. In our study, continuous variables were described by mean ± standard deviation (SD), which were statistically analyzed by Student's t-test or Mann–Whitney U test according to its distribution. Categorical variables were described by frequency (percentage), which were statistically analyzed by Chi-square tests or Fisher's exact tests as appropriate. We evaluated the unadjusted odds ratio (OR) based on the proportion of malignant tumors in the experimental group and the control group, which was described as unadjusted OR, 95% CI. In order to eliminate confounding factors, including age, gender, and TI-RADS classification, we used multivariate logistic regression analysis to evaluate the adjusted odds ratio, expressed as adjusted OR, 95% CI. p value ≤ 0.05 was considered statistically significant. All statistics were performed with SPSS version 25.0.

3. Results

The review and grouping of the study are shown in Figure 1. Our institution, a tertiary regional medical center, performed 330 thyroid procedures due to thyroid nodules within 1 year. A total of 137 eligible patients were divided into the experimental group ($n = 84$) and the control group ($n = 53$).

After excluding 12 patients with incomplete information, the distribution of TI-RADS grades for 261 bilateral nodules and 57 unilateral nodules is shown in Table 1. We saw that bilateral thyroid nodules were more common (81.5% versus 18.5%). Moreover, most thyroid nodules were TI-RADS 3 and 4 ones, and TI-RADS 2 and 5 nodules were extremely rare, especially in unilateral thyroid nodules.

The demographic characteristics of the experimental group and the control group are shown in Table 2. We saw that femal were more common in both the experimental group and the control group; however, there was a statistical difference between the two groups (p = 0.008). The average age in the experimental group and the control group was 50.8 ± 11.0 years and 47.7 ± 9.6 years, respectively, and there was no difference between the two groups (p = 0.246).

The ratio of malignant nodules in the two groups is shown in Table 3. There was a significant difference in the proportion of malignant nodules between the a-side of the experimental group and the control group (29.8% versus 58.5%, unadjusted OR 0.30, 95%CI: 0.17–0.82, p = 0.001). It showed that thyroid cancer does not increase the malignant risk of the contralateral TI-RADS 3 and 4 nodules; on the contrary, its risk was lower. However, we used multivariate logistic analysis to investigate whether age, gender, and TI-RADS grade, respectively, affect the proportion of malignant nodules in the two groups and found that age (p = 0.004) and TI-RADS classification ($p \leq 0.001$) were statistically significant, while gender was not statistically significant (p = 0.775). Therefore, after controlling for potential confounding factors, such as age (p = 0.004), gender (p = 0.775), and TI-RADS classification ($p \leq 0.001$), we found that thyroid cancer does not affect the malignant risk of the contralateral TI-RADS 3 and 4 nodules (adjusted OR 1.08, 95% CI: 0.39–3.01, p = 0.886).

The characteristics and surgical procedures of the a-side of the experimental group and the control group are shown in Table 4.

The distribution of TI-RADS classification on the a-side of the experimental group and the control group were significantly different ($p \leq 0.001$). The nodules on the a-side of the experimental group were more TI-RADS3 nodules; on the contrary, the control group was TI-RADS4 nodules. In the a-side of the experimental group and the control group, all malignant nodules were papillary thyroid cancer, and the proportion of micropapillary cancer was not different between the two groups (p = 0.282). We knew that the b-side in the experimental group was thyroid cancer, and the a-side surgical procedures varied with its pathology.

When the nodules on the a-side of the experimental group and the control group were malignant, there was no difference in surgical procedures between the two groups (92.0% versus 96.8%, p = 0.581). However, when it was benign, there was a significant statistical difference between the two groups (50.8% versus 13.6%, p = 0.002), and the a-side of the experimental group was more inclined to unilateral lobectomy.

The pathological distribution of b-side thyroid cancer in the experimental group is shown in Table 5. It included 82 (97.6%) papillary carcinomas, 1 (1.2%) medullary carcinoma, and 1 (1.2%) anaplastic carcinoma. We saw that the vast majority of them were low-to-medium risk papillary cancers, and the more indolent micropapillary cancers were relatively high.

4. Discussion

Thyroid nodules are an extremely common disease, with a high incidence in the general population. In China, more and more thyroid procedures are due to physical examinations or incidentally identified thyroid nodules, which is consistent with studies from other countries and regions. In order to take appropriate treatment for thyroid nodules, the ACR developed TI-RADS in 2017. However, the treatment of TI-RADS 3 and 4 nodules is controversial, especially its procedures and scope. At present, thyroid nodules encountered in clinical practice are basically TI-RADS 3 and 4 nodules. In our study, its proportion reached 100% and 97.62% in unilateral and bilateral nodules, respectively. Thyroid nodules are usually characterized by bilateral nodules, which leads to more complicated and confusing surgical procedures for TI-RADS 3 and 4 nodules [20]. The procedures for patients with both benign and malignant nodules are clear. However, patients with benign on one side and malignant on the contralateral are controversial. Among them, there are some patients whose one side has been pathologically confirmed as malignant, but the contralateral TI-RADS 3 or 4 nodules may not be palpable during the operation. Whether this side requires procedure, if necessary, what is its scope, there is no consensus on these issues. Similarly, this controversy also exists in those patients whose nodules on one side have been confirmed as low-to-medium risk papillary carcinoma and contralateral micropapillary carcinoma.

A systematic review including 14 studies at a moderate risk of bias found the odds ratio for thyroid cancer to be lower in patients with a multinodular goiter than in those with single nodule [21]. In our study, we found that thyroid cancer significantly reduced the malignant risk of the contralateral TI-RADS 3 and 4 nodules (29.8% versus 58.5%, unadjusted OR 0.30, 95% CI: 0.17–0.82, p = 0.001). However, we used multivariate logistic regression analysis to control potential confounding factors, including age (p = 0.004), gender (p = 0.775), and TI-RADS classification ($p \leq 0.001$), and found that the difference did not reach statistical difference (adjusted OR 1.08, 95% CI: 0.39–3.01, p = 0.886).

We know that more than 90% have no clinical significance, especially nodules smaller than 1 cm. Therefore, not all thyroid nodules require surgery [18, 22–27]. Benign thyroid nodules only require regular ultrasound follow-up unless the nodules are large (>4 cm) or based on clinical

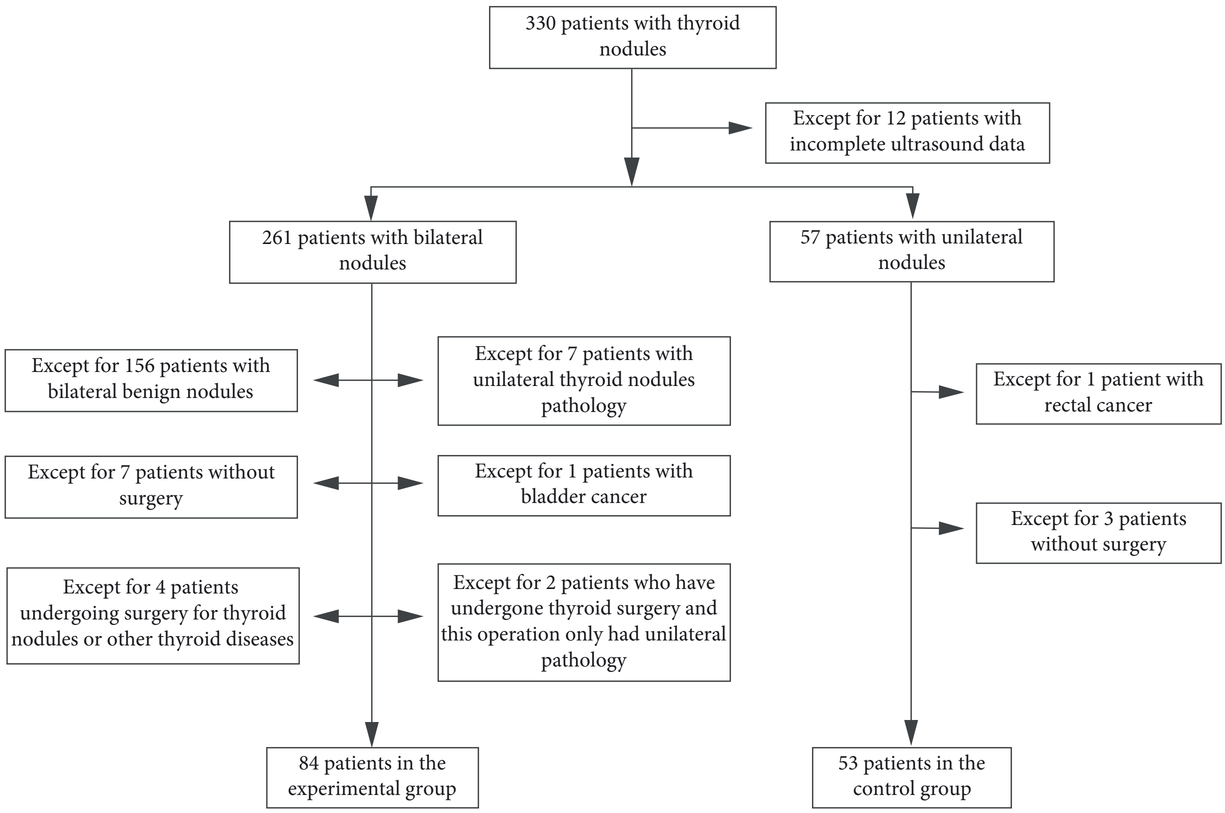

Figure 1: Flowchart of review and grouping of the study.

Table 1: Distribution of thyroid nodule TI-RADS classification.

	Unilateral nodules n (%)	Bilateral nodules n (%)
2/2	0 (0)	0 (0)
2/3	—	1 (0.4)
2/4	—	3 (1.2)
2/5	—	0 (0)
3/3	17 (29.8)	122 (46.7)
3/4	—	102 (39.1)
3/5	—	12 (4.6)
4/4	40 (70.2)	19 (7.3)
4/5	—	0 (0)
5/5	0 (0)	2 (0.7)
Total	57 (18.5)	261 (81.5)

Table 2: Demographic characteristics of the experimental group and the control group.

	Experimental group	Control group	p value
Gender			
Male n (%)	10 (11.9)	16 (30.2)	0.008
Female n (%)	74 (88.1)	37 (69.8)	
Age, years, (mean ± SD)	50.8 ± 11.0	47.7 ± 9.6	0.246

SD: standard deviation.

considerations or cause compression or structural symptoms [22, 28]. For thyroid cancer, the proportion of papillary cancer is extremely high, and other thyroid cancers are rare. In our study, there were 1 medullary carcinoma and 1 anaplastic carcinoma. Moreover, papillary thyroid cancers have a favorable prognosis, with mortality rates of 1% to 2% at 20 years [29]. It is generally perceived as low-risk thyroid cancer [30] and is not associated with well-recognized predictors of mortality [31, 32]. The American Thyroid Association (ATA) guidelines recommend lobectomy for low-risk nodules and thyroidectomy (including total thyroidectomy and subtotal thyroidectomy) or lobectomy for intermediate-risk nodules [1]. Moreover, many studies have demonstrated that overall survival and disease-free survival are not negatively impacted by lobectomy compared with thyroidectomy [33–39]. However, for those patients whose one side nodules have been proven to be low-to-medium risk papillary cancer and the contralateral nodules are micropapillary cancer, or even benign ones, surgeons in China usually prefer total thyroidectomy. In our study, we did not find that thyroid cancer increases the risk of malignancy of the contralateral TI-RADS 3 and 4 nodules. However, in our study, we saw that the a-side nodules were malignant, even though 72% of them were micropapillary carcinomas and 92% of them had undergone lobectomy. Similarly, even if the a-side nodules were benign, the a-side of the experimental group was more inclined to lobectomy (50.8% versus 13.6%, $p = 0.002$). To a certain extent, this indicates a more active management strategy, which is common not only in China but also in other regions.

The increase in the incidence of thyroid nodules can be seen worldwide [40]. In the US, a retrospective population-

Table 3: The ratio of malignant tumors on the a-side of the experimental group and the control group.

	Experimental group ($N = 84$)	Control group ($N = 53$)	Unadjusted OR (95% CI)	p value	Adjusted OR (95% CI)	p value
Benign n (%)	59 (70.2)	22 (41.5)	0.30 (0.17, 0.82)	0.001	1.08 (0.39, 3.01)	0.886
Malignant n (%)	25 (29.8)	31 (58.5)				

OR: odds ratio; adjusted OR: control for confounding factors, including age ($p = 0.004$), gender ($p = 0.775$), and TI-RADS classification ($p \le 0.001$).

Table 4: Characteristics and surgical procedures of the a-side of the experimental group and the control group.

	Experimental group	Control group	p value
TI-RADS classification			
TI-RADS 3 n (%)	65 (77.4)	15 (28.3)	≤0.001
TI-RADS 4 n (%)	19 (22.6)	38 (71.7)	
Pathology			
Micropapillary n (%)	18 (72.0)	26 (83.9)	0.282
Papillary n (%)	7 (28.0)	5 (16.1)	
Surgical procedures			
Malignant*			
UL□ n(%)	23 (92.0)	30 (96.8)	0.581
UPL△ n(%)	2 (8.0)	1 (3.2)	
Benign*			
UL□ n(%)	30 (50.8)	3 (13.6)	0.002
UPL△ n(%)	29 (49.2)	19 (86.4)	

UL□: unilateral lobectomy; UPL△: unilateral partial lobectomy; malignant*and benign*: pathology of the a-side of the experimental group and the control group.

based evaluation of patients with thyroid cancer found that the incidence increased from 3.6/100000 in 1973 to 8.7/100000 in 2002, a 2.4-fold increase [41]; similarly, it increased 15 times in South Korea between 1993 and 2011 [42, 43]. However, the mortality rate of thyroid cancer remained stable or even declined [41–46]. At the same time, we have also noticed that the number of thyroid procedures increased dramatically, reaching 2–4 times [44, 45]. Another study showed that it increased from 99,613 to 130,216 per year in the United States from 2006 to 2011, with an average annual growth rate of 12% [47]. Moreover, the number of thyroid procedures has increased disproportionately with its morbidity and mortality. This evidence also indirectly indicated that thyroid nodules tend to be more aggressive management strategies in clinical practice. Similarly, many studies have confirmed that more resources were used for the diagnosis, treatment, and follow-up of those thyroid cancers, which may not affect the life of the patient or even have no symptoms [48, 49]. A large observational study based on the SEER database found that after controlling tumor size, for those patients with low-risk tumors, aggressive surgical treatment has no benefit in survival [36]. Several studies have indirectly demonstrated the current status of overtreatment of thyroid nodules [21, 45, 47–50].

When it comes to procedure, postoperative complications are an inevitable issue. A study showed that there was recurrent laryngeal nerve injury (2.5%, rare on both sides), hypocalcemia (8.1%) after total thyroidectomy [51]. Do more aggressive procedures for thyroid nodules increase the risk of postoperative complications? A study showed that there is no correlation between surgical procedures and the incidence of postoperative hypocalcemia [52]. However, another study found that total thyroidectomy is more prone to postoperative complications than subtotal thyroidectomy, including permanent nerve damage (7.0% versus 1.3%, $p < 0.005$) and temporary nerve damage (8.6% versus 2.2%, $p < 0.005$) and transient hypoparathyroidism (18.0% versus 2.1%, $p < 0.005$) [33]. Moreover, lobectomy can provide histological diagnosis and tumor removal with a lower risk of complications [18]. In our study, we did not find that thyroid cancer increases the risk of malignancy of the contralateral nodule. Therefore, the current more aggressive treatment strategy for thyroid nodules may not be a good choice for patients and society. For those patients with low-to-medium risk papillary cancer on one side, if the contralateral TI-RADS 3 and 4 nodules cannot be palpated during the operation, they can be followed up instead of lobectomy [20]. If the contralateral side is micropapillary carcinoma, or benign, partial lobectomy can be performed, which can retain enough thyroid tissue to meet normal physiological needs without affecting the prognosis of the patient while reducing the possibility of postoperative complications [20]. Moreover, in recent years, the epidemic has led to inadequate medical funding in various countries. These issues are worthy of our understanding of the current status of the treatment of thyroid nodules, and further research on its management strategies.

In our study, we found that thyroid cancer does not affect the malignant risk of the contralateral TI-RADS 3 and 4 nodules. However, there are still many limitations to be improved. First, our study is a single-center retrospective study with its own limitations, and we hope that it can be carried out in multicenter and larger-scale cases in the future. Second, we only investigated the effect of thyroid cancer on the contralateral TI-RADS 3 and 4 nodules, while TI-RADS 5 nodules did not. This effect may be more significant in TI-RADS 5 nodules. Similarly, because almost all thyroid cancers in our study are papillary cancers, whether this effect of other thyroid cancers may be more significant remains to be studied in the future. Third, our research is lacking in terms of postoperative complications and survival rates. Moreover, there are few studies on the correlation between the scope of surgery and postoperative complications and survival rate. Therefore, we need to do further research on comprehensive management strategies to find a balance between the treatment effect, the risk of postoperative complications, and the economy. It enables timely and appropriate treatment of clinically significant thyroid nodules and does not increase the patient's physical,

Table 5: Pathological types of b-side thyroid cancer in the experimental group.

	Papillary thyroid cancer		Medullary	Follicular	Anaplastic
	Yes*	no			
Experimental group n (%)	38 (45.2)	44 (52.4)	1 (1.2)	0 (0.0)	1 (1.2)

*Thyroid micropapillary carcinoma.

psychological, and economic burdens and cause a waste of medical resources. At the same time, other conservative treatment methods, such as thermal ablation, laser ablation, radiofrequency ablation, and microwave ablation, also provide alternative options.

Finally, the issue of fine-needle aspiration biopsy (FNAB) of thyroid nodules is specifically explained. Many thyroid treatment guidelines recommend FNAB before surgery, but FNAB has a high proportion of insufficient biopsy specimens and indeterminate pathological results. For those patients with insufficient biopsy specimens or indeterminate pathological results, FNAB may need to be performed again. However, some patients may not have clear pathological results after repeated FNAB. In our study, surgeons advised all patients with thyroid nodules to perform FNAB but fully informed them of the pros and cons, and almost all patients refused to perform FNAB. Because of the improvement of surgical techniques, anesthesia, and nursing care, the length of hospital stay has been shortened, which is another reason.

5. Conclusions

In our study, there is no evidence that thyroid cancer affects the malignant risk of the contralateral TI-RADS 3 and 4 nodules.

Data Availability

The data used during the current research are available from the corresponding author on reasonable request.

Disclosure

In order to share their article with other interested researchers, the authors chose the preprint in Research Square, but they disclosed that their article has not been published in other journals.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this article.

Authors' Contributions

HL participated in research design, literature review, data collection and statistical analysis, discussion, and article writing. JJ and QC participated in data collection, analysis, and discussion. ZL participated in research design, analysis, discussion, and review. All authors read and approved the final manuscript.

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Review Article

Long-Term Outcomes of Thermal Ablation for Benign Thyroid Nodules: The Issue of Regrowth

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Thermal ablation (TA) for benign thyroid nodules (BTNs) is widely accepted as an effective and safe alternative to surgery. However, studies on the long-term outcomes of TA have reported problems with nodule regrowth and symptom recurrence, which have raised the need for adequate control of regrowth. Therefore, a more complete TA with a longer-lasting treatment effect may be required. In this study, we review and discuss long-term outcomes and regrowth of BTNs following TA and evaluate factors affecting the long-term outcomes. We also discuss the management of regrowth based on long-term outcomes.

1. Introduction

Thermal ablation (TA) for benign thyroid nodules (BTNs) was introduced in the early 2000s with the clinical application of laser ablation (LA) and radiofrequency ablation (RFA), after which the efficacy and safety of TA were established [1, 2]. Since the 2010s, studies reporting >3 years of follow-up results of LA and RFA have been published [3, 4], and other modalities such as microwave ablation (MWA), bipolar RFA, and high-intensity focused ultrasound (HIFU) have begun to be used for the treatment of BTNs [5–9]. TA has now been widely used not only for the treatment of BTNs, but also for goiter, bilateral tumors, recurrent thyroid cancer, and papillary thyroid microcarcinoma [10–13].

The initially published studies reported relatively short-term follow-up, mainly of around 1 year, and usually considered successful treatment to be that achieving 50% or more volume reduction and symptom resolution [10]. However, with the publication of follow-up results over >2 years, nodule regrowth and symptom recurrence have been reported [14, 15]. Some patients showing recurrence were treated with additional TA, but some underwent surgery, which raises the need for adequate control of regrowth [16, 17]. Therefore, a more complete TA with a longer-lasting treatment effect is required as an alternative to surgery [18].

In this study, we review and discuss long-term outcomes and regrowth of BTNs following TA and evaluate the factors affecting the long-term outcomes. We also discuss the management of regrowth based on long-term outcomes.

2. Consensus of the Term "Long Term"

There is currently no consensus on the definition of "long-term follow-up". Given that regrowth is clinically important after TA, the timing of regrowth can be a determinant of long-term follow-up [19]. According to previous studies, "long-term follow-up" varies from 2 to 5 years [3, 17, 20–23]. However, a meta-analysis and systematic review on the long-term outcomes of TA included studies with follow-up of >3 years [24, 25]. Regrowth is rarely mentioned in papers reporting results up to 1 year but is often mentioned in papers with follow-up periods of >2 years. Several studies reported a regrowth rate of 20% to 30% after RFA and LA, and regrowth appears to occur after 2 or 3 years, depending on the degree of complete treatment of the nodule margin [16, 17, 21, 26–28]. In this context, we suggest that 3 years is appropriate for the description "long term" in respect to the follow-up of BTNs treated with TA.

3. Definition of Regrowth

Various definitions of regrowth have been suggested, including a nodule volume increase of >50% compared with the minimum recorded volume [29, 30], a nodule volume 20% larger than the volume at 1 year after treatment [21], and volume increase over the initial nodule volume [26]. The definition achieving the biggest consensus to date is a nodule volume increase of >50% compared with the minimum recorded volume. We strongly suggest that a definition with full agreement is necessary for the following reasons: (1) standardization of regrowth reporting, (2) validation of regrowth rates, and (3) development of a management plan for patients with regrowth.

Recurrence has been used interchangeably with regrowth [23, 31]; sometimes, it is used to mean that the nodule volume has increased again [4, 14, 32], whereas other times, it is used to mean that the symptom has reappeared [17].

An early sign of regrowth was proposed by Sim et al. [16]. Nodules treated with TA were typically composed of two areas: a centrally located hypoechoic ablated volume (Va) and a peripherally located viable area, which is an undertreated area surrounding the Va. The total nodule volume (Vt) is the sum of the Va and viable area volume (Vv). Vv, which is practically impossible to measure, can be calculated by the formula $Vv = Vt - Va$ (Figure 1). Regrowth is typically the result of the growth of the Vv. However, as Vv is generally small, it has little influence on change in Vt shortly after the procedure, whereas Va has a great influence on change in Vt as it is generally absorbed quickly in the year following TA. Therefore, even if Vv regrowth occurs within 2 years after the procedure, it can be offset by Va absorption. Thus, if Vv is traced separately, then regrowth may be detected earlier, even when Vt is decreasing (Figure 1). A Vv increase may be an early sign of regrowth and can be considered a predicting factor of regrowth; it was reported that a Vv increase precedes regrowth by 1 year [16].

It is worthwhile emphasizing that repeat cytology or biopsy is recommended because nodule regrowth can be a potential sign of overlooked malignancy [4, 19]; however, its value is debatable. Ha et al. [33] revealed that BTNs showing regrowth after RFA did not show cytomorphological alteration or any malignant transformation on biopsy.

4. Factors Related to the Long-Term Outcomes: Nodule Factors

Regrowth from marginal undertreated tissue, which is usually observed 2 or 3 years after the procedure, is closely related to long-term outcomes [34]. The baseline nodule volume influences both the regrowth rate and long-term outcomes [35]. TA can be used for symptomatic and cosmetic improvement of diffuse and/or multinodular goiter, but these uses have a different context from this review [12, 13]. Vascular nodules are resistant to TA because they disperse the input energy [36]. During follow-up, the development of vascularity can lead to regrowth [37]. Nodules with a cystic component and spongiform nodules have a tendency to show a greater volume reduction ratio (VRR) over both the short term [36, 38] and long term [32].

4.1. Baseline Nodule Volume. The baseline nodule volume is a major variable affecting long-term outcomes in respect to achieving a VRR >50% after 1 year, the regrowth rate, and normalization of thyroid function [17, 23]. The results of several studies support this view, with the larger the baseline nodule volume, the higher the regrowth rate and the lower the VRR. Some researchers have argued that there is no correlation between baseline nodule volume and outcomes, but studies making this claim appear to be low in number and present an inferior quality of evidence [21, 26, 32, 39].

Studies finding that the baseline nodule volume is associated with VRR are more numerous. Lim et al. [4] reported that, for nodules with a baseline volume < 10 mL, the final VRR was 94.5% after an average of 1.7 treatments, whereas nodules larger than 20 mL had a final VRR of 88.2% after an average of 3.8 treatments. Their multiple linear regression analysis showed that initial nodule volume ($P < 0.001$) was an independent factor predicting the final VRR. However, appropriate volume reduction can be achieved in larger thyroid nodules through the use of more treatment sessions. Deandrea et al. [23] showed that nodules with a volume < 10 mL were reduced by 82%, whereas nodules with a volume between 10 and 20 mL and those with a volume > 20 mL were reduced by 75% and 65%, respectively.

Bernardi et al. [17] found associations between baseline volume and retreatment; for RFA, a baseline volume of 22.1 mL and a 1 year VRR < 66% predicted retreatment, whereas for LA, a baseline volume of 14.5 mL and a 1 year VRR < 54% predicted retreatment. However, they did not find a clear association between baseline volume and regrowth.

Gambelunghe et al. [35] and Cesareo et al. [40] reported that TA was effective for treating autonomously functioning thyroid nodules, especially when the baseline volume was small and that nodule volume seems to be a significant predictive factor of the efficacy of TA. A meta-analysis also indicated that the baseline nodule volume was associated with the rate of thyroid-stimulating hormone normalization [41].

4.2. Vascularity. Nodule vascularity influences the VRR, regrowth rate, and long-term outcomes [9, 15, 36]. Blood vessels in nodules disperse the heat generated by ablation devices, creating the so-called heat-sink effect [2]. Ahn et al. described the vascularity of marginal viable tissue as a factor influencing volume reduction [42]. Moreover, vascularity is also a factor influencing regrowth [37]. During follow-up, if

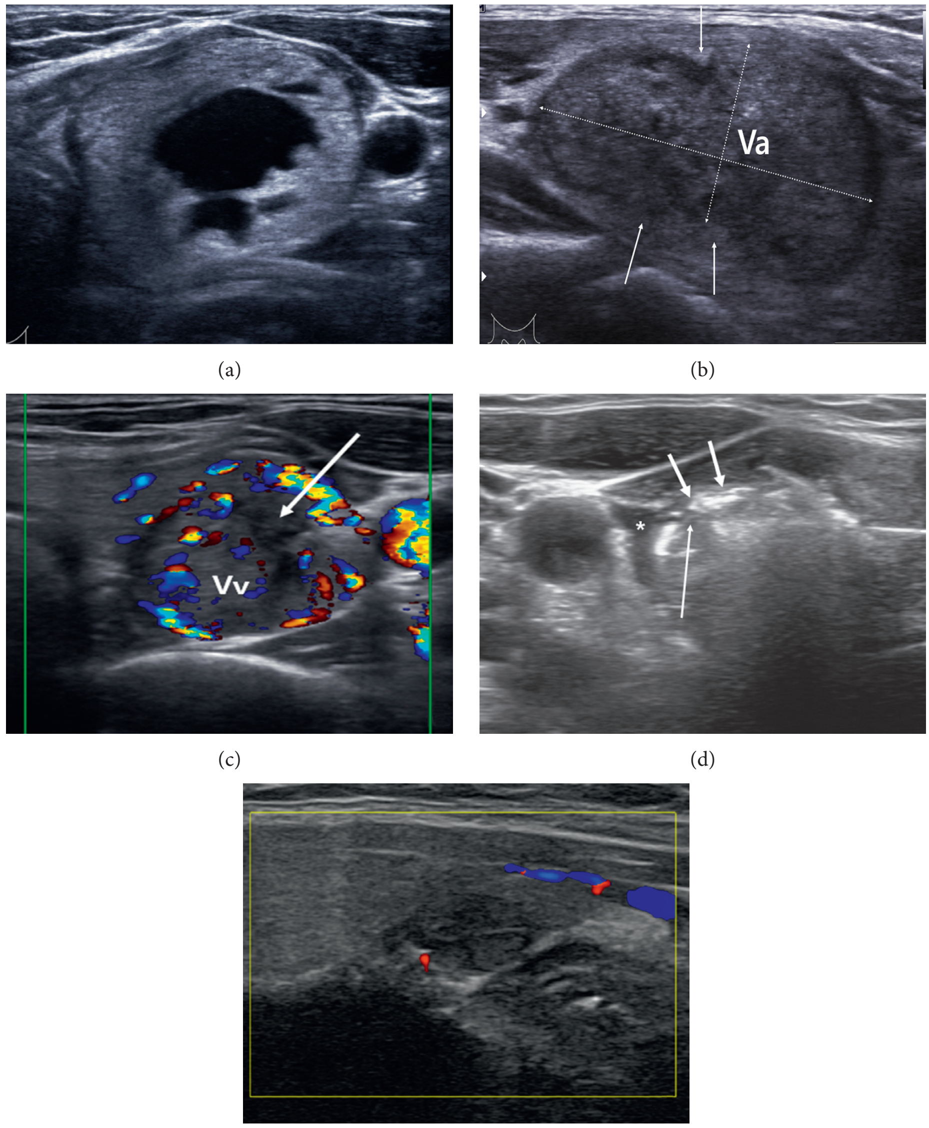

Figure 1: A benign symptomatic thyroid nodule in a 36-year-old female treated with three sessions of radiofrequency ablation (RFA). (a) The nodule was in the patient's left lower lobe. The longest diameter was 4.7 cm, and the volume was 20.6 mL. There was no vascularity in and around the nodule. (b) Longitudinal image of the RFA-treated nodule 1 month after the procedure. The total nodule volume (*Vt*) was reduced to 14.5 mL and the longest diameter to 3.8 cm. The volume reduction ratio was 30%. Ablated tissue located in the central portion of the treated nodule (*Va*) is surrounded by the peripherally located small amount of remaining viable tissue (arrows). The dotted lines indicate the measurements for *Va*, which best represent the volume of the complex and irregularly shaped ablated area. There was no vascularity. At this time, *Va* was 11.2 mL, the viable volume (*Vv*) was 3.2 mL, and the initial ablation ratio was 84%. (c) Color Doppler image of the treated nodule 19 months after the procedure shows the development of vascularity in the nodule. *Vt* had decreased to 6.8 mL, but *Va* (arrow) had regressed to 1.1 mL and *Vv* had increased to 5.7 mL. Such a *Vv* increase is an early sign that can predict regrowth, even while *Vt* is decreasing. As regrowth was expected, the patient received a second RFA in the following month. (d) Thirty-four months after the second RFA, the nodule showed a *Vv* increase again, and a third RFA was performed. Five percent dextrose injected for hydrodissection can be seen as an anechoic area between the nodule margin and carotid sheath (*). The tip of the electrode (long arrow) is located near the veins of the nodule margin to achieve venous ablation. Air bubbles formed by ablation are compactly filling the venous lumen (arrows). (e) Ten months after the third RFA, the nodule had turned into a small scar-like region of tissue without vascularity. The *Vt* was 0.4 mL with no demonstrable *Vv*.

a nodule shows or develops vascularity, it has considerable potential for regrowth [14, 43]. Yan et al. reported that vascularity was an independent factor associated with regrowth [36], and Wang et al. reported that a patient group showing regrowth demonstrated more vascularity than a nonregrowth group [44].

5. Factors Related to Long-Term Outcomes: Technical Factors

Long-term outcomes differ depending on the modality used [24] and the energy delivered [17]. As it is not possible to ablate all nodule tissues in a single session of TA, a better long-term outcome can be achieved by applying a multiple-session treatment strategy [18]. Recently, techniques targeting the margin control have been introduced [9].

5.1. TA Modalities. Most studies comparing modalities report that VRR is influenced by the TA modality [45–47]. Although LA and RFA are generally known to be very effective and safe, prospective studies comparing them are currently limited. A randomized open-label parallel trial comparing LA with RFA at 6 months was reported. In this study, Cesareo et al. [45] concluded that RFA achieved a larger nodule volume reduction than LA. However, Mauri et al. [48] reported that RFA and LA are similarly feasible, safe, and effective for treating BTNs. RFA is faster than LA but requires significantly higher energy. In a Bayesian network meta-analysis, RFA achieved better VRR than LA (77.8% vs. 49.5%) [47]. Two meta-analyses and systematic reviews that compared the long-term outcomes of RFA and LA reported that the final VRR of RFA was higher, at 92.2% vs. 43.3% at 3 years or more and 87% vs. 44% at 3 years [24, 25]. The Italian minimally invasive treatments of the thyroid group reported that both RFA and LA resulted in significantly reduced nodule volume but that RFA was superior to LA [17].

Ha et al. [47] and Cho et al. [24] claimed that the difference between RFA and LA in the final VRR depends on whether marginal undertreated tissue is controlled. RFA uses a moving-shot technique with internally cooled electrodes. Because of its high maneuverability, this device can ablate marginally located nodule tissue as much as possible while minimizing thermal damage to surrounding tissues [2, 49]. By contrast, with the laser delivery fibers used in LA, ablation of the margin may be incomplete because the range of treatment is concentrated in the center of the nodule [26].

There are reports of LA outperforming RFA at 1 year follow-up. In a propensity score matching analysis, Pacella et al. [50] showed mean nodule reduction at 12 months of 70% ± 19% in an LA group vs. 62% ± 22% in an RFA group. They mentioned that the operator's skills could be crucial in determining the extent of nodule volume reduction, regardless of the technique used. Ben Hamou et al. [51] reported that the nodule volume had significantly decreased by 75.0% in an RFA group and 83.9% in an LA group at 18 months.

MWA and HIFU have only recently begun to be used, and long-term follow-up results are, therefore, rare. Monpeyssen et al. reported a VRR after HIFU of 33.3% at 2 years and 31.9% at 3 years [52], while Lang et al. [31] and Trimboli et al. [53] reported an average VRR at 2 year follow-up of 70.4% and 43.3%, respectively. HIFU has the advantage of being a truly noninvasive technique that does not require the insertion of electrodes or fibers through the patient's skin [52] but has the disadvantage of requiring a deeper anesthesia or sedation level because it is more painful than RFA or LA [54]. To our knowledge, there has been no report of the results of MWA or BTNs after >2 years of follow-up. Articles comparing the efficacy of RFA and MWA after a 1 year follow-up period reported that the results were similar [46, 55].

5.2. Energy Delivered. Another factor affecting long-term outcomes is the energy delivered. Bernardi et al. [17] reported that RFA with a cutoff of 1360 J/mL predicted VRR > 50% and RFA with a cutoff of 918 J/mL predicted retreatment. Trimboli et al. [56] found that the energy delivered was significantly correlated with VRR in nodules < 10 mL at 1 year, and Deandrea et al. [57] demonstrated that delivering 756 J/mL and 2670 J/mL gave a probability of VRR > 50% in 50% and 99% of patients, respectively, at 1 year.

5.3. Multiple-Session Ablation. Additional VRR is gained through multiple-session treatment [4]. However, sufficient effects can be obtained only when the method and timing of the additional treatment are selected appropriately [16, 47]. Huh et al. reported a randomized trial comparing single-session vs two-session RFA for benign nodules. Their results showed that single-session RFA achieved significant volume reduction and a satisfactory clinical response in most patients, but that additional RFA was effective in patients with a large nodule (>20 mL) or unresolved clinical problems [58]. Deandrea et al. reported no VRR gain from one or two lots of additional LA [3]. In a systematic review and meta-analysis of the efficacy of TA for benign nonfunctioning solid thyroid nodules, Trimboli et al. reported no significant difference in VRR between single- and multiple-session LA [25].

However, contrasting results have also been reported. Lim et al. achieved >90% VRR after 4 years through multiple-session RFA [4], and in their meta-analyses and systematic reviews, Ha et al. and Cho et al. found that the long-term VRRs of RFA were higher than those of LA. The authors argued that the reason the final VRR of RFA was higher is that it could effectively control marginally located viable tissue with multiple-session treatment [24, 47].

As in the report of Huh et al., when a nodule is large or clinical problems are not resolved, additional ablation gains further efficacy [58]. From our point of view, the differences in reported results are based on whether marginal undertreated tissue could be effectively controlled or not, and the main reason for differences in efficacy is the maneuverability of the device.

5.4. Recently Introduced Techniques for Margin Control. For it to be a comparable alternative to surgery, TA has to achieve sustainable efficacy, such as life-long problem resolution. For this, some advanced techniques were recently introduced [59]. Park et al. proposed an advanced RFA technique to control marginal regrowth that they named vascular ablation. Two different vascular ablation techniques are available: artery-first ablation and marginal venous ablation. The artery-first ablation technique can be applied to hypervascular thyroid nodules with a prominent feeding artery. However, the marginal venous ablation technique is useful for most thyroid nodules because thyroid nodules usually have marginal draining veins [9]. Offi et al. reported that the VRR of RFA after ablation of the feeding artery was higher than that of RFA using the conventional technique [36].

Hydrodissection is another important technique for improving safety during margin ablation. Injecting 5% dextrose between the nodule margin and the surrounding tissues can create a space that helps in achieving complete ablation of marginal nodule tissue (Figure 1) [9].

6. Conclusions

TA for BTNs is effective and safe according to the reports of short-term follow-up studies, but as long-term outcomes have been announced, it is becoming evident that the problem of regrowth is important. We should understand that regrowth from marginal undertreated tissue is frequently reported 2–3 years after TA. To minimize regrowth, complete ablation of the nodule margin using advanced techniques and an understanding of the influencing factors are necessary. In patients with large nodules or incompletely resolved clinical symptoms, additional treatment is required to achieve a long-term satisfactory effect. We hope that this review may help establish TA as a long-lasting treatment method with comparable outcomes to surgery in clinical practice.

Data Availability

The data used to support the findings of this study are included within the article.

Conflicts of Interest

Jung Hwan Baek has been a consultant to two radiofrequency companies, STARmed and RF Medical, since 2017. Jung Suk Sim has nothing to declare.

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