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Clinical Research Article

Radioactive Iodine Therapy Decreases the Recurrence of Intermediate-Risk PTC With Low Thyroglobulin Levels

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Abstract

Context: Whether radioactive iodine therapy (RAIT) is necessary for intermediate-risk papillary thyroid cancer (PTC) after total thyroidectomy is still lacking reliable evidence, especially for patients with low postoperative thyroglobulin (Tg) levels.

Objective: This study conducted a propensity score matching (PSM) analysis to investigate whether RAIT is effective in reducing the recurrence of intermediate-risk PTC with low Tg levels.

Methods: In total, 1487 patients with intermediate-risk PTC with unstimulated Tg ≤ 1 ng/mL or stimulated Tg ≤ 10 ng/mL after total thyroidectomy were enrolled retrospectively. The clinicopathological characteristics were compared between the non-RAIT and RAIT groups before and after PSM (1:4 matching). The impact of RAIT on biochemical recurrence and structural recurrence was evaluated.

Results: Overall, 1349 (90.7%) patients underwent RAIT, and 138 (9.3%) did not. After a median follow-up time of 51 months, 30 patients presented with recurrence, including 11 structural and 19 biochemical recurrences. After PSM, the non-RAIT group had a higher rate of structural recurrence (5/138 vs 5/552, $P = .046$) and biochemical recurrence (6/138 vs 4/552, $P = .005$) than the RAIT group. Multivariate analysis showed that not receiving RAIT was an independent risk factor for structural recurrence (hazard ratio [HR] 10.572, 95% CI 2.439-45.843, $P = .002$) and biochemical recurrence (HR 16.568, 95% CI 3.670-74.803, $P < .001$). Kaplan–Meier analysis showed that the non-RAIT

- ATA management guidelines have proposed a clinicopathological risk stratification system to classify patients with DTC as low, intermediate, or high risk for recurrence after thyroidectomy

- **Radioactive iodine therapy (RAIT)** is recommended routinely for patients with **high-risk DTC after total thyroidectomy**, while it is considered **selectively for patients with intermediate-risk DTC because of conflicting or inadequate data**

- Several retrospective studies based on public data sources have shown that **RAIT** can **improve overall survival or disease-specific death** in patients with **intermediate-risk PTC**
- Other studies with contrasting perspectives thought RAIT did not decrease the risk of recurrence or death in intermediate risk patients
- However, the retrospective design of these studies was prone to selection bias, and some of the studies had a relatively small sample size. Furthermore, none of the above studies considered the effect of Tg on clinical outcomes.

- **Tg** levels after total thyroidectomy provide an excellent predictive value for persistent and recurrent disease in patients with PTC

- Our previous study demonstrated that disease persistence/recurrence occurred in only 4.1% of intermediate-risk patients with a stimulated Tg≤10 ng/mL, much less than in patients with Tg>10 ng/mL (37.9%)

- The necessity of **RAIT** in **intermediate**-risk patients with **low Tg** levels lacked evidence from a random, prospective study, with the previous retrospective studies yielding biased results.
- The propensity score matching method (PSM) is a statistical method used to establish a new control group which attempts to alleviate the interference of confounding bias from observational cohorts, allowing for the proper assessment of the intended variable
- **Thus, our study investigated the efficacy of RAIT in patients with intermediate-risk PTC with unstimulated Tg≤1 ng/mL or stimulated Tg≤ 10 ng/mL after total thyroidectomy using the PSM method.**

Materials and Methods
Patients

- This was a single-center, retrospective, observational cohort study. The present study was approved by the Institutional Review Board of Sichuan University, West China Hospital
- Inclusion criteria were (1) patients who underwent total thyroidectomy or near-total thyroidectomy at our center between August 2009 and June 2020; (2) patients with postoperative pathologically confirmed PTC; (3) patients defined as intermediate risk according to the ATA initial risk stratification system; (4) and patients with postoperative serum thyroglobulin antibody (TgAb)≤40 IU/mL and stimulated Tg level≤10 ng/ mL or unstimulated Tg level≤1 ng/mL after total thyroidectomy.
- exclusion criteria : neck ultrasound, computed tomography, or 131I whole-body scan indicating the existence of a structural disease within 6 months after surgery, follow-up duration <1 year, or incomplete follow-up information.

Surgical Treatment

- All patients underwent total thyroidectomy and lymph node dissection in the central or lateral cervical region at the discretion of experienced surgeons
- The entire surgical specimen of the thyroid and the resected lymph node were sent for pathological examination. The tumor size, extrathyroidal extension (ETE), and the total number of retrieved and lymph node metastases (LNM) were recorded.

Thyrotropin, Tg, TgAb Measurement

- All the patients were tested for thyrotropin (TSH), Tg, and TgAb after total thyroidectomy in the same laboratory at the West China Hospital, Sichuan University.
- The stimulated Tg was defined as the Tg measured at TSH>30 μIU/mL following thyroid hormone withdrawal after total thyroidectomy.
- Stimulated Tg was measured before the first RAIT treatment, while unstimulated Tg was measured 1 to 2 months after total thyroidectomy.
- TSH, Tg, and TgAb were tested every 6 months to 1 year during the follow-up period.

Radioactive Iodine Administration

- RAIT was initiated 1 to 6 months after surgery.
- After maintaining a low-iodine diet for 2 weeks and implementing the withdrawal from levothyroxine for 2 to 3 weeks to ensure that TSH levels were greater than 30 μIU/mL in all the patients, we empirically adopted 3.7 GBq of 131I for all included patients.
- Planar anterior and posterior 131I- whole-body scan were obtained 3 to 5 days after the administration of 131I, The imaging results were interpreted by 2 nuclear medicine physicians.

Primary Endpoint

- **primary endpoint** was **recurrence-free survival (RFS) between the RAI and non-RAI groups after PSM.**
- **Structural recurrence** was defined as the new biopsy-confirmed PTC metastasis (cytology or histology) occurring **after 6 months** postoperatively.
- **Biochemical recurrence** was defined as unstimulated Tg>1 ng/mL during the follow-up and without evidence of structural disease.
- **RFS structural** was defined as the time interval between the total thyroidectomy and the occurrence of structural recurrence.
- **RFS biochemical** was defined as the time interval between the total thyroidectomy and the occurrence of biochemical recurrence.

Statistical Analysis

- We used PSM to eliminate possible confounding factors and selection bias with SPSS 22.0
- PSM analysis was performed with 1:4 matching and a caliper value of 0.02 using the following clinicopathological characteristics: sex, age, multifocality, bilateral tumor, ETE, number of LNM, a ratio of LNM, primary tumor size, N stage, and American Joint Committee on Cancer stage.

Results Study Cohort

- From August 2009 to June 2020, 4263 consecutive patients with PTC with total thyroidectomies were referred to our department. Of these, 2625 patients were classified as intermediate risk according to ATA guidelines. A total of 1138 patients were excluded based on exclusion criteria, and the remaining 1487 PTC constituted our study cohort (Fig. 1).

- median age of 41 years (range 18-75 years). Of these, 979 (65.8%) were female, and 508 (34.2%) were male. Most patients were classified as stage I (93.0%, 1383/1487), while 104 (7.0%) were classified as stage II. 2.4% (36/1487) of patients having a larger size (≥4 cm). Microscopic ETE was found in 23.8% (354/1487) of patients. The ratio of LNM a median value of 44.0% (Table 1).

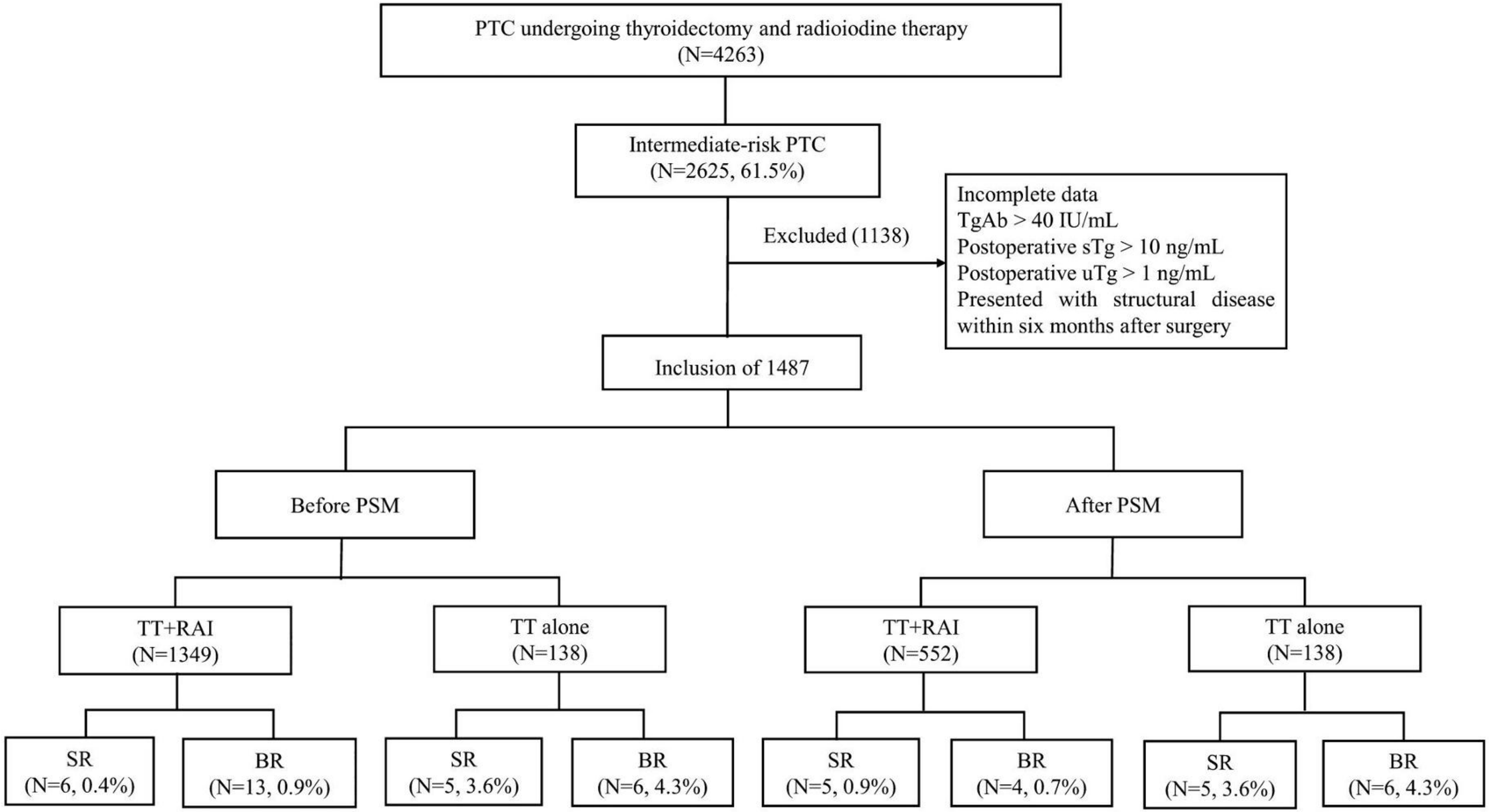

Figure 1. Flow chart of patient selection. PTC, papillary thyroid cancer; TgAb, thyroglobulin antibody; sTg, stimulated thyroglobulin; uTg, unstimulated thyroglobulin; SR, structural recurrence; BR, biochemical recurrence.

Comparison of Clinicopathological Characteristics Before and After PSM

- Table 1 shows the baseline clinicopathological characteristics of the patients before and after PSM
- A total of 1349 (90.7%) underwent RAIT after a total thyroidectomy, while 138 (9.3%) did not
- Compared with the RAIT group, patients **who did not receive RAIT** were characterized by **older** age P=.001), **less N1b** disease (P=.006), **lower stage** (P= .001), **fewer numbers of LNM** (P=.010), and **lower** proportions of LNM (P=.037).
- 690 patients were matched **successfully by the PSM analysis (1:4 matching), including 138 patients without RAIT and 552 patients with RAIT.** There were **no** significant differences in the clinicopathological characteristics **between the matched groups** (all P>.05, Table 1).

Table 1. Comparison of clinicopathological characteristics before and after propensity score matching

Parameters	Total n=1487	Before PSM			After PSM		
		TT + RAI n = 1349	TT alone n = 138	*P* value	TT + RAI n = 552	TT alone n = 138	*P* value
Age, years	41 (18-75)			.001			.890
<55	1288 (86.6%)	1181 (87.5%)	107 (77.5%)		431 (78.1%)	107 (77.5%)	
≥55	199 (13.4%)	168 (12.5%)	31 (22.5%)		121 (21.9%)	31 (22.5%)	
Sex				.727			.518
Male	508 (34.2%)	459 (34.0%)	49 (35.5%)		180 (32.6%)	49 (35.5%)	
Female	979 (65.8%)	890 (66.0%)	89 (64.5%)		372 (67.4%)	89 (64.5%)	
Number of LNM	3 (0-35)			.010			.611
<5	996 (67.0%)	890 (66.0%)	106 (76.8%)		435 (78.8%)	106 (76.8%)	
≥5 or x[a]	491 (33.0%)	459 (34.0%)	32 (23.2%)		117 (21.2%)	32 (23.2%)	
Ratio of LNM(%)	44.1 (0-100)			.037			1
<50	1061 (71.4%)	952 (70.6%)	109 (79.0%)		436 (79.0%)	109 (79.0%)	
≥50	426 (28.6%)	397 (29.4%)	29 (21.0%)		116 (21.0%)	29 (21.0%)	
ETE				<.001			.885
Negative	1133 (76.2%)	1061 (78.7%)	72 (52.2%)		288 (52.2%)	72 (52.2%)	
Positive	354 (23.8%)	288 (21.3%)	66 (47.8%)		264 (47.8%)	66 (47.8%)	
Multifocality				.100			1
Negative	995 (66.9%)	894 (66.3%)	101 (73.2%)		404 (73.2%)	101 (73.2%)	
Positive	492 (33.1%)	455 (33.7%)	37 (26.8%)		148 (26.8%)	37 (26.8%)	
Bilateral tumor				.206			.420
Negative	1108 (74.5%)	999 (74.1%)	109 (79.0%)		418 (75.7%)	109 (79.0%)	
Positive	379 (25.5%)	350 (25.9%)	29 (21.0%)		134 (24.3%)	29 (21.0%)	
Primary tumor size				.843			1
≤4 cm	1451 (97.6%)	1316 (97.6%)	135 (97.8%)		541 (98.0%)	135 (97.8%)	
>4 cm	36 (2.4%)	33 (2.4%)	3 (2.2%)		11 (2.0%)	3 (2.2%)	
N stage				.006			.860
N0 + N1a	1169 (78.6%)	1048 (77.7%)	121 (87.7%)		481 (87.1%)	121 (87.7%)	
N1b	318 (21.4%)	301 (22.3%)	17 (12.3%)		71 (12.9%)	17 (12.3%)	
Stage[b]				.001			1
I	1383 (93.0%)	1245 (92.3%)	138 (100%)		550 (99.6%)	138 (100%)	
II	104 (7.0%)	104 (7.7%)	0 (0%)		2 (0.4%)	0	

Clinical Outcome

- The median follow-up duration for the enrolled patients with intermediate risk PTC was 51 months (range 12-142 months)
- **Overall recurrence** was observed in 30 (2.0%) patients, including 11 structural recurrences and 19 biochemical recurrences,
- median RFS was 52 months, with a range of 10 to 142 months
- **Before** PSM, the **overall recurrence rates** were **1.4**% (19/1349) and **8.0**% (11/138) in the RAIT and non-RAIT groups, respectively ($\chi 2=27.275$, $P<.001$). **After PSM,** the overall recurrence rates were **1.6**% (9/552) and **7.9**% (11/138) in the RAIT and non-RAIT groups, respectively ($\chi 2 =15.770$, $P<.001$).

Impact of RAIT on Structural Recurrence in Patients With Intermediate-Risk PTC

- Structural recurrence was observed in 11 patients (0.7%), all of which were in the cervical lymph nodes

- The structural recurrence rate was **0.4%** (6/1349) in the RAIT group compared with **3.6%** (5/138) in the non-RAIT groups (χ^2=17.224, P<.001). As shown in Kaplan–Meier curves, the cumulative **RFSstructural** rate in the non-RAIT group was **53.8**% at 5 years, lower than that in the RAIT group (**98.1**% at 5 years) (P<.001, Fig. 2A)

- Ten patients presented with structural recurrence in the cohort after calibration using **PSM**. The structural re-currence rate was **0.9**% (5/552) in the RAIT group, and **3.6**% (5/138) in the non-RAIT group (χ^2=3.964, P=.046), and the 5-year RFSstructural rates were **98.8% and 53.8%** in the RAIT and non-RAIT groups, respectively (P=.007, Fig. 2B).

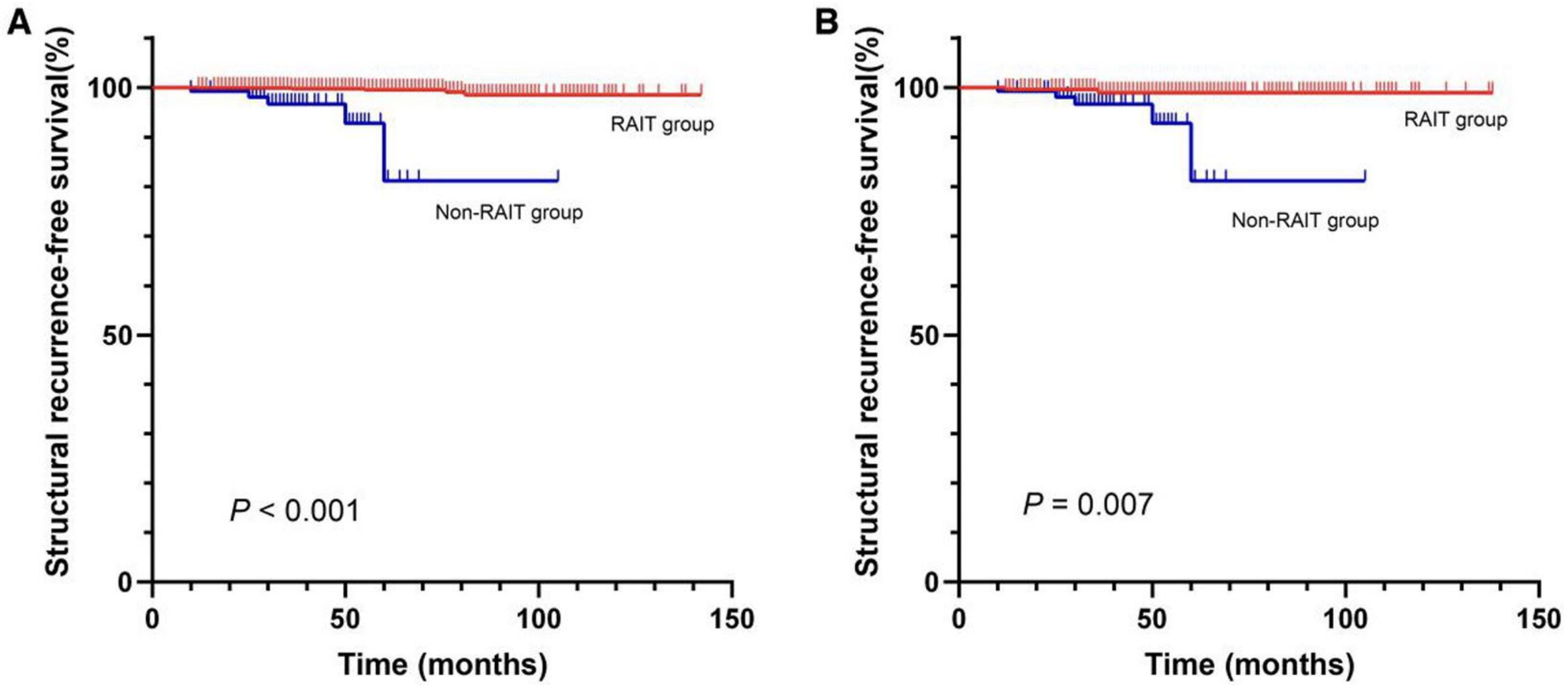

Figure 2. Kaplan–Meier curves for $RFS_{structural}$ of patients with intermediate-risk PTC with unstimulated Tg ≤ 1 ng/mL or stimulated Tg ≤ 10 ng/mL according to RAIT before (A) and after (B) propensity score matching. $RFS_{structural}$, structural recurrence-free survival; PTC, papillary thyroid cancer; RAIT, radioactive iodine therapy.

- Univariate and Cox regression analyses revealed that the **absence of RAIT was a risk factor for structural recurrence, both before and after PSM (Table 3**).

- **After PSM:**

- univariate analysis revealed that **ETE** (P=.006), primary tumor **size** (P <.001), **stage** (P<.001), and **RAIT** (P=.046) were associated with structural recurrence.

- The **Cox regression analysis** identified that **non-RAIT** (hazard ratio [HR] 10.572, 95% CI 2.439-45.843, P=.002), primary tumor **size**>4 cm (HR 5.787, 95% CI 1.114-30.056, P=.037), and **stage II** (HR 29.764, 95% CI 3.718-238.290, P=.001) were risk factors for disease recurrence

Table 3. Univariate and multivariate analyses of risk factors for structural recurrence

	Before PSM				After PSM			
Parameters	NED	SR	χ^2	Cox regression HR (95% CI, *P* value)	NED	SR	χ^2	Cox regression HR (95% CI, *P* value)
Age, years			0.639				0.589	
<55	1279	9			529	9		
≥55	197	2			151	1		
Sex			0.629				0.225	
Male	505	3			226	3		
Female	971	8			454	7		
Number of LNM			0.684				0.792	
<5	988	8			534	7		
x or ≥5	488	3			146	3		
Ratio of LNM			0.441				0.394	
<50%	1052	9			537	8		
≥50%	424	2			143	2		
ETE			0.250				0.006	
Negative	1123	10			350	10		1
Positive	353	1			330	0		−(*P* = .932)
Multifocality			0.817				0.819	
Negative	988	7			498	7		
Positive	488	4			182	3		
Bilateral tumor			0.210				0.518	
Negative	1098	10			518	9		
Positive	378	1			162	1		
Tumor size			0.001				<0.001	
≤4 cm	1442	9		1	668	8		1
>4 cm	34	2		6.71 (1.42-31.64, *P* = .016)	12	2		5.79 (1.11-30.06, *P* = .037)
N stage			0.051				0.227	
N0/N1a	1163	6			594	8		
N1b	313	5			86	2		
Stage			0.784				<0.001	
I	1373	10			680	8		1
II	103	1			0	2		29.76(3.72-238.29, *P* = .001)
Treatment			<0.001				0.046	
TT + RAI	1343	6		1	547	5		1
TT alone	133	5		22.18(6.01-81.91, *P* < .001)	133	5		10.57 (2.44-45.83, *P* = .002)

Impact of RAIT on Biochemical Recurrence in Patients With Intermediate-Risk PTC

- Biochemical recurrence was observed in 19 patients (1.4%)
- patients with biochemical recurrence had a median unstimulated Tg of 1.96 ng/mL (range 1.06-22.21 ng/mL).
- Before PSM, the biochemical recurrence rates were **1.0**% (13/1349) and **4.3**% (6/138) in the RAIT and non-RAIT groups, respectively ($\chi 2=8.842$, P=.003); the Kaplan–Meier curves showed longer RFSbiochemical in the RAIT group than in the non-RAIT group (5-year RFSbiochemical: **98.3**% vs **63.6**%, P<.001, Fig. 3A).

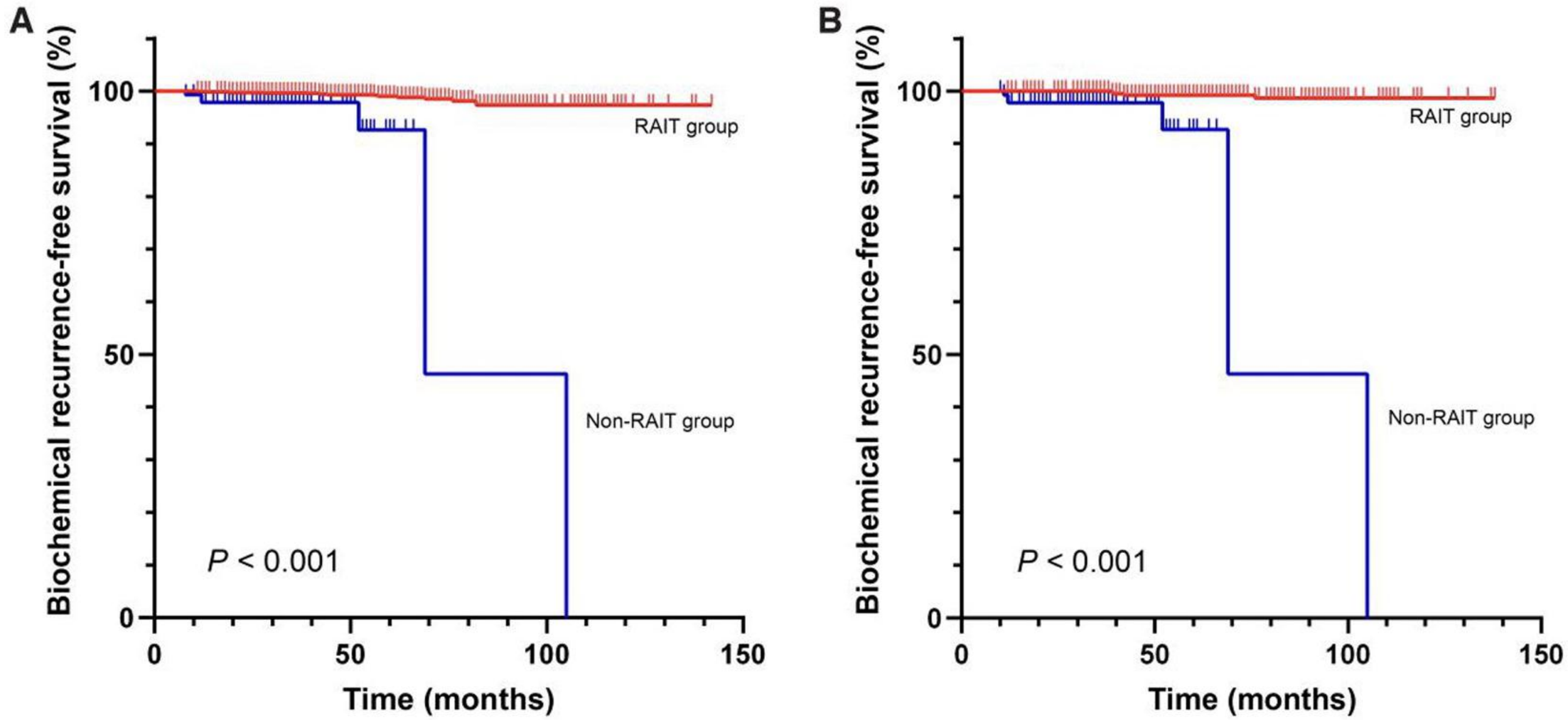

Figure 3. Kaplan–Meier curves for $RFS_{biochemical}$ of intermediate-risk PTC patients with unstimulated Tg ≤ 1 ng/mL or stimulated Tg ≤ 10 ng/mL according to RAIT before (A) and after (B) the propensity score matching. $RFS_{biochemical}$, biochemical recurrence-free survival; PTC, papillary thyroid cancer; RAIT, radioactive iodine therapy.

- Ten (1.9%) patients experienced biochemical recurrence in the co-hort **after calibration with PSM.**
- The recurrence rates were **0.7**% (4/552) and **4.3**% (6/138) in the RAIT and non-RAIT groups, respectively (χ2=7.769, P=.005); the Kaplan– Meier curves showed that the 5-year RFSbiochemical was **98.9**% and **63.6**% in the RAIT and non-RAIT groups, re-spectively (P<.001, Fig. 3B).
- Univariate and Cox regression analyses revealed that the **absence of RAIT was a risk factor for biochemical recurrence, both before and after PSM** (Table 4)
- After PSM, univariate analysis revealed that the numbers of **LNM** (P=.010), pri-mary tumor **size** (P=.016), **N stage** (P=.002), and **RAIT** (P =.005) were associated with biochemical recurrence. Cox regression indicated that **only RAIT** (HR 16.568, 95% CI 3.670-74.803, P<.001) was the **independent predictor of bio-chemical recurrence.**

Table 4. Univariate and multivariate analyses of risk factors for biochemical recurrence

Parameters	Before PSM				After PSM			
	NED	BR	χ^2	Cox regression HR (95% CI, *P* value)	NED	BR	χ^2	Cox regression HR (95% CI, *P* value)
Age, years			0.756				0.876	
<55	1272	16			530	8		
≥55	196	3			150	2		
Sex			0.804				0.829	
Male	501	7			226	3		
Female	967	12			454	7		
Number of LNM			0.020				0.010	
<5	988	8		1	537	4		1
x or ≥5	480	11		2.85 (0.99-8.17, *P* = .051)	143	6		4.59(0.87-24.18, *P* = .073)
Ratio of LNM			0.212				0.755	
<50%	1045	16			538	7		
≥50%	423	3			142	3		
ETE			0.801				0.146	
Negative	1118	15			352	8		
Positive	350	4			328	2		
Multifocality			0.726				0.896	
Negative	983	12			497	8		
Positive	485	7			183	2		
Bilateral tumor			0.477				0.786	
Negative	1092	16			519	8		
Positive	376	3			161	2		
Tumor size			0.010				0.016	
≤4 cm	1435	16		1	668	8		1
>4 cm	33	3		3.83 (1.04-14.09, *P* = .043)	12	2		4.03 (0.67-24.47, *P* = .130)
N stage			0.002				0.002	
N0/N1a	1160	9		1	597	5		1
N1b	308	10		2.29 (0.79-6.68, *P* = .128)	83	5		2.68 (0.51-14.077, *P* = .244)
Stage			0.766				0.864	
I	1365	18			678	10		
II	103	1			2	0		
Treatment			0.003				0.005	
TT + RAI	1336	13		1	548	4		1
TT alone	132	6		14.31 (4.96-41.29, *P* < .001)	132	6		16.57 (3.67-74.80, *P* < .001)

Abbreviation: BR, biochemical recurrence; HR, hazard ratio; PSM, propensity score matching; NED; no evidence of disease; RAI, radioactive iodine; TT, total thyroidectomy.

Discussion

- The recurrence risk of intermediate-risk PTC patients ranges from 5% to 20%
- In recent years, there have been controversies regarding RAIT decisions for intermediate-risk patients, especially for the relatively low recurrence subgroup
- A recent retrospective study that analyzed the SEER database showed that RAIT significantly decreased disease-specific mortality in patients with intermediate-risk PTC and that male patients aged ≥45 years and with tumor size >20 mm may benefit from RAIT

- In our study, patients who **did not receive RAIT** had an approximately **10-fold and 16-fold increased risk of structural and biochemical recurren**ce, respectively.
- **Structural** recurrence was found in **0.7%** of patients, and all recurrence lesions were in the cervical lymph nodes, indicating a **better prognosis** for patients with intermediate-risk PTC with **low Tg levels.**
- Even with such a low recurrence rate, the *regression analysis after adjusting for confounders con-firme*d that **RAIT significantly decreased the risk of structural recurrence and improved RFSstructur**al in intermediate-risk patients with PTC.

- However, it is worthwhile considering whether RAIT should be withheld in patients willing to undergo reoperation and concerned about the financial burden and side effects of RAIT **because the recurrence rate of this group was relatively low, rarely leading to death or distant metastasis.**

- In other studies, RAIT also failed to improve recurrence, but the sample size was small, and there was selection bias in selecting patients

- All patients in our cohort underwent total thyroidectomy and therapeutic or prophylactic CND
- A recent study with a large sample size confirmed that **prophylactic CND** does not decrease locoregional recurrence in patients.However, **prophylactic CND identified 28% to 33% of LNM** that could not be detected on preoperative examination, thus altering the patients' postoperative staging and management
- Therefore, all patients undergoing total thyroidectomy in our center received prophylactic CND, which is not common practice in the rest of the world.

- Patients with low Tg levels have been shown to have an excellent prognosis, especially those with *stimulated Tg ≤10 ng/ mL or unstimulated Tg≤1 ng/mL*
- intermediate-risk patients with low Tg levels present a low recurrence rate (12, 14, 26, 27); therefore, the need for RAIT in intermediate-risk PTC patients with low Tg levels is more **controversial** than in those with high Tg levels.
- Thus, our study focused on determining whether RAIT helps decrease recurrence in intermediate-risk patients with unstimulated Tg≤1 ng/mL or stimulated Tg≤ 10 ng/mL.

- limitations. Firstly, this study was retrospective; we could not exclude selection bias resulting from physician and patient preferences, even though we performed adjustments using the PSM method.
- Secondly, due to the small number of recurrences observed in the study, subgroup analysis could not be performed;

Conclusion

- Intermediate-risk PTC with unstimulated Tg≤1 ng/mL or stimulated Tg≤10 ng/mL exhibits low risk of relapse.
- RAIT decreases the risk of structural and biochemical recurrence in patients with intermediate-risk PTC with low Tg levels.
- Further prospective, randomized studies are needed to **con-firm** these findings and to **identify the subclinical characteris-tics of patients who should receive RAIT.**