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Original Article

Decision-making value of a 1-cm tumor diameter cut-off for postoperative ^{131}I treatment in papillary thyroid microcarcinoma

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Abstract: Objective: To evaluate the decision-making value of a 1-cm tumor diameter cut-off for radioactive iodine (^{131}I) therapy in papillary thyroid microcarcinoma (PTMC). Methods: This retrospective study included 291 patients who received post-operative ^{131}I treatment: 123 with PTMC (≤1 cm, n=123) and 168 with papillary thyroid non-microcarcinoma (PTNMC, >1 cm, n=168). Clinicopathologic characteristics, initial treatment goals (remnant ablation, adjuvant therapy, eliminate residual lesions), administered dose (100/150 mCi), and serologic indices [pre-therapy thyroid-stimulating hormone (TSH) and stimulated thyroglobulin (sTg), as well as 6-month sTg] were compared. Therapeutic response was assessed at the last follow-up based on recurrence risk stratification and initial treatment goals. Results: Compared to the PTNMC group, the PTMC group showed lower rates of capsular invasion (40.65% vs. 59.52%), extraadenal invasion (12.20% vs. 23.21%), >5 lymph node metastases (38.21% vs. 57.74%), T3b/T4 stage (5.69% vs. 16.07%), pre-therapy sTg ≥10 μg/L (17.89% vs. 37.50%), and high recurrence risk (13.01% vs. 24.40%) (all P<0.05). PTMC patients more frequently underwent remnant ablation (64.23% vs. 44.64%) and received 100 mCi (78.86% vs. 57.14%), while PTNMC patients more often received adjuvant therapy (50.00% vs. 32.52%) and 150 mCi (42.86% vs. 21.14%) (all P<0.05). Pre-therapy sTg (6.78 ± 3.11 vs. 11.23 ± 5.91 μg/L) and 6-month sTg (1.52 ± 0.75 vs. 2.89 ± 1.37 μg/L) were lower in the PTMC group (P<0.001). Conclusion: A 1-cm diameter cut-off had limited standalone value in guiding ^{131}I treatment decisions for PTC.

Keywords: Papillary thyroid microcarcinoma, papillary thyroid non-microcarcinoma, iodine-131 therapy, diameter threshold, decision value

Introduction

The global incidence of papillary thyroid carcinoma (PTC) has risen rapidly in recent years, primarily attributed to the increased detection of papillary thyroid microcarcinoma (PTMC). PTMC is defined as a PTC with a maximum tumor diameter of no more than 1 cm [1]. According to the 2022 World Health Organization Global Cancer Report, over 50% of new thyroid cancer cases are PTMC [2]. Most PTMCs, especially low-risk ones, display indolent biologic behavior and have favorable prognosis [3]. However, certain subcategories show more aggressive behavior, including early lymph node spread, extraglandular extension, and distant metastasis, suggesting that even tumors within this size group can present with a wide spectrum of behavior [4].

Radioactive iodine (^{131}I) plays a key role in the treatment of differentiated thyroid cancer (DTC), but its utility in PTMC remains controversial [5, 6]. Some studies suggest that ^{131}I has minimal effect on clinical outcomes, even with a complete PTCM resection. In contrast, other studies have shown that ^{131}I treatment reduces the risk of recurrence and metastasis in PTMC patients [7]. This ongoing debate shows the difficulty in identifying which PTMC patients truly benefit from extra iodine treatment.

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Traditionally, tumor size has been considered an important indicator of prognosis. However, the biologic behavior of PTMC is highly heterogeneous. Tumors accompanied by lymph node metastasis, distant metastasis, extraglandular invasion, or aggressive pathologic subtypes require active treatment [8, 9]. Contemporary guidelines, therefore, emphasize comprehensive risk stratification that incorporates these multifactorial features rather than relying on a single measurement. Furthermore, molecular biomarkers are increasingly are recognized for their role in elucidating tumor biology, predicting aggressiveness, and estimating response to ^{131}I therapy. An ideal risk assessment would integrate both clinicopathologic and molecular dimensions. Over-reliance on tumor size may lead to overtreatment in low-risk patients while neglecting the treatment needs of high-risk patients [10-12]. While the limited standalone value of the 1-cm tumor diameter cut-off is recognized, its precise role within the subset of patients already selected for ^{131}I therapy based on a comprehensive assessment remains unclear. This study aimed to address this gap by evaluating whether, among patients selected for postoperative ^{131}I treatment, the 1-cm diameter cut-off retained independent prognostic value for treatment response, when analyzed within comparable clinical contexts (i.e., similar recurrence risk strata or initial treatment goals).

Materials and methods

Study design and participants

This retrospective study included patients with PTC who received ^{131}I treatment after total resection at the Department of Nuclear Medicine, Shandong Provincial Hospital Affiliated to Shandong First Medical University from November 2021 to December 2024. Clinicopathologic characteristics, ^{131}I treatment conditions, and ^{131}I treatment efficacy were compared between the PTMC (≤1 cm) and PTNMC (>1 cm) groups.

Inclusion criteria: 1. All patients underwent total thyroidectomy and cervical lymph node dissection, with postoperative pathology confirming PRC; 2. The tumor diameter and the area of lymph node metastasis were clearly defined; 3. Patients received postoperative ^{131}I treatment at the Department of Nuclear Medicine; 4. At least one follow-up record; 5. Complete clinical data available.

Exclusion criteria: 1. Patients who did not undergo thyroidectomy or regional lymph node dissection; 2. Postoperative pathology showing other thyroid malignancies, such as follicular thyroid carcinoma, medullary carcinoma, and undifferentiated carcinoma; 3. The tumor size and the lymph node metastasis zone were not well-defined; 4. Positive thyroglobulin antibody (TgAb) before the first ^{131}I treatment (reference range 0-40 U/mL); 5. Concurrent malignancy; 6. Incomplete clinical data.

This retrospective study was conducted in accordance with the Declaration of Helsinki and approved by the Research Ethics Committee of Shandong Provincial Hospital Affiliated to Shandong First Medical University. The requirement for informed consent was waived due to the retrospective nature of the study.

Treatment preparation and administration

Prior to ^{131}I treatment, patients were instructed to stop taking sodium levothyroxine and follow a low-iodine diet for 3 to 4 weeks. Thyroid stimulating hormone (TSH) levels were then tested. If TSH ≥30 U/mL was achieved, ^{131}I treatment was initiated. Postoperative staging was performed using the 8th edition of TNM staging, jointly developed by the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC). The risk of recurrence was stratified according to the 2015 American Thyroid Association (ATA) guidelines. The initial treatment goal was determined through a comprehensive analysis based on intraoperative findings, TNM stage, postoperative serology, imaging, and recurrence risk stratification. The initial treatment goals were categorized into remnant ablation, adjuvant therapy, and eliminate residual lesions. Remnant ablation: For patients at low-to-medium risk of recurrence, with stimulated thyroglobulin (sTg) <10 μg/L, and no definite structural lesion, the treatment dose was either 3.7 (100 mCi) or 5.55GBq (150 mCi).

Adjuvant therapy: For patients with high-risk or medium-risk recurrence (invasive pathologic

subtype, maximum diameter of lymph node metastasis >1 cm or exonodal invasion, age >55 years), suspected cervical lymph node metastasis by ultrasound, or sTg >10 μg/L, the dosage was either 3.7 (100 mCi) or 5.55GBq (150 mCi).

Eliminate residual lesions: For patients with distant metastases, local recurrent or persistent lesions, or local metastatic lesions, the dosage was either 5.55 (150 mCi) or 7.40GBq (200 mCi).

Response evaluation

The therapeutic efficacy was evaluated 6 months after ^{131}I treatment. The evaluation indicators included serological and imaging findings. The serological markers included TSH, Tg and TgAb. Imaging studies included neck ultrasound and chest CT.

The therapeutic efficacy was evaluated at the last follow-up in accordance with the 2015 ATA guidelines for therapeutic response evaluation. The therapeutic response was divided into excellent response (ER), indeterminate response (IDR), biochemical incomplete response (BIR), and structural incomplete response (SIR). Incomplete response (IR) was defined as either BIR or SIR.

Statistical processing

Statistical analyses were performed using IBM SPSS Statistics software (version 27.0). Continuous variables were assessed for normality using the Shapiro-Wilk test and were presented as mean ± standard deviation, as they were confirmed to be normally distributed. Categorical variables were presented as numbers and percentages. Differences between the PTMC and PTNMC groups were compared using the independent samples t-test for continuous variables and the Chi-square test (or Fisher's exact test where appropriate) for categorical variables. Multivariate logistic regression analysis was conducted to identify independent factors associated with an ER, with results expressed as odds ratios (ORs) and 95% confidence intervals (CIs). All tests were two-sided, and a P value of <0.05 was considered significant.

Results

Clinicopathologic features

A total of 291 cases were enrolled, including 100 males and 191 females, aged 12-68 (42.36 ± 11.42) years. The median follow-up time was 18.00 months. Among the 291 cases, 123 cases (42.27%) were diagnosed with PTMC and 168 cases (57.73%) with PTNMC.

The proportions of capsular invasion, extraadenal invasion, total number of lymph node metastases >5, T3b/T4, and high-risk recurrence in the PTMC group were all lower than those in the PTNMC group (P<0.05). There were no significant differences between the two groups in terms of sex, age, number of lesions, involved glandular lobes, lymph node stage, or distant metastasis (P>0.05) (**Table 1**).

Initial treatment situation

There was a significant difference in the initial treatment target of ^{131}I therapy between the PTMC and PTNMC groups (P<0.05). In the PTMC group, 64.23% of patients had remnant ablation as the initial treatment goal, followed by adjuvant therapy in 32.25%. In the PTNMC group, up to 50.00% of patients received adjuvant therapy initially, followed by remnant ablation in 44.64%. In terms of therapeutic dose, the proportion of 100 mCi was higher in the PTMC group than that of the PTNMC group (78.86% *vs.* 57.14%), and the proportion of 150 mCi was higher in the PTNMC group than that of the PTMC group (42.86% *vs.* 21.14%) (P< 0.05) (**Table 2**).

Comparison of treatment-related serologic values

Serum values related to treatment preparation and early response were compared between the groups. No significant difference in pre-therapy TSH levels was observed, confirming adequate preparation in both groups (P>0.05). As expected, the pre-therapy sTg level was significantly lower in the PTMC group compared to the PTNMC group (6.78 ± 3.11 vs. 11.23 ± 5.91, t=8.307, P<0.001). At the 6-month follow-up, the sTg level in the PTMC group remained significantly lower than that in the

Table 1. Differences in clinicopathologic characteristics between the PTMC and PTNMC groups

Clinicopathologic characteristic		PTMC group (n=123)	PTNMC group (n=168)	Chi-square value	*P*
Sex	Male	43 (34.96)	57 (33.93)	0.033	0.855
	Female	80 (65.04)	111 (66.07)		
Age	<55	101 (82.11)	138 (82.14)	0.000	0.995
	≥55	22 (17.89)	30 (17.86)		
Number of lesions	Single	36 (29.27)	62 (36.90)	1.854	0.173
	Multiple	87 (70.73)	106 (63.10)		
Glandular lobe involvement	Single lobe	54 (43.90)	80 (47.62)	0.395	0.53
	Bi-lobes	69 (56.10)	88 (52.38)		
Capsular invasion	Yes	50 (40.65)	100 (59.52)	10.127	0.001
	No	73 (59.35)	68 (40.48)		
Extraadenal invasion	Yes	15 (12.20)	39 (23.21)	5.705	0.017
	No	108 (87.80)	129 (76.79)		
Total number of lymph node metastases	≤5	76 (61.79)	71 (42.26)	10.831	0.001
	>5	47 (38.21)	97 (57.74)		
T3b/T4	Yes	7 (5.69)	27 (16.07)	7.415	0.006
	No	116 (94.31)	141 (83.93)		
Lymph node stage	N0	5 (4.07)	5 (2.98)	6.883	0.076
	N1a	56 (45.53)	53 (31.55)		
	N1b	7 (5.69)	10 (5.95)		
	N1	55 (44.72)	100 (59.52)		
Distant metastasis	Yes	4 (3.25)	7 (4.17)	0.009	0.926
	No	119 (96.75)	161 (95.83)		
Recurrence risk	Low	64 (52.03)	49 (29.17)	16.516	0.001
	Medium	43 (34.96)	78 (46.43)		
	High	16 (13.01)	41 (24.40)		

PTMC: Papillary Thyroid Microcarcinoma; PTNMC: Papillary Thyroid Non-Microcarcinoma; sTg: stimulated thyroglobulin.

Table 2. Differences in the initial treatment goal of ^{131}I between the PTMC and PTNMC groups

Initial treatment of ^{131}I		PTMC group (n=123)	PTNMC group (n=168)	Chi-square value	*P*
Initial treatment objective	Remnant ablation	79 (64.23)	75 (44.64)	10.943	0.004
	Adjuvant therapy	40 (32.52)	84 (50.00)		
	Elimination of residual lesions	4 (3.25)	9 (5.36)		
Dosage	100 mCi	97 (78.86)	96 (57.14)	14.997	0.001
	150 mCi	26 (21.14)	72 (42.86)		

^{131}I: Iodine-131; PTMC: Papillary Thyroid Microcarcinoma; PTNMC: Papillary Thyroid Non-Microcarcinoma; mCi: millicurie.

PTNMC group (1.52 ± 0.75 vs. 2.89 ± 1.37, t=10.878, P<0.001) (**Figure 1**).

Therapeutic effect evaluation

Stratification based on recurrence risk: The rates of ER, IDR, BIR, SIR and IR for low-risk PTMC and PTNMC groups are shown in **Table 3**. There were no significant differences between the two groups (P>0.05), suggesting that for PTC patients classified as at low risk for recurrence, tumor classification by a 1 cm diameter does not significantly impact the therapeutic response to iodine treatment.

The ER, IDR, BIR, SIR and IR rates for medium-risk PTMC and PTNMC groups are shown in **Table 4**. Similarly, no significant differences were observed between the two groups (P> 0.05), indicating that for PTC patients with mod-

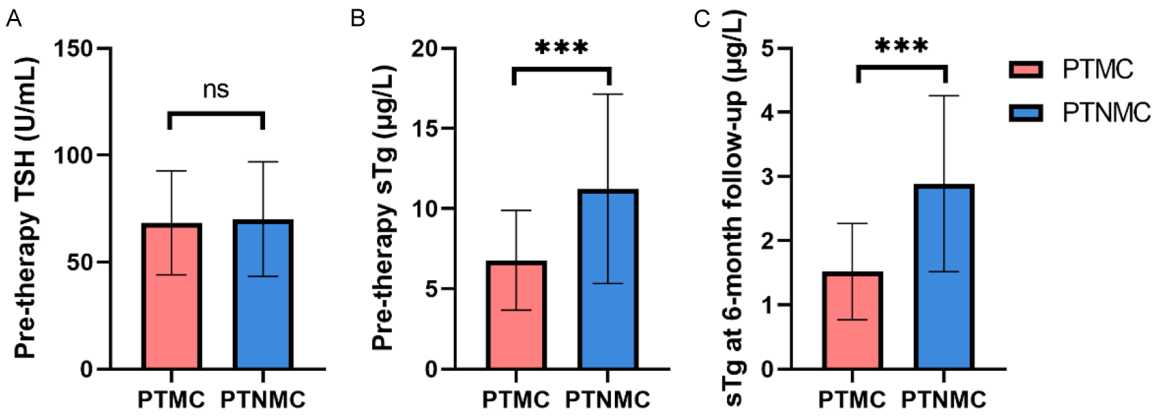

Figure 1. Comparison of treatment-related serologic values between PTMC and PTNMC groups. A. Pre-therapy TSH levels; B. Pre-therapy stimulated sTg level; C. 6-month follow-up sTg level. ns: no significant difference; ***: P<0.001. PTMC: Papillary Thyroid Microcarcinoma; PTNMC: Papillary Thyroid Non-Microcarcinoma; TSH: Thyroid Stimulating Hormone; sTg: stimulated thyroglobulin.

Table 3. Comparison of therapy efficacy between the low-risk PTMC and PTNMC groups

Efficacy evaluation		PTMC 64 (%)	PTNMC 49 (%)	Chi-square value	*P*
Response	ER	48 (75.00)	30 (61.22)	3.835	0.280
	IDR	8 (12.50)	6 (12.24)		
	BIR	3 (4.69)	6 (12.24)		
	SIR	5 (7.81)	7 (14.30)		
ER	Yes	48 (75.00)	30 (61.22)	2.463	0.117
	No	16 (25.00)	19 (38.78)		
IR	Yes	8 (12.50)	13 (26.53)	3.611	0.057
	No	56 (87.50)	36 (73.47)		
SIR	Yes	5 (7.81)	7 (14.29)	1.225	0.268
	No	59 (92.19)	42 (85.71)		

PTMC: Papillary Thyroid Microcarcinoma; PTNMC: Papillary Thyroid Non-Microcarcinoma; ER: Excellent Response; IDR: Indeterminate Response; BIR: Biochemical Incomplete Response; SIR: Structural Incomplete Response; IR: Incomplete Response.

erate recurrence risk, tumor size classification by a 1 cm diameter has no effect on the therapeutic response of iodine treatment.

The rates of ER, IDR, BIR, SIR and IR for high-risk PTMC and PTNMC groups are shown in **Table 5**. There were no significant differences between the two groups (*P*>0.05), demonstrating that for PTC patients with a high-risk recurrence, the 1 cm tumor size cut-off did not influence the therapeutic response to iodine treatment.

Stratification according to the initial treatment goals: Among the 123 PTMC cases, 79 received remnant ablation, while 75 out of 168 PTNMC cases underwent this treatment. There were no significant differences in the therapeutic response (ER, IDR, BIR and SIR Rate), or in the ER/non-ER, IR/non-IR, SIR/non-SIR classifications between the two groups of patients with remnant ablation as the initial treatment goal (*P*>0.05). As shown in **Table 6**, the 1 cm diameter cut-off value had limited significance for guiding ^{131}I treatment with remnant ablation as the initial treatment goal.

Among the 123 PTMC cases, 40 cases received adjuvant therapy, while 84 of the 168 PTNMC cases underwent this approach. There were no significant differences in the therapeutic response (ER, IDR, BIR and SIR Rate), or ER/non-ER, IR/non-IR, SIR/non-SIR classification between the two groups of patients with adjuvant therapy as the initial treatment goal (*P*>0.05). As shown in **Table 7**, the 1 cm diameter cut-off value has limited significance in guiding ^{131}I treatment when adjuvant therapy is the initial treatment goal.

Among the 123 PTMC cases, 4 cases received eliminate residual lesions, and 9 out of 168 PTNMC cases received the same treatment. There were no significant differences in the therapeutic response (ER, IDR, BIR and SIR

Table 4. Comparison of therapy efficacy between the medium-risk PTMC and PTNMC groups

Efficacy evaluation		PTMC 43 (%)	PTNMC 78 (%)	Chi-square value	*P*
Response	ER	27 (62.79)	41 (52.56)	4.569	0.206
	IDR	7 (16.28)	8 (10.26)		
	BIR	2 (4.65)	11 (14.10)		
	SIR	7 (16.28)	18 (23.08)		
ER	Yes	27 (62.79)	41 (52.56)	1.178	0.278
	No	16 (37.21)	37 (47.44)		
IR	Yes	9 (20.93)	29 (37.18)	3.397	0.065
	No	34 (79.07)	49 (62.82)		
SIR	Yes	7 (16.28)	18 (23.08)	0.781	0.377
	No	36 (83.72)	60 (76.92)		

PTMC: Papillary Thyroid Microcarcinoma; PTNMC: Papillary Thyroid Non-Microcarcinoma; ER: Excellent Response; IDR: Indeterminate Response; BIR: Biochemical Incomplete Response; SIR: Structural Incomplete Response; IR: Incomplete Response.

Table 5. Comparison of therapy efficacy between the high-risk PTMC and PTNMC groups

Efficacy evaluation		PTMC 16 (%)	PTNMC 41 (%)	Chi-square value	*P*
Response	ER	9 (56.25)	14 (34.15)	2.808	0.422
	IDR	1 (6.25)	6 (14.63)		
	BIR	3 (18.75)	8 (19.51)		
	SIR	3 (18.75)	13 (31.71)		
ER	Yes	9 (56.25)	14 (34.15)	2.336	0.126
	No	7 (43.75)	27 (65.85)		
IR	Yes	6 (37.50)	21 (51.22)	0.869	0.351
	No	10 (62.50)	20 (48.78)		
SIR	Yes	3 (18.75)	13 (31.71)	0.423	0.516
	No	13 (81.25)	28 (68.29)		

PTMC: Papillary Thyroid Microcarcinoma; PTNMC: Papillary Thyroid Non-Microcarcinoma; ER: Excellent Response; IDR: Indeterminate Response; BIR: Biochemical Incomplete Response; SIR: Structural Incomplete Response; IR: Incomplete Response.

Rate), or ER/non-ER, IR/non-IR, SIR/non-SIR classification between the two groups of patients with elimination of residual lesions as the initial treatment goal (P>0.05). As shown in **Table 8**, the 1 cm diameter cut-off has limited significance in guiding ^{131}I treatment with the initial goal of eliminate residual lesions.

Multivariate analysis of factors associated with treatment response

A multivariate logistic regression analysis was performed to identify independent factors associated with achieving an ER, adjusting for potential confounders (**Table 9**). Tumor group (PTMC vs. PTNMC) was not an independent predictor of ER (OR=1.15, 95% CI 0.70-1.89, P=0.580). However, the initial treatment goal of adjuvant therapy (OR=0.41, 95% CI 0.24-0.69, P=0.001) or residual lesion elimination (OR=0.17, 95% CI 0.05-0.55, P=0.003) were significantly associated with a lower likelihood of ER, compared to remnant ablation. Age ≥55 years, male gender, presence of N1 disease, and an initial dose of 150 mCi were not independently associated with ER in this model (P>0.05).

Discussion

Our new data reinforce the consensus embodied in current guidelines-namely, that the 1-cm diameter threshold should not be used in isolation to guide ^{131}I therapy for PTC. Rather than challenging existing paradigms, our results underscore and empirically validate the necessity of multifactorial risk assessment in clinical practice.

Two key insights emerged from this retrospective analysis of PTC management with RAI (^{131}I). First, significant differences in clinicopathologic risk factors and initial treatment strategies were observed between patients with tumors ≤1 cm (PTMC) and those with >1 cm (PTNMC). However, when treatment outcomes were appraised within matched frameworks of recurrence risk or particular curative goals, no significant differences in treatment effectiveness were observed between the two groups based on tumor size. This discrepancy between the initial tumor characteristics and the ultimate therapeutic response calls into question the use of 1-cm diameter as an isolated criterion.

Table 6. Comparison of therapeutic effects of remnant ablation between the PTMC and PTNMC groups

Efficacy evaluation		PTMC 79 (%)	PTNMC 75 (%)	Chi-square value	*P*
Response	ER	64 (81.01)	56 (74.67)	2.986	0.394
	IDR	9 (11.39)	7 (9.33)		
	BIR	1 (1.27)	1 (1.33)		
	SIR	5 (6.33)	11 (14.67)		
ER	Yes	64 (81.01)	56 (74.67)	0.901	0.343
	No	15 (18.99)	19 (25.33)		
IR	Yes	6 (7.59)	12 (16.00)	2.633	0.105
	No	73 (92.41)	63 (84.00)		
SIR	Yes	5 (6.33)	11 (14.67)	2.873	0.090
	No	74 (93.67)	64 (85.33)		

PTMC: Papillary Thyroid Microcarcinoma; PTNMC: Papillary Thyroid Non-Microcarcinoma; ER: Excellent Response; IDR: Indeterminate Response; BIR: Biochemical Incomplete Response; SIR: Structural Incomplete Response; IR: Incomplete Response.

Table 7. Comparison of therapeutic effects of adjuvant therapy between the PTMC and PTNMC groups

Efficacy evaluation		PTMC 40 (%)	PTNMC 84 (%)	Chi-square value	*P*
Response	ER	19 (47.50)	28 (33.33)	4.345	0.227
	IDR	7 (17.50)	12 (14.29)		
	BIR	5 (12.50)	23 (27.38)		
	SIR	9 (22.50)	21 (25.00)		
ER	Yes	19 (47.50)	28 (33.33)	2.311	0.129
	No	21 (52.50)	56 (66.67)		
IR	Yes	14 (35.00)	44 (52.38)	3.288	0.070
	No	26 (65.00)	40 (47.62)		
SIR	Yes	9 (22.50)	21 (25.00)	0.092	0.761
	No	31 (77.50)	63 (75.00)		

PTMC: Papillary Thyroid Microcarcinoma; PTNMC: Papillary Thyroid Non-Microcarcinoma; ER: Excellent Response; IDR: Indeterminate Response; BIR: Biochemical Incomplete Response; SIR: Structural Incomplete Response; IR: Incomplete Response.

Therefore, the focus should be on comprehensive risk stratification.

Our findings align with the well-established relationship between tumor size and biological aggressiveness. The PTMC group exhibited less capsular invasion, extraglandular spread, more lymph node invasion (over 5 nodes), and higher T stage (T3b/T4). Additionally, a higher pre-ablation sTg level was observed in this group. These findings support the concept that larger tumors have a larger cellular reservoir, a longer time frame for acquiring driver mutations, and a greater potential for invasive behavior, including local tissue destruction and neovascularization [13, 14]. The higher sTg levels in the PTNMC group indicate more residual tumor or functional thyroid tissue post-thyroidectomy.

However, the biological variability of PTMC is substantial. The fact that many PTMC patients showed multifocal disease and required ^{131}I treatment demonstrates that factors beyond size-such as tumor focus count and specific pathologic characteristics-are critical in determining clinically meaningful disease. Recent molecular studies have identified various genomic and transcriptomic alterations in more aggressive PTMCs, particularly those associated with the MAPK pathway and metastases. These changes may contribute to lymph node involvement even in tumors of subcentimeter size [15-17]. This deeper biological complexity underscores that tumor behavior cannot be predicted by size alone. The high rate of lymph node metastasis observed in our PTMC cohort is not an anomaly, but rather a reflection of a selected subgroup where factors like multifocality and certain molecular profiles contribute to the need for adjuvant therapy, as described in the literature. Studies have mentioned that the metastatic potential of PTC is not always size-dependent [18-20].

It is crucial to interpret our findings within the specific context of our study design. This investigation specifically focused on PTC patients who, based on contemporary multi-parameter assessment (including factors like multifocality, lymph node status, and other clinical features), were deemed clinically appropriate for postoperative ^{131}I therapy. Our PTMC group

Table 8. Comparison of therapeutic effects of eliminating residual lesions between the PTMC and PTNMC groups

Efficacy evaluation		PTMC 4 (%)	PTNMC 9 (%)	Chi-square value	*P*
Response	ER	1 (25.00)	1 (11.11)	3.715	0.294
	IDR	0 (0.00)	1 (11.11)		
	BIR	2 (50.00)	1 (11.11)		
	SIR	1 (25.00)	6 (66.67)		
ER	Yes	1 (25.00)	1 (11.11)	--	1.000
	No	3 (75.00)	8 (88.89)		
IR	Yes	3 (75.00)	7 (77.78)	--	1.000
	No	1 (25.00)	2 (22.22)		
SIR	Yes	1 (25.00)	6 (66.67)	0.621	0.431
	No	3 (75.00)	3 (33.33)		

PTMC: Papillary Thyroid Microcarcinoma; PTNMC: Papillary Thyroid Non-Microcarcinoma; ER: Excellent Response; IDR: Indeterminate Response; BIR: Biochemical Incomplete Response; SIR: Structural Incomplete Response; IR: Incomplete Response.

does not represent the broader PTMC population, which includes many low-risk tumors managed with surveillance or surgery alone. Instead, it comprises a selected subgroup of "high-risk" PTMCs, in which clinicians, after comprehensive evaluation, determined that the benefits of ^{131}I outweighed the potential risks. Therefore, our study directly addresses the decision-making value of the 1-cm tumor size cut-off within this specific, clinically relevant cohort of patients already indicated for ^{131}I treatment. The central question we aimed to answer was: among patients selected for ^{131}I treatment, does tumor size (below or above 1 cm), when other risk factors are accounted for (by stratification), predict a differential treatment response? Our answer, within this framework, was no.

It is worth noting that while the PTMC group had a higher number of multifocal and bilobar involvements compared to the PTNMC group, the difference was not statistically significant. This is contrary to the conventional belief that larger tumors are inherently more aggressive. The key point to recognize here is the inherent selection bias in our study population, as these were patients that needed postoperative ^{131}I treatment. Hence, the PTMC patients in our study had high enough risk profiles to receive adjuvant therapy if the tumor was multifocal. This emphasizes that clinical decision-making for ^{131}I treatment involves a constellation of risk factors, with multifocality emerging as a strong clinical tool that can override size criteria, thus including smaller tumors with more aggressive pathologic features.

Due to the distinct risk profiles of the PTMC and PTNMC groups, initial treatment strategies varied significantly. PTMC patients were more often treated with remnant ablation using 100 mCi to eliminate normal residual thyroid tissue in a low-risk setting. On the contrary, PTNMC patients typically received 150 mCi for adjuvant treatment, targeting potential microscopic disease in a high-risk scenario. This difference underscored the natural incorporation of tumor size into a broader, multi-factorial risk evaluation, which resulted in an ascending hierarchy of therapy [21, 22]. The selection of activity is related to the ablation and adjuvant activity. For remnant ablation, sufficient radiation is necessary to destroy ordinary follicular cells, a dose that is usually standardized. However, for adjuvant therapy, the goal is to target any remaining radioresistant cancer cells, which may require a higher dose. Even though smaller tumors may have a lower iodine uptake, the desire to maximize the chances of eliminating residual malignant cells justifies using a higher dose for high-risk cases. This clinical decision-making cannot rely solely on a single value like tumor diameter [23, 24].

Most importantly, the study findings demonstrated that there is no significant difference in therapeutic outcomes between the PTMC and the PTNMC groups when the analysis was conducted within a similar clinical context, such as different categories of recurrence risk or predefined treatment intent. This outcome is central to the ongoing debate on the utility of ^{131}I therapy in PTMC. It suggests that the efficacy of ^{131}I is not solely determined by the primary tumor diameter but rather by the biologic characteristics captured in the risk stratification process and the specific therapeutic goals. The radiobiological effectiveness of ^{131}I depends on the concentration of the isotope within target

Table 9. Multivariate logistic regression analysis for factors associated with ER

Variable	*P* value	OR (95% CI)
Tumor Group (PTMC/PTNMC)	0.580	1.15 (0.70-1.89)
Age (≥55/<55 years)	0.285	0.74 (0.42-1.29)
Sex (Male/Female)	0.395	0.81 (0.50-1.32)
Lymph Node Status (N1/N0/N1a/N1b)	0.092	0.65 (0.39-1.07)
Initial Treatment Goal (Adjuvant Therapy/Remnant Ablation)	0.001	0.41 (0.24-0.69)
Initial Treatment Goal (Eliminate Residual Lesions/Remnant Ablation)	0.003	0.17 (0.05-0.55)
Initial Dose (150 mCi/100 mCi)	0.185	0.72 (0.44-1.18)

PTMC: Papillary Thyroid Microcarcinoma; PTNMC: Papillary Thyroid Non-Microcarcinoma; OR: Odds Ratio; CI: Confidence Interval.

tissues (iodine avidity) and the radiation dose delivered to those tissues. There is no established physiologic mechanism by which the pre-operative diameter of a tumor, once completely resected, directly influences the avidity of potential microscopic metastases for radioiodine or the radiosensitivity of residual cells [25, 26]. Instead, treatment response is primarily governed by the inherent biological properties of the tumor cells (e.g., expression of the sodium-iodide symporter), the extent of residual disease, and the delivered radiation dose. Therefore, a PTMC with high-risk features (e.g., extrathyroidal extension, N1b metastasis) and a PTNMC with similar high-risk characteristics likely share similar tumor biology regarding aggressiveness and iodine metabolism [27, 28]. When both groups receive appropriately dosed adjuvant therapy targeting this high-risk biology, similar outcomes are plausible. This is supported by clinical evidence from Geneş et al. [22], which demonstrated that ^{131}I efficacy in multifocal PTMC is linked more to the presence of risk factors rather than to tumor size. Our data further demonstrate that even for remnant ablation, where the goal is to target presumed benign tissue, outcomes were comparable across size groups, suggesting that the success of the procedure is independent of the original tumor size but more related to surgical completeness and postoperative thyroid physiology [29-31].

The primary clinical implication of our findings was that the 1-cm tumor diameter threshold has limited standalone decision-making value for ^{131}I therapy. It should be integrated into contemporary, multi-dimensional risk stratification systems, including those outlined in the ATA guidelines. Over-reliance on this cut-off could result in two types of clinical errors: overtreatment of low-risk PTMCs (where ablation may offer minimal benefit) and undertreatment of high-risk PTMCs (where withholding adjuvant therapy due to tumor size may result in adverse outcomes). Clinical management should be based on a comprehensive evaluation of features that directly reflect tumor biology and burden, including lymph node metastases, number and location of involved nodes, extraglandular extension, multifocality, variant histology, and postoperative thyroglobulin levels. This approach is in line with individualized medicine principles in thyroid cancer.

Regarding the core question of how to improve clinical decision-making, our data, while not proposing a novel validated model, reinforce the operational path outlined by guidelines: synthesizing key risk features. For instance, in our cohort, factors such as lymph node metastasis burden (>5 nodes), extraglandular extension, and elevated pre-therapy sTg (≥10 μg/L) were more prevalent in the PTNMC group, but these features were also present in a subset of PTMC patients who received adjuvant therapy. This suggests that a practical clinical approach should sequentially consider not just tumor size, but also the presence of these higher-risk features (e.g., nodal disease, sTg level) when evaluating the need for adjuvant ^{131}I therapy. A simple, heuristic assessment integrating these elements may provide greater clinical precision than relying on size alone. Future research with larger datasets could focus on developing and validating a quantitative risk score that incorporates such readily available clinicopathologic variables to further refine decision thresholds.

This study also has some limitations. As a retrospective, single-center study, our analysis is inherently subject to selections biases. Specifically, we only included patients who underwent ^{131}I treatment, which creates a cohort of higher-risk PTMCs, precluding any assessment of the broader generalizability of the 1-cm cutoff to the general PTMC population, including those for whom ^{131}I is not indicated. Our conclusions are strictly applicable to the decision-making context among patients already considered candidates for ^{131}I therapy based on a comprehensive risk assessment. Additionally, the median follow-up time of 18 months is relatively short and insufficient to draw conclusions about late recurrences or survival outcomes, which may differ over a longer time horizon.

Another key limitation of our analysis is that it relied solely on traditional clinicopathologic values, without incorporating molecular profiling data (e.g., BRAF, TERT, NIS). These biomarkers are critical to understanding tumor biology and iodine avidity, and their absence restricts our ability to provide mechanistic insights into the underlying processes that drive ^{131}I response. We fully acknowledge that incorporating such molecular data is essential for advancing individualized decision-making. Future prospective studies with integrated genomic analysis are needed to validate our findings and develop more precise predictive models that can identify, across all tumor sizes, the patients who will derive a definite net benefit from ^{131}I therapy.

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Disclosure of conflict of interest

None.

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