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Ablation therapy using a low dose of radioiodine may be sufficient in low- to intermediate-risk patients with follicular variant papillary thyroid carcinoma

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Abstract

Objectives: Follicular variant papillary thyroid carcinoma (FVPTC) is treated similarly to classical variant papillary thyroid carcinoma (cPTC). However, FVPTC has unique tumour features and behaviours. We investigated whether a low dose of radioiodine was as effective as a high dose for remnant ablation in patients with FVPTC and evaluated the recurrence of low-intermediate risk FVPTC.

Methods: Data from cPTC and FVPTC patients treated with I-131 from 2004 to 2014 were reviewed. Demographics, tumour behaviour, lymph node metastasis, and local recurrence data were compared between FVPTC and cPTC patients. Then, low-intermediate risk FVPTC patients were divided into low, intermediate, and high I-131 dose groups, and postoperative I-131 activities were analysed to evaluate the effectiveness of I-131 therapy for thyroid remnant ablation.

Results: In total, 799 cases of FVPTC (n = 168) and cPTC (n = 631) treated with I-131 were identified. Patients with FVPTC had a larger primary nodule size than cPTC, but lymph node metastases and local recurrence were more prevalent in cPTC than in FVPTC. For the low-, intermediate-, and high-dose groups, success rates of ablation did not differ (82.0%, 80%, and 81.3%, respectively).

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Conclusion: FVPTC differs from cPTC in behaviour. Low-dose ablation may be sufficient in FVPTC patients with low-intermediate disease risk.

Keywords
Follicular variant papillary thyroid carcinoma, classical variant papillary thyroid carcinoma, radioactive iodine, nuclear medicine, thyroid cancer, remnant ablation

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Introduction

Follicular variant papillary thyroid carcinoma (FVPTC) is a subtype of papillary thyroid carcinoma (PTC), and approximately 23% to 41% of well-differentiated thyroid carcinomas are FVPTC.[1–3] FVPTC can have distinct clinical behaviours and long-term outcomes compared with classical variant PTC (cPTC).[4] Initially, some studies found that FVPTC had more distant metastases than cPTC.[3,5,6] Researchers have also shown that FVPTC has a larger mean tumour size, less opportunity for thyroid capsule invasion, less extrathyroidal extension, fewer lymph node metastases, and a higher local recurrence rate than cPTC during follow-up, and that FVPTC and cPTC have similar disease-specific mortalities.[3,4,6,7] These studies suggest that FVPTC represents an intermediate entity, with clinical features between those of cPTC and follicular thyroid carcinoma (FTC). Like cPTC, FVPTC is currently treated with I-131 after total thyroidectomy if adjuvant treatment is necessary.

Based on the 2015 American Thyroid Association (ATA) guidelines, low-risk differentiated thyroid carcinoma (DTC) patients are not routinely recommended to receive radioactive iodine (RAI). If RAI remnant ablation is performed after total thyroidectomy for ATA low-risk thyroid cancer, a low dose [1110 MBq (30 mCi)] is recommended instead. Intermediate-risk patients should undergo RAI treatment.[8] If necessary, high-dose RAI [5500 MBq (150 mCi)] is considered for adjuvant therapy. Compared with high-dose RAI therapy, low-dose RAI is less expensive and causes fewer side effects. A low RAI dose (30 mCi) is sufficient for remnant ablation, but the results are controversial. The clinical behaviour of FVPTC is unique, and FVPTC has less aggressive characteristics than cPTC. The aim of this study was to determine what dose of RAI is sufficient for remnant ablation in FVPTC. We retrospectively assessed the efficacy of I-131 therapy between FVPTC and cPTC groups that received different doses of RAI for thyroid remnant ablation after total thyroidectomy in low-intermediate risk groups.

Materials and methods

Patients

All patients who underwent total thyroidectomy, cervical lymph node dissection, and RAI at Tianjin Medical University General Hospital in China, and at New York Presbyterian Hospital–Weill Cornell Medicine in the United States from January 2004 to December 2014 were included. Data were obtained through a retrospective review of records and underwent post hoc stratification using the 2015 ATA guidelines.[6,9] Inclusion criteria were (1) diagnosed with DTC on pathologic examination, (2) underwent postoperative RAI therapy, and (3) received thyroid hormone

suppressive. Exclusion criteria were (1) follow-up time of less than 1 year, or (2) diagnosed with aggressive PTC or FTC.

A total of 1021 patients were initially included; 129 patients were excluded for follow-up times of less than 1 year, and 93 patients were excluded for aggressive PTC or FTC. A total of 799 patients, including 168 patients with FVPTC and 631 patients with cPTC, were analysed. In a second analysis, 139 patients with low- to intermediate-risk FVPTC were included. The protocol of this study was approved by New York Presbyterian Hospital–Weill Cornell Medicine (New York, NY, USA) and Tianjin Medical University General Hospital Ethics Committee (Tianjin, China), and this study was conducted according to the guidelines outlined in the Declaration of Helsinki. All patients provided written informed consent before the start of the study.

RAI therapy

Within 6 months after total thyroidectomy, all patients received RAI remnant ablation. All patients routinely prepared with a low-iodine diet and recombinant human TSH (rhTSH; Thyrogen, Genzyme Therapeutics, Cambridge, MA, USA) or levothyroxine withdrawal. The RAI ablation treatment criteria included tumours of any size with lymph node metastasis or microscopic or macroscopic extrathyroidal extension. RAI ablation was considered appropriate only when the thyroid stimulating hormone (TSH) level measured immediately before therapy was >30 μIU/mL.[8,10] Only the initial postoperative dose of RAI was considered in the primary analysis.

Response to therapy and follow-up

The patients were followed every 6 to 12 months with neck ultrasounds and measurement of serum thyroglobulin (Tg) levels. New York Presbyterian Hospital–Weill Cornell Medicine used an IBL-America test kit (Minneapolis, MN, USA) to measure Tg (normal level: 1.4–29.2 ng/mL) and thyroglobulin antibodies (TgAb; normal level: <40 IU/mL). Tianjin Medical University General Hospital used a Siemens (Munich, Germany) enzyme immunoassay kit to measure Tg (normal level of Tg: <50 ng/mL) and TgAb (normal level: <40 IU/mL). Time to follow-up was defined as the interval between the date of surgery and the date of the last follow-up record. Medical records were reviewed for age, sex, histopathologic features, lymph node metastasis, local recurrence, distant metastasis, and mortality during follow-up. Successful ablation was defined as the absence of remnant thyroid tissue (no visible accumulation) with I-131 in the thyroid bed and in the cervical region on the whole-body scan and an undetectable serum Tg level (<0.2 ng/mL) when TSH was >30 μIU/mL.[11] Ultrasound findings of the neck that did not show remnant tissue and abnormal lymph nodes were used as additional criteria.

Patients who had lymph node recurrence or lymph node metastasis were usually identified by neck ultrasound, computed tomography (CT), I-131 scan (single-photon-emission computed tomography/CT; SPECT/CT) or positron emission tomography (PET)-CT and confirmed by pathological inspections of neck fine needle biopsy and surgical specimens. Recurrent disease was defined as a serum Tg level that increased by more than 20%, or positive imaging findings on the ultrasound of the neck region, I-131 whole-body scan, PET-CT, or confirmation of pathology upon second surgery.[8,12] Distant metastases were generally confirmed by chest CT, I-131 scans (SPECT/CT), and PET/CT findings.[13,14]

Statistical analysis

Data analysis was carried out using SPSS software (version 22.0; IBM Corp., Armonk, NY, USA). Categorical data were described in terms of mean ± standard deviation, and Student's *t*-test and chi-square tests were performed. To evaluate significant differences in the type of operation, we analysed 2×5 (2×3) contingency tables using Fisher's exact tests. *P*-values <0.05 were considered statistically significant.

Results

Characteristics of patients with FVPTC and cPTC

A total of 799 patients with cPTC and FVPTC were included in the study. The demographics, clinicopathologic features, and treatment are compared in Table 1. Patients with FVPTC (56 years) were older than patients with cPTC (52 years) ($P < 0.01$). More patients with FVPTC (47.6%) belonged to the low-risk group and fewer to the intermediate- (35.1%) and high- (17.3%) risk groups compared with patients with cPTC (33.4%, 46.8%, and 19.8%, respectively) ($P < 0.01$). The mean size of the primary tumour of FVPTC was approximately 2.81 cm, larger than that of cPTC (1.5 cm) ($P < 0.05$). The incidence of pathologically confirmed lymph node metastases was 26% in FVPTC, lower than the rate in cPTC (36%) ($P < 0.01$). The sex distribution, rates of multiple focal malignant nodules, bilateral malignant nodules, extrathyroidal extension, and local recurrence were similar between FVPTC and cPTC patients. However, the rate of local recurrence was significantly lower for FVPTC than for cPTC: 1.2% versus 6% ($P < 0.01$). No difference was observed in the number of distant metastases between patients with FVPTC and cPTC.

Clinical findings between different RAI doses

A total of 139 low-intermediate risk FVPTC patients were included in the analysis. According to their RAI dose, patients with FVPTC were divided into three groups: (1) RAI dose ≤1850 MBq (<50 mCi); (2) RAI dose between 1850 and 3700 MBq (50–100 mCi); and (3) RAI dose >3700 MBq (>100 mCi). There were no statistically significant differences in age, sex, risk levels, primary nodule size, presence of lymph node metastasis, multiple focal malignant nodules, bilateral malignant nodules, or extrathyroidal extension between the different RAI dose groups. After application of I-131, local recurrence and disease-free survival rates did not differ significantly between patients receiving the low, intermediate, and high doses (Table 2 and Figure 1).

Factors associated with ablation success in patients with FVPTC

To analyse factors associated with successful ablation in FVPTC patients, all FVPTC patients were divided into two groups based on ablation results. Follow-up after RAI ablation was performed within 6 months of total thyroidectomy. The rate of initial successful ablation was 82.0% in all low- to intermediate-risk FVPTC patients. Ablation was considered successful in 80%, 81.3%, and 83.6% of patients who received the low, intermediate, and high dose of I-131; ablation success did not differ significantly between RAI dose groups. The clinical data demonstrated that all factors among patients with successful and unsuccessful ablation (sex, risk level, primary nodule size, Tg and TgAb levels, presence of lymph node metastasis,

Table 1. Baseline characteristics of patients with follicular variant of papillary thyroid carcinoma (FVPTC) and classical variant papillary thyroid carcinoma (cPTC).

Characteristic	FVPTC	cPTC	*P*-value
Number of patients	168	631	
Age (years)	55.88 ± 13.71	52.38 ± 13.35	0.003
Female	126 (75%)	480 (76.1%)	0.762
Male	42 (25%)	151 (23.9%)	
Low risk[1]	80 (47.6%)	211 (33.4%)	0.003
Intermediate risk[2]	59 (35.1%)	295 (46.8%)	
High risk[3]	29 (17.3%)	125 (19.8%)	
Primary nodule size (cm)	2.81 ± 9.06	1.50 ± 1.11	0.013
Lymph node metastasis present	0.26 ± 0.31	0.36 ± 0.33	0.005
Multiple-focal malignant nodule			
Yes	77 (45.8%)	282 (44.7%)	0.794
No	91 (54.2%)	349 (55.3%)	
Bilateral malignant nodule			
Yes	61 (36.3%)	250 (39.6%)	0.477
No	107 (63.7%)	381 (60.4%)	
Microscopic extrathyroidal extension			
Yes	33 (19.6%)	116 (18.4%)	0.738
No	135 (80.4%)	515 (81.6%)	
Metastasis			
Yes	9 (5.4%)	45 (6.8%)	0.492
No	159 (94.6%)	586 (93.2%)	
Local recurrence			
Yes	2 (1.2%)	38 (6%)	0.008
No	166 (98.8%)	593 (94%)	
Tg level before RAI[4] (ng/mL)	43.47 ± 5.31	54.21 ± 2.51	0.687
TgAb level before RAI[4] (IU/mL)	48.40 ± 237.30	26.48 ± 120.56	0.315

[1]Papillary thyroid cancer (with all of the following): no local or distant metastases; all macroscopic tumour has been resected; no tumour invasion of loco-regional tissues or structures; the tumour does not have aggressive histology (e.g., tall cell, hobnail variant, columnar cell carcinoma). If ^{131}I is given, there are no radioactive iodine (RAI)-avid metastatic foci outside the thyroid bed on the first posttreatment whole-body RAI scan. No vascular invasion. Clinical N0 or <5 pathologic N1 micro metastases (<0.2 cm in largest dimension). Intrathyroidal, encapsulated follicular variant of papillary thyroid cancer. Intrathyroidal, well-differentiated follicular thyroid cancer with capsular invasion and no or minimal (<4 foci) vascular invasion. Intrathyroidal, papillary microcarcinoma, unifocal or multifocal, including $BRAF^{V600E}$ mutated (if known).

[2]Microscopic invasion of tumour into the perithyroidal soft tissues. RAI-avid metastatic foci in the neck on the first posttreatment whole-body RAI scan. Aggressive histology (e.g., tall cell, hobnail variant, columnar cell carcinoma). Papillary thyroid cancer with vascular invasion. Clinical N1 or >5 pathologic N1 with all involved lymph nodes <3 cm in largest dimension. Multifocal papillary microcarcinoma with extrathyroid infiltration and $BRAF^{V600E}$ mutated (if known).

[3]Macroscopic invasion of tumour into the perithyroidal soft tissues (gross extrathyroid infiltration). Incomplete tumour resection. Distant metastases. Postoperative serum thyroglobulin suggestive of distant metastases. Pathologic N1 with any metastatic lymph node ≥3 cm in largest dimension. Follicular thyroid cancer with extensive vascular invasion (>4 foci of vascular invasion).

[4]Thyroglobulin (Tg) and Tg antibody (TgAb) levels were measured after Thyrogen or levothyroxine withdrawal therapy.

multiple focal malignant nodules, bilateral malignant nodules, and extrathyroidal extension) were similar before RAI treatment. After RAI, patients in the successful group had a lower Tg value than those in the unsuccessful group ($P < 0.05$). There was no significant difference in the response to different RAI ablation doses between the

Table 2. Comparison of patients with follicular variant of papillary thyroid carcinoma (FVPTC) with low (<1850 MBq), intermediate (1850–3700 MBq), or high doses (>3700 mBq) of radioactive iodine therapy.

	FVPTC			
	Low dose	Intermediate dose	High dose	*P*-value
Number of patients	25	59	55	
Age (years)	58.56 ± 14.74	56.54 ± 13.37	54.36 ± 12.08	0.389
Female	20 (80%)	43 (72.9%)	44 (80%)	0.615
Male	5 (20%)	16 (27.1%)	11 (20%)	
Low risk	18 (72%)	31 (52.5%)	31 (56.4%)	0.25
Intermediate risk	7 (28%)	28 (47.5%)	24 (43.6%)	
Primary nodule size (cm)	1.93 ± 1.32	1.75 ± 0.94	2.19 ± 1.94	0.436
Lymph node metastasis present	0.13 ± 0.29	0.23 ± 0.28	0.29 ± 0.34	0.267
Multiple-focal malignant nodule				
Yes	11 (44%)	21 (35.6%)	25 (45.5%)	0.533
No	14 (56%)	38 (64.4%)	30 (54.5%)	
Bilateral malignant nodule				
Yes	8 (32%)	17 (28.8%)	19 (34.5%)	0.805
No	17 (68%)	42 (71.2%)	36 (65.5%)	
Microscopical extrathyroidal extension				
Yes	3 (12%)	2 (3.4%)	7 (12.7%)	0.167
No	22 (88%)	57 (96.6%)	48 (87.3%)	
Local recurrence				
Yes	0	3 (5.1%)	3 (5.5%)	0.5
No	25	56 (94.9%)	52 (94.5%)	
Median life (months; range)	61 (12–152)	60 (12–144)	63 (12–150)	
Tg level before RAI[1] (ng/mL)	7.14 ± 9.79	10.03 ± 13.58	8.91 ± 12.23	0.38
TgAb level before RAI[1] (IU/mL)	42.39 ± 118.04	12.70 ± 62.02	15.64 ± 57.65	0.219
Tg level after RAI (ng/mL)	0.26 ± 0.56	0.75 ± 2.32	0.93 ± 2.66	0.615
TgAb level after RAI (IU/mL)	24.44 ± 92.84	11.29 ± 10.33	14.87 ± 58.15	0.839
Follow date	66.84 ± 42.39	65.27 ± 30.83	61.35 ± 31.02	0.734

[1]Thyroglobulin (Tg) and Tg antibody (TgAb) levels were measured after Thyrogen or levothyroxine withdrawal therapy. RAI, radioactive iodine.

two groups. The responses to RAI ablation are shown in Table 3.

Discussion

Current opinions regarding the clinical behaviour and prognosis of FVPTC compared with cPTC are controversial. Most studies have indicated that FVPTC has less aggressive clinical behaviour and a lower incidence of extrathyroidal extension and lymph node metastasis than cPTC. A large-scale population-based study in 2013 and a retrospective study in 2016 revealed that FVPTC patients had a lower incidence of extrathyroidal extension and lymph node metastasis than cPTC patients.[3,6] However, during follow-up, disease-specific mortality did not differ significantly between FVPTC and cPTC patients.[3,6,7] Some studies have suggested that the rate of distant metastasis of FVPTC is higher than that of cPTC,[3,15] whereas others have found no significant difference between the two groups.[6,7] In this study, we did not observe any difference in the rate of metastases between patients with FVPTC and cPTC. Our data

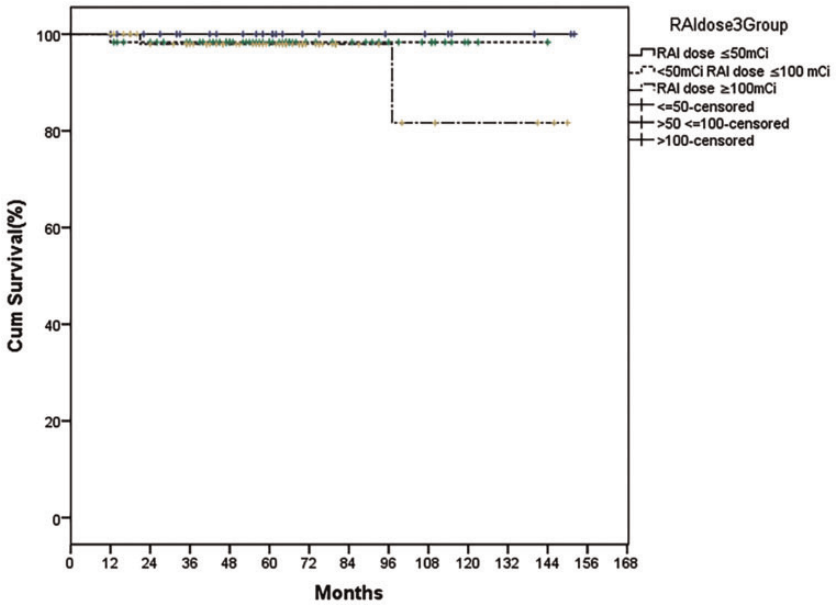

Figure 1. Disease-free survival curve. Kaplan–Meier estimates for cumulative (Cum) disease-free survival in three groups of patients: treated with a low (<1850 MBq, 50 mCi), intermediate (1850–3700 MBq, 50–100 mCi), or high dose (>3700 mBq, >100 mCi) of radioactive iodine (RAI; I-131) ($P = 0.448$ between cPTC and FVPTC, by log-rank test).
PTC, papillary thyroid carcinoma; FVPTC, follicular variant papillary thyroid carcinoma.

also showed that FVPTC patients had a lower risk for local recurrence and larger primary tumours (in terms of mean size) than cPTC patients, which agrees with results of previous studies.[3,6] Previous data revealed that FVPTC has less thyroid capsule invasion, less extrathyroidal extension, fewer lymph node metastases, and fewer bilateral malignant nodules than cPTC.[3,6,7] According to our data and previous studies, FVPTC has unique tumour features and behaviour. The molecular profiles of FVPTC and cPTC tumours also differ. Encapsulated FVPTC has fewer *BRAF* mutations than infiltrated FVPTC, which is a more aggressive phenotype. Microarray expression analysis identified the *CD14*, *CD74*, and *DPP6* genes as being significantly associated with FVPTC morphology compared with cPTC.[16,17]

Post-thyroidectomy RAI therapy is suggested for DTC. RAI has long been used for adjuvant therapy, remnant ablation, and the treatment of metastatic disease in DTC patients. Tg is a more reliable marker than other thyroid blood test markers. Post-operative, TSH-stimulated serum Tg is recognised as an indicator of remnant thyroid tissue when residual or recurrent disease and metastases have been excluded. Some studies have indicated that a combination of radioactive iodine uptake and Tg concentration can be helpful in characterising thyroid remnants and predicting optimal activity for successful RAI ablation,[18] and 1.1 GBq of I-131 is sufficient for post-operative ablation in patients with low-risk thyroid cancer.[19]

To date, few studies have demonstrated that low-dose RAI ablation provides

Table 3. Factors associated with the successful ablation in patients with follicular variant of papillary thyroid carcinoma (FVPTC).

	Ablation result		
	Unsuccessful	Successful	*P*-value
RAI dose $\leq$50 mCi	5 (20%)	20 (80%)	0.912
50 mCi $<$ RAI dose $\leq$100 mCi	11 (18.7 %)	48 (81.3%)	
RAI dose $\geq$100 mCi	9 (16.4%)	46 (83.6%)	
Number of patients	25	114	
Age (years)	55.16 $\pm$ 13.03	60.08 $\pm$ 13.05	0.096
Female	20 (80%)	87 (76.3%)	0.798
Male	5 (20%)	27 (23.7%)	
Low risk	14 (56%)	66 (57.9%)	1.0
Intermediate risk	11 (44%)	48 (42.1%)	
Primary nodule size (cm)	1.9 $\pm$ 1.29	2.01 $\pm$ 1.89	0.854
Lymph node metastasis (%)	0.22 $\pm$ 0.30	0.27 $\pm$ 0.33	0.569
Multiple focal malignant nodule			
Yes	9 (36%)	48 (42.1%)	0.657
No	16 (64%)	66 (57.9%)	
Bilateral malignant nodule			
Yes	6 (24%)	38 (33.3%)	0.478
No	19 (76%)	76 (66.7%)	
Extrathyroidal extension			
Yes	2 (8%)	10 (8.8%)	1.00
No	23 (92%)	104 (91.2%)	
Local recurrence			
Yes	1 (4%)	5 (4.4%)	1.0
No	24 (96%)	109 (95.6%)	
Tg level before RAI[1] (ng/mL)	8.45 $\pm$ 11.38	10.50 $\pm$ 15.29	0.599
TgAb level before RAI[1] (IU/mL)	23.03 $\pm$ 81.11	27.75 $\pm$ 60.63	0.660
Tg level after RAI (ng/mL)	2.83 $\pm$ 3.78	0.01 $\pm$ 0.02	0.000
TgAb level after RAI (IU/mL)	18.87 $\pm$ 72.46	21.52 $\pm$ 82.92	0.872

[1]Thyroglobulin (Tg) and Tg antibody (TgAb) levels were measured after Thyrogen or levothyroxine withdrawal therapy.
RAI, radioactive iodine.

sufficient treatment for low- to intermediate-risk patients with FVPTC. Rather, studies have consistently shown that RAI can improve overall and recurrence-free survival among patients with DTC.[8,20,21] However, high-dose RAI ablation can lead to many side effects, including dry mouth, swelling and tenderness of the salivary glands, and reduction in tear production.[22–25] All medical treatments should consider the risks versus benefits. Low-dose RAI results in less radioiodine exposure, less potential for side effects, reduced financial cost incurred by the health service provider, and reduced environmental exposure to I-131 compared with high-dose RAI. High-risk patients with PTC are generally at risk for recurrence foci and distant metastases and receive high-dose RAI; thus, to minimise selection bias, only low- and intermediate-risk patients were included in this study. Some researchers have hypothesised that even though high doses increase the

number of side effects, undesirable outcomes after low-dose therapy may result in repeated administration of I-131 and a higher cumulative I-131 dosage, which would be a cause for concern.[26] In contrast, other studies have shown that low doses of RAI can provide similar rates of remnant ablation and adjuvant therapy in low- and intermediate-risk patients without adversely affecting recurrence rates or mortality.[27,28] Previous studies have reached conflicting conclusions regarding the dose of RAI required for thyroid remnant ablation in PTC. In the clinic, different I-131 ablative doses are currently used in different medical centres. However, FVPTC has been shown to have distinct tumour features and behaviours from cPTC. Therefore, the question remains whether low-dose RAI is sufficient for successful remnant ablation in FVPTC.

Here, we retrospectively analysed the efficacy of different RAI doses to treat FVPTC patients. Overall, the results showed that low- or intermediate-dose RAI therapy achieved the same efficacy as high-activity treatment according to our median 5-year follow-up results. The patients in the three RAI dose groups had similar pretreatment states. Among the 139 patients with low- to intermediate-risk FVPTC, no significant differences were observed in recurrence rate with different doses of RAI, similar to findings of other studies with low- to intermediate-risk PTC patients. Several studies suggest that the results of the thyroid remnant ablation and the response to therapy did not differ significantly between low- and high-dose groups in the treatment of low- or intermediate-risk patients with DTC.[29–32] We also calculated factors associated with successful ablation in FVPTC patients. The data indicated that all factors were similar among successful and unsuccessful ablation groups, including sex, risk level, primary nodule size, Tg level, presence of lymph node metastasis, multiple focal malignant nodule, bilateral malignant nodule, and extrathyroidal extension before RAI for low- to intermediate-risk FVPTC patients. Currently, few studies have reported outcomes for RAI treatment in patients with FVPTC. The 2015 ATA guidelines recommend that if RAI is used for remnant ablation, a dose of 30 mCi is preferred over higher doses.[8] Additionally, some authors have concluded that a low dose of radioiodine is as effective as a high dose of radioiodine for ablation of the thyroid remnant after total thyroidectomy for low-risk DTC.[33–35]

Several factors are associated with unsuccessful RAI ablation, but in most studies, only lymph node recurrence was a significant factor.[36] In this research, in addition to lymph node recurrence, we found persistent positive Tg value and some false positive I-131 imaging, like thyroglossal duct cyst and thymoma uptaking I-131, all led to multiple RAI.

The present study has some limitations. We reviewed the outcomes of therapy in 139 nonrandomised patients in a retrospective study. This research excluded patients with high-risk features (e.g., distant metastasis). The final decision on RAI dose was made by physicians in different medical centres. Therefore, potential selection bias occurred regarding RAI therapy.

Conclusion

FVPTC has less aggressive clinical behaviour than cPTC. Low-dose ablation may be sufficient in FVPTC patients with low-intermediate risk disease after total thyroidectomy.

Author contributions

Wei Li designed the study and wrote the manuscript; Fuxin Li, Rasa Zarnegar, and Katherine D. Gray collected and analysed the clinical data; Dan Wang performed pathology review; and Thomas J. Fahey reviewed and edited the

manuscript. All authors read and approved the manuscript.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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