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

Fuxin Li¹*, Wei Li²*, Katherine D. Gray⁴, Rasa Zarnegar⁴, Dan Wang³ and Thomas J. Fahey III⁴

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).

¹Department of Surgery, Tianjin Medical University General Hospital, Tianjin, China
²Department of Nuclear Medicine, Tianjin Medical University General Hospital, Tianjin, China
³Department of Pathology, Tianjin Medical University General Hospital, Tianjin, China
⁴New York Presbyterian Hospital–Weill Cornell Medicine Department of Surgery, New York, USA

*These authors contributed equally to this work.

Corresponding author:
Wei Li, Tianjin Medical University General Hospital, Department of Nuclear Medicine, Anshan Road 154, 300052, Tianjin, China.
Email: liwei01@tmu.edu.cn
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

Date received: 21 March 2020; accepted: 24 September 2020

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 $>30 \, \mu\text{IU/mL}$. 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: $<40 \, \text{IU/mL}$). Tianjin Medical University General Hospital used a Siemens (Munich, Germany) enzyme immunoassay kit to measure Tg (normal level of Tg: $<50 \, \text{ng/mL}$) and TgAb (normal level: $<40 \, \text{IU/mL}$). 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 ($<0.2 \, \text{ng/mL}$) when TSH was $>30 \, \mu\text{IU/mL}$.

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. Distant metastases were generally confirmed by chest CT, I-131 scans (SPECT/CT), and PET/CT findings.
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,
multiple focal malignant nodules, bilateral malignant nodules, and extrathyroidal extension) were similar before RAI treat-
ment. 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

| Characteristic                                      | FVPTC   | cPTC    | $P$-value |
|-----------------------------------------------------|---------|---------|-----------|
| Number of patients                                  | 168     | 631     | 0.003     |
| 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 parathyroidal 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.
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. However, during follow-up, disease-specific mortality did not differ significantly between FVPTC and cPTC patients. Some studies have suggested that the rate of distant metastasis of FVPTC is higher than that of cPTC, whereas others have found no significant difference between the two groups. In this study, we did not observe any difference in the rate of metastases between patients with FVPTC and cPTC. Our data

---

**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 | FVPTC Intermediate dose | FVPTC 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 (94.9%)      |         |
| 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   | 0.734   |

$^1$Thyroglobulin (Tg) and Tg antibody (TgAb) levels were measured after Thyrogen or levothyroxine withdrawal therapy. RAI, radioactive iodine.
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,\(^{18,19}\) 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
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

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 ≤50 mCi | 5 (20%) | 20 (80%) | 0.912   |
| 50 mCi < RAI dose ≤100 mCi | 11 (18.7%) | 48 (81.3%) | |
| RAI dose ≥100 mCi | 9 (16.4%) | 46 (83.6%) | |
| Number of patients | 25 | 114 | |
| Age (years) | 55.16 ± 13.03 | 60.08 ± 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 ± 1.29 | 2.01 ± 1.89 | 0.854 |
| Lymph node metastasis (%) | 0.22 ± 0.30 | 0.27 ± 0.33 | 0.569 |
| Multiple focal malignant nodule | 9 (36%) | 48 (42.1%) | 0.657 |
| No | 16 (64%) | 66 (57.9%) | |
| Bilateral malignant nodule | 6 (24%) | 38 (33.3%) | 0.478 |
| No | 19 (76%) | 76 (66.7%) | |
| Extrathyroidal extension | 2 (8%) | 10 (8.8%) | 1.00 |
| No | 23 (92%) | 104 (91.2%) | |
| Local recurrence | 1 (4%) | 5 (4.4%) | 1.0 |
| No | 24 (96%) | 109 (95.6%) | |
| Tg level before RAI¹ (ng/mL) | 8.45 ± 11.38 | 10.50 ± 15.29 | 0.599 |
| TgAb level before RAI¹ (IU/mL) | 23.03 ± 81.11 | 27.75 ± 60.63 | 0.660 |
| Tg level after RAI (ng/mL) | 2.83 ± 3.78 | 0.01 ± 0.02 | 0.000 |
| TgAb level after RAI (IU/mL) | 18.87 ± 72.46 | 21.52 ± 82.92 | 0.872 |

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

Several factors are associated with unsuccessful RAI ablation, but in most studies, only lymph node recurrence was a significant factor. 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.

Funding
This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

ORCID iD
Wei Li https://orcid.org/0000-0002-2035-0134

References
1. Zidan J, Karen D, Stein M, et al. Pure versus follicular variant of papillary thyroid carcinoma: clinical features, prognostic factors, treatment, and survival. Cancer 2003; 97: 1181–1185.
2. Ito Y, Miyauchi A, Kakudo K, et al. Prognostic significance of Ki-67 labeling index in papillary thyroid carcinoma. World J Surg 2010; 34: 3015–3021.
3. Yu XM, Schneider DF, Levenson G, et al. Follicular variant of papillary thyroid carcinoma is a unique clinical entity: a population-based study of 10,740 cases. Thyroid 2013; 23: 1263–1268.
4. Finnerty BM, Kleiman DA, Scognamiglio T, et al. Navigating the management of follicular variant papillary thyroid carcinoma subtypes: a classic PTC comparison. Ann Surg Oncol 2015; 22: 1200–1206.
5. LiVolsi VA and Asa SL. The demise of follicular carcinoma of the thyroid gland. Thyroid 1994; 4: 233–236.
6. Shi X, Liu R, Basolo F, et al. Differential clinicopathological risk and prognosis of major papillary thyroid cancer variants. J Clin Endocrinol Metab 2016; 101: 264–274.
7. Tunca F, Sormaz IC, Iscan Y, et al. Comparison of histopathological features and prognosis of classical and follicular variant papillary thyroid carcinoma. J Endocrinol Invest 2015; 38: 1327–1334.
8. Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid 2016; 26: 1–133.
9. Haugen BR. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: what is new and what has changed? Cancer 2017; 123: 372–381.
10. Zhao T, Liang J, Guo Z, et al. Serum thyrotropin level of 30 muIU/mL is inadequate for preablative thyroglobulin to serve as a prognostic marker for differentiated thyroid cancer. Endocrine 2016; 53: 166–173.
11. Caglar M, Bozkurt FM, Akca CK, et al. Comparison of 800 and 3700 MBq iodine-131 for the postoperative ablation of thyroid remnant in patients with low-risk differentiated thyroid cancer. Nucl Med Commun 2012; 33: 268–274.
12. Park S, Jeon MJ, Oh HS, et al. Changes in serum thyroglobulin levels after lobectomy in patients with low-risk papillary thyroid cancer. Thyroid 2018; 28: 997–1003.
13. Choudhury PS and Gupta M. Differentiated thyroid cancer theranostics: radioiodine and beyond. Br J Radiol 2018; 91: 20180136.
14. Avram AM, Rosculet N, Esfandiari NH, et al. Differentiated thyroid cancer outcomes after surgery and activity-adjusted 131I theragnostics. Clin Nucl Med 2019; 44: 11–20.
15. Carcangiu ML, Zampi G, Pupi A, et al. Papillary carcinoma of the thyroid. A clinicopathologic study of 241 cases treated at the University of Florence, Italy. Cancer 1985; 55: 805–828.
16. Finn SP, Smyth P, Cahill S, et al. Expression microarray analysis of papillary thyroid carcinoma and benign thyroid tissue: emphasis on the follicular variant and potential markers of malignancy. Virchows Arch 2007; 450: 249–260.
17. Rivera M, Ricarte-Filho J, Knauf J, et al. Molecular genotyping of papillary thyroid carcinoma follicular variant according to its histological subtypes (encapsulated vs
infiltrative) reveals distinct BRAF and RAS mutation patterns. Mod Pathol 2010; 23: 1191–1200.
18. Jin Y, Ruan M, Cheng L, et al. Radioiodine uptake and thyroglobulin-guided radioiodine remnant ablation in patients with differentiated thyroid cancer: a prospective, randomized, open-label, controlled trial. Thyroid 2019; 29: 101–110.
19. Schlumberger M, Leboulleux S, Catargi B, et al. Outcome after ablation in patients with low-risk thyroid cancer (ESTIMABL1): 5-year follow-up results of a randomised, phase 3, equivalence trial. Lancet Diabetes Endocrinol 2018; 6: 618–626.
20. Pacini F, Schlumberger M, Dralle H, et al. [European consensus on the management of patients with differentiated carcinoma of the thyroid from follicular epithelium]. Vestn Khir Im I I Grek 2008; 167: 52–56.
21. Haymart MR, Muenz DG, Stewart AK, et al. Disease severity and radioactive iodine use for thyroid cancer. J Clin Endocrinol Metab 2013; 98: 678–686.
22. Solans R, Bosch JA, Galofre P, et al. Salivary and lacrimal gland dysfunction (sicca syndrome) after radioiodine therapy. J Nucl Med 2001; 42: 738–743.
23. Burns JA, Morgenstern KE, Cahill KV, et al. Nasolacrimal obstruction secondary to I(131) therapy. Ophthalmic Plast Reconstr Surg 2004; 20: 126–129.
24. Florenzano P, Guarda FJ, Jaimovich R, et al. Radioactive iodine administration is associated with persistent related symptoms in patients with differentiated thyroid cancer. Int J Endocrinol 2016; 2016: 2586512.
25. Haymart MR, Esfandiari NH, Stang MT, et al. Controversies in the management of low-risk differentiated thyroid cancer. Endocr Rev 2017; 38: 351–378.
26. Andresen NS, Buatti JM, Tewfik HH, et al. Radioiodine ablation following thyroidectomy for differentiated thyroid cancer: literature review of utility, dose, and toxicity. Eur Thyroid J 2017; 6: 187–196.
27. Bohine BN and Perkins JM. Appropriate dosing of adjuvant radioactive iodine for differentiated thyroid cancer. Curr Opin Oncol 2014; 26: 31–35.
28. Carhill AA, Litofsky DR, Ross DS, et al. Long-term outcomes following therapy in differentiated thyroid carcinoma: NTCTCS Registry analysis 1987-2012. J Clin Endocrinol Metab 2015; 100: 3270–3279.
29. Fatima N, Zaman MU, Zaman A, et al. Comparable ablation efficiency of 30 and 100 mCi of I-131 for low to intermediate risk thyroid cancers using triple negative criteria. Asian Pac J Cancer Prev 2016; 17: 1115–1158.
30. Aghaei A, Ayati N, Shafiei S, et al. Comparison of treatment efficacy 1 and 2 years after thyroid remnant ablation with 1110 versus 5550 MBq of iodine-131 in patients with intermediate-risk differentiated thyroid cancer. Nucl Med Commun 2017; 38: 927–931.
31. Ma C, Feng F, Wang S, et al. Chinese data of efficacy of low- and high-dose iodine-131 for the ablation of thyroid remnant. Thyroid 2017; 27: 832–837.
32. Qu Y, Huang R and Li L. Low- and high-dose radioiodine therapy for low-/intermediate-risk differentiated thyroid cancer: a preliminary clinical trial. Ann Nucl Med 2017; 31: 71–83.
33. Schlumberger M, Catargi B, Borget I, et al. Strategies of radioiodine ablation in patients with low-risk thyroid cancer. N Engl J Med 2012; 366: 1663–1673.
34. Lv RB, Wang QG, Liu C, et al. Low versus high radioiodine activity for ablation of the thyroid remnant after thyroidectomy in Han Chinese with low-risk differentiated thyroid cancer. Onco Targets Ther 2017; 10: 4051–4057.
35. Jimenez Londono GA, Garcia Vicente AM, Sastre Marcos J, et al. Low-dose radioiodine ablation in patients with low-risk differentiated thyroid cancer. Eur Thyroid J 2018; 7: 218–224.
36. Seo M, Kim YS, Lee JC, et al. Low-dose radioactive iodine ablation is sufficient in patients with small papillary thyroid cancer having minor extrathyroidal extension and central lymph node metastasis (T3 N1a). Clin Nucl Med 2017; 42: 842–846.