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ORIGINAL ARTICLE – ENDOCRINE TUMORS

Lack of Efficacy of Radioiodine Remnant Ablation for Papillary Thyroid Microcarcinoma: Verification Using Inverse Probability of Treatment Weighting

Hyemi Kwon, MD[1,2], Min Ji Jeon, MD, PhD[1], Won Gu Kim, MD, PhD[1], Suyeon Park, MD[1], Mijin Kim, MD[1], Tae Yong Kim, MD, PhD[1], Minkyu Han, PhD[3], Dong Eun Song, MD, PhD[4], Tae-Yon Sung, MD, PhD[5], Jong Ho Yoon, MD, PhD[5], Suck Joon Hong, MD, PhD[5], Jin-Sook Ryu, MD, PhD[6], Young Kee Shong, MD, PhD[1], and Won Bae Kim, MD, PhD[1]

[1]Division of Endocrinology and Metabolism, Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea; [2]Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Korea; [3]Department of Clinical Epidemiology and Biostatistics, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea; [4]Department of Pathology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea; [5]Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea; [6]Department of Nuclear Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

ABSTRACT

Background. Most of the increase in thyroid cancer in recent decades has been due to papillary thyroid microcarcinoma (PTMC). We evaluated the efficacy of radioiodine remnant ablation (RRA) in patients with PTMC.

Methods. This historical cohort study included 1932 PTMC patients without lateral cervical lymph node (LN) or distant metastasis who underwent total thyroidectomy (TT) during the median 8.3 years of follow-up. The clinical outcomes of patients with or without RRA were compared using weighted logistic regression models with the inverse probability of treatment weighting (IPTW) method and considering risk factors, including age, sex, primary tumor size, extrathyroidal extension, multifocality, and central cervical LN metastasis.

Results. The median primary tumor size of the RRA group was significantly larger than that of the no-RRA group (0.7 vs. 0.5 cm, $P < 0.001$). There were significantly more patients with multifocality, extrathyroidal extension, and cervical LN metastasis in the RRA group compared with the no-RRA group. There was no significant difference in recurrence-free survival between the two groups ($P = 0.11$). Cox proportional–hazard analysis with IPTW by adjusting for clinicopathological risk factors demonstrated no significant difference in recurrence of PTMC according to RRA treatment (hazard ratio [HR] 2.02; 95% confidence interval [CI] 0.65–6.25; $P = 0.2$).

Conclusions. RRA had no therapeutic effect on the clinical outcomes of patients with PTMC who underwent TT. Surgical treatment without RRA could be applicable for patients with PTMC if there is no evidence of lateral cervical LN metastasis or distant metastasis.

Radioiodine remnant ablation (RRA) therapy after total thyroidectomy in patients with differentiated thyroid carcinoma (DTC) facilitates the detection of recurrent disease by remnant ablation and treats persistent disease or potential metastatic disease.[1,2] The American Thyroid Association guidelines recommend routine RRA therapy for the high-risk group of patients with DTCs.[1] However, RRA is not routinely recommended for low- or intermediate-risk DTC groups because of conflicting evidence on the effect of RRA.[1]

Most of the increase in thyroid cancer in recent decades has been due to papillary thyroid microcarcinoma (PTMC), which is defined as papillary thyroid carcinoma (PTC) that is $\leq$1 cm in the greatest dimension.[3,4] PTMC usually has

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W. B. Kim, MD, PhD
e-mail: kimwb@amc.seoul.kr

TABLE 1 Comparison of clinicopathological features in patients with PTMC between the no-RRA and RRA groups

	Total ($n = 1932$)	No-RRA ($n = 284$)	RRA ($n = 1648$)	P
Age (year)	50 (43–57)	50 (42–58)	50 (43–57)	0.84[a]
≥45	1356 (70)	198 (70)	1158 (70)	0.91[b]
Sex (female)	1689 (87)	259 (91)	1430 (87)	0.05[b]
Primary tumor size (cm)	0.7 (0.5–0.8)	0.5 (0.4–0.7)	0.7 (0.5–0.8)	<0.001[a]
Extrathyroidal extension (Y)	995 (52)	92 (33)	903 (55)	<0.001[b]
Multifocality (Y)	639 (33)	84 (30)	555 (34)	0.20[b]
Cervical LN metastasis (Y)	564 (29)	12 (4)	552 (34)	<0.001[b]

Continuous variables are presented as medians (inter-quartile range)

Categorical variables are presented as numbers with percentages

RRA radioactive remnant ablation, *LN* lymph node

[a] P value estimated by Mann–Whitney U test

[b] P value estimated by Chi square test

an excellent prognosis with 2–4% locoregional recurrence and 1–2% distant metastases.[5–7] Several clinicopathological factors, such as age, large primary tumor size, extrathyroidal extension (ETE), multifocal tumor, and cervical lymph node (LN) metastasis, are associated with recurrence in patients with PTMCs.[7–13]

Currently, there is no evidence for the clinical benefit of RRA on overall or disease-specific survival in patients with low-risk DTC including PTMC.[14–16] One study suggested that RRA might decrease the risk of recurrences in patients with PTMC, whereas others demonstrated that RRA could not reduce recurrences.[11,17,18] However, these studies had a critical bias because the impacts of clinicopathological risk factors associated with recurrent disease were not fully considered. In some studies, patients with lateral cervical LN metastasis (N1b) were included, and the follow-up duration was relatively short for evaluating recurrent disease.

In this study, we evaluated the effect of RRA in PTMC patients without lateral cervical LN metastases or distant metastases who underwent total thyroidectomy (TT). We compared recurrent disease in patients with or without RRA using a logistic regression model with inverse-probability-of-treatment weighting (IPTW) to control for the clinicopathological risk factors associated with recurrent PTMC and to minimize selection bias in the decision for RRA treatment.

METHODS

Study Design and Patients

This historical cohort study included 1932 patients with PTMC who underwent TT and routine prophylactic central compartment LN dissection between 1998 and 2009 at Asan Medical Center in Seoul, Korea. Patients with lateral cervical LN metastasis (N1b, $n = 166$) or distant metastasis (M1, $n = 5$) at initial presentation were excluded. Of the 1932 patients, 1648 (85%) underwent RRA treatment, whereas 284 (15%) did not (Table 1). Applying weighted Cox proportional-hazards regression models with IPTW, we compared the clinical outcomes of 1932 patients with PTMC according to RRA treatment. We used the IPTW method to adjust for risk factors, including age, sex, primary tumor size, ETE, multifocality, and central cervical LN metastasis (pN1a). This study was approved by the institutional review board of Asan Medical Center.

Management and Follow-up Protocol

Whether to perform RRA was determined depending on the clinicopathological risk factors, the decision of the physician, and patient preference. As previously described, some patients who underwent TT received ablative doses (2.96–5.55 GBq) of I-131 according to their tumor stage 5–6 weeks after the initial surgery.[19,20] Patients who underwent TT were administered levothyroxine for thyroid-stimulating hormone (TSH) suppression regardless of RRA treatment. All patients underwent regular follow-up with physical examination, thyroid function tests, and serum thyroglobulin (Tg) and anti-Tg antibody (Ab) measurement every 6–12 months.[21] Neck ultrasonography (US) was performed during the first 6–12 months after initial therapy and repeated thereafter at 12–24 month intervals. Diagnostic whole-body scans (WBS) were performed for some patients after TT and RRA treatment. Additional diagnostic imaging studies were performed to detect recurrence or distant metastasis in some patients.

Definition and Response-to-Initial Therapy

No evidence of disease (NED) was defined as an undetectable level of serum stimulated Tg (<1 ng/mL), negative TgAb, and no suspicious structural disease in the RRA group.[22] Final clinical outcomes were defined as no structural evidence of disease or recurrence in both RRA and no-RRA groups. Recurrence was defined as a newly developed pathologically or cytologically proven lesion based on imaging studies.[22] Because serum Tg levels could not be used to diagnose recurrence in patients of no-RRA group, serum Tg levels were not used in the definition of recurrence.[23] Recurrence-free survival (RFS) was defined as the time interval between initial surgery and the detection of structural recurrent disease.

According to the response-to-therapy of dynamic risk stratification (DRS), patients were classified into four response categories based on the clinical, biochemical, and imaging findings.[23–26] The best response during the first 2 years of follow-up was used to define the response to initial therapy. In patients treated with TT and RRA, excellent response was defined as no structural disease and either suppressed Tg < 0.2 ng/mL or stimulated Tg < 1 ng/mL.[1,24,25] A biochemical incomplete response was defined as no structural disease and suppressed Tg ≥ 1 ng/mL, stimulated Tg ≥ 10 ng/mL or rising anti-Tg Ab levels.[1,24,25]

In patients who underwent TT without RRA treatment, excellent response was defined as no structural disease and either suppressed Tg < 0.2 ng/mL or stimulated Tg < 2 ng/mL.[23,26] A biochemical incomplete response was defined as no structural disease and suppressed Tg > 5 ng/mL, or stimulated Tg > 10 ng/mL, or increasing anti-Tg Ab levels.[23,26] For all of the patients, structural incomplete response was defined as structural or functional evidence of disease regardless of Tg or anti-Tg Ab levels.[23–26] Indeterminate response was defined as non-specific biochemical or structural findings that cannot be classified as either biochemical or structural incomplete response.[23–26]

Statistical Analysis

For the statistical analysis, SAS version 9.4 was used (SAS Institute Inc., Cary, NC). Continuous variables are presented as medians with interquartile ranges (IQR). Categorical variables are presented as numbers with percentages. The Mann–Whitney *U* test was used to compare continuous variables. The Chi square test and Fisher's exact test were used to compare categorical variables. Using weighted Cox proportional-hazards regression models with the IPTW, risk factors, such as age, sex, primary tumor size, ETE, multifocality, and central compartment LN metastasis (pN1a), were adjusted. With that technique, weights for the no-RRA group were the inverse of (1—the propensity score), and weights for the RRA group were the inverse of the propensity score. The propensity scores, which indicate the predicted probability of being underwent RRA conditional on the observed covariates, were estimated by multiple logistic-regression analysis. Hazard ratios (HRs) with 95% confidence intervals (CIs) or odds ratios (ORs) with 95% CIs were used to evaluate the risks of recurrence or excellent response according to RRA treatment. RFS curves were constructed using the Kaplan–Meier method, and the log-rank test was used to evaluate differences in RFS between two groups. *P* values <0.05 were considered statistically significant.

RESULTS

Baseline Clinicopathological Characteristics of Patients

The baseline characteristics of the 1932 patients with PTMC are listed in Table 1. The median age of patients was 50 years (IQR 43–57) and 1356 patients (70%) were older than 45 years. In total, 87% of patients were female. The median primary tumor size was 0.7 cm (IQR 0.5–0.8), and 995 patients (52%) had ETE. Multifocal tumors were present in 639 patients (33%), and 564 patients (29%) had cervical LN metastases.

There was no significant difference in age, sex, and the presence of multifocal tumors between the no-RRA group and RRA group (Table 1). The primary tumor size in the RRA group was significantly larger than that in the no-RRA group (0.7 vs. 0.5 cm, $P < 0.001$). The proportion of patients with ETE was significantly higher in the RRA group than in the no-RRA group (55 vs. 33%, $P < 0.001$). The proportion of patients with cervical LN metastasis was significantly higher in the RRA group than in the no-RRA group (34 vs. 4%, $P < 0.001$). The median dose of I-131 in the RRA group was 2.8 GBq (IQR 1.1–5.6).

Clinicopathological Factors Associated with Recurrent Disease of PTMC

During a median 8.3 years (range 6.7–10.0) of follow-up, 50 patients (3.0%) in the RRA group and 3 patients (1.1%) in the no-RRA group had recurrence. There was no significant difference in RFS between the two groups (*P* for log-rank = 0.11; Fig. 1).

We evaluated clinicopathological factors associated with RFS by Cox proportional-hazards regression models (Table 2). In univariate analyses, RRA was not associated with RFS. Older age (HR 0.95, 95% CI 0.92–0.98;

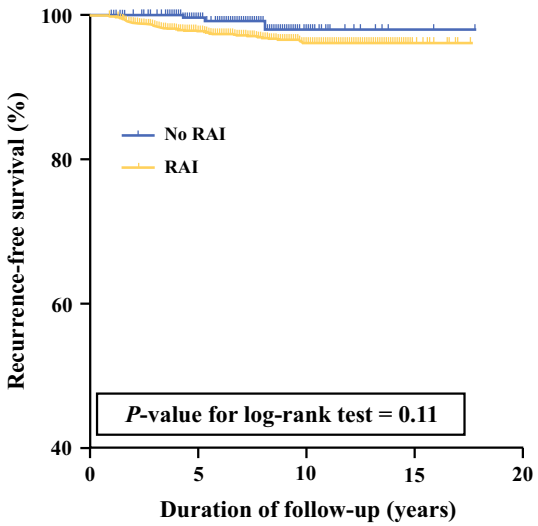

FIG. 1 Recurrence-free survival (RFS) according to radioiodine remnant ablation (RRA). There was no significant difference in RFS between RRA and no-RRA group for PTMC patients

$P < 0.001$) and female gender (HR 0.32, 95% CI 0.18–0.58; $P < 0.001$) were associated with better RFS. Larger primary tumor size (HR 1.03, 95% CI 1.01–1.04; $P < 0.001$), ETE (HR 2.18, 95% CI 1.21–3.92; $P = 0.009$), multifocal tumor (HR 2.19, 95% CI 1.28–3.75; $P = 0.004$), and cervical LN metastasis (HR 5.52, 95% CI 3.07–9.92; $P < 0.001$) were significantly associated with increased recurrence during the follow-up. RRA treatment was not associated with RFS in multivariate analyses (model 1 and model 2) after adjusting for age, sex, primary tumor size, ETE, multifocality, and cervical LN metastases (Table 2). Younger age, male gender, ETE, multifocality, and cervical LN metastasis were independent risk factors for recurrence in patients with PTMC.

When we applied weighted Cox proportional-hazards regression models with the IPTW method to adjust for other risk factors, RRA therapy was not related to recurrent disease during the follow-up (HR 2.02, 95% CI 0.65–6.25; $P = 0.22$).

Most recurrences (80%, 40 of 50 patients) in the RRA group occurred in lateral cervical LNs. The remaining ten patients had recurrences at operation bed. The median duration from initial thyroid surgery to recurrence was 3.1 years (IQR 1.8–5.5). In the no-RRA group, two patients had recurrent diseases at operation bed and one patient had a lateral cervical LN recurrence. The median duration from initial thyroid surgery to recurrence was 5.3 years (IQR 4.8–6.5).

Clinicopathological Factors Associated with Excellent Response in DRS of PTMC

In total, 1410 patients (85.6%) in the RRA group and 257 patients (90.5%) in the no-RRA group had an excellent response during the first 2 years of follow-up. We evaluated clinicopathological factors associated with excellent

TABLE 2 Cox proportional-hazard models to evaluate clinicopathological factors associated with recurrence-free survival

	Univariate analysis				Multivariable analysis 1[a]				Multivariable analysis 2[b]				IPTW[c]			
	HR	95% CI		*P*	HR	95% CI		*P*	HR	95% CI		*P*	HR	95% CI		*P*
		Lower	Upper			Lower	Upper			Lower	Upper			Lower	Upper	
RRA	2.57	0.80	8.24	0.11	0.90	0.26	3.09	0.86	1.03	0.30	3.53	0.96	2.02	0.65	6.25	0.22
Age (year)	0.95	0.92	0.98	<0.001	0.95	0.92	0.98	<0.001								
≥45	0.30	0.18	0.52	<0.001					0.34	0.20	0.59	<0.001				
Sex (female)	0.32	0.18	0.58	<0.001	0.40	0.22	0.73	0.003	0.44	0.24	0.80	0.007				
Primary tumor size (mm)	1.03	1.01	1.04	<0.001	1.02	1.00	1.03	0.03								
ETE (Y)	2.18	1.21	3.91	0.009	1.62	0.89	2.96	0.12	1.71	0.94	3.12	0.08				
Multifocality (Y)	2.19	1.28	3.76	0.004	1.80	1.04	3.11	0.04	1.76	1.02	3.04	0.04				
LN metastasis (Y)	5.48	3.05	9.86	<0.001	3.66	1.96	6.87	<0.001	4.02	2.15	7.50	<0.001				

The adjustment using weighted Cox proportional-hazards regression models with the IPTW was applied. With that technique, weights for the no-RRA group were the inverse of (1—the propensity score), and weights for the RRA group were the inverse of the propensity score. The propensity scores, which indicate the predicted probability of being underwent RRA conditional on the observed covariates, were estimated by multivariable logistic-regression analysis

RRA radioactive remnant ablation, *ETE* extrathyroidal extension, *LN* lymph node, *IPTW* inverse-probability-of-treatment, *HR* hazard ratio, *CI* confidence interval

[a] Multivariate analysis 1 was adjusted for age, sex, primary tumor size, ETE, multifocality, and cervical LN metastasis after variable selection

[b] Multivariate analysis 2 was adjusted for age ≥45 year, sex, ETE, multifocality, and cervical LN metastasis after variable selection

[c] Inverse-probability-of-treatment weighted (IPTW) method

response by logistic regression models (Table 3). In univariate analyses, RRA was associated with excellent response (OR 0.62, 95% CI 0.40–0.93; $P = 0.03$). Older age (OR 1.03, 95% CI 1.02–1.05; $P < 0.001$), smaller primary tumor size (OR 0.99, 95% CI 0.98–0.99; $P < 0.001$), unifocal tumor (OR 0.76, 95% CI 0.58–0.99; $P = 0.04$), and no cervical LN metastasis (OR 0.45, 95% CI 0.34–0.58; $P < 0.001$) were significantly associated with excellent response. Sex and ETE were not associated with excellent response.

RRA treatment was not associated with excellent response in multivariate analyses (model 1 and model 2) after adjusting for age, sex, primary tumor size, ETE, multifocality, and cervical LN metastases (Table 3). Younger age, larger primary tumor size, and cervical LN metastasis were independent risk factors for non-excellent response in patients with PTMC. When we applied weighted logistic regression models with the IPTW method to adjust for other risk factors, RRA therapy was significantly related with excellent response (OR 0.63, 95% CI 0.40–0.95; $P = 0.03$).

DISCUSSION

In this study, we evaluated the clinical outcomes of 1932 patients with PTMC who underwent TT and prophylactic central LN dissection according to RRA therapy. Weighted Cox proportional-hazards regression models with the IPTW method were applied to adjust for risk factors, including age, sex, primary tumor size, ETE, multifocality, and central compartment LN metastasis (pN1a). This approach was used to control the risk factors that might affect the prognosis of PTMC and to minimize selection bias in the decision for RRA therapy. There was no significant difference in risk of recurrence according to RRA after adjusting for risk factors using IPTW (HR 2.02, 95% CI 0.65–6.25; $P = 0.22$). The proportion of patients with excellent response was lower in the RRA group than in the no-RRA group. No-RRA therapy was significantly associated with excellent response after adjusting for risk factors using IPTW (OR 0.63, 95% CI 0.40–0.95; $P = 0.03$). These findings suggest that surgical treatment without RRA could be sufficient for patients with PTMC even if they have any risk factors, such as ETE, multifocality, and central LN metastasis.

If there was no evidence of lateral cervical LN metastasis or distant metastasis, most patients with PTMC had an excellent prognosis. These findings are consistent with those of previous studies.[5–9] In multivariate analyses, younger age, male gender, multifocality, and cervical LN metastasis were associated with recurrent disease as in previous studies.[7–12] In this study, the baseline clinicopathological features were significantly different between the no-RRA and RRA groups because the clinical decisions

TABLE 3 Logistic regression models to evaluate clinicopathological factors associated with excellent response

	Univariate analysis				Multivariable analysis1[a]				Multivariable analysis2[b]				IPTW[c]			
	OR	95% CI		*P*	OR	95% CI		*P*	OR	95% CI		*P*	OR	95% CI		*P*
		Lower	Upper			Lower	Upper			Lower	Upper			Lower	Upper	
RRA	0.62	0.40	0.93	0.03	0.84	0.53	1.29	0.45	0.82	0.52	1.25	0.37	0.63	0.40	0.95	0.03
Age (year)	1.03	1.02	1.05	<0.001	1.03	1.02	1.04	<0.001								
≥45	1.80	1.37	2.34	<0.001					1.68	1.28	2.20	<0.001				
Sex (female)	1.42	0.98	2.02	0.06												
Primary tumor size (mm)	0.99	0.98	0.99	<0.001	0.99	0.98	1.00	0.001								
ETE (Y)	1.04	0.81	1.35	0.74	1.26	0.96	1.66	0.10	1.25	0.95	1.65	0.11				
Multifocality (Y)	0.76	0.58	0.99	0.04	0.81	0.61	1.07	0.14	0.81	0.62	1.08	0.14				
LN metastasis (Y)	0.45	0.34	0.58	<0.001	0.52	0.39	0.69	<0.001	0.50	0.38	0.66	<0.001				

The adjustment using weighted Cox proportional-hazards regression models with the IPTW was applied. With that technique, weights for the no-RRA group were the inverse of (1—the propensity score), and weights for RRA group were the inverse of the propensity score. The propensity scores, which indicate the predicted probability of being underwent RRA conditional on the observed covariates, were estimated by multivariable logistic-regression analysis

RRA radioactive remnant ablation, *ETE* extrathyroidal extension, *LN* lymph node, *IPTW* inverse-probability-of-treatment, *OR* odds ratio, *CI* confidence interval

[a] Multivariate analysis 1 was adjusted for age, sex, primary tumor size, ETE, multifocality, and cervical LN metastasis after variable selection

[b] Multivariate analysis 2 was adjusted for age ≥45 year, sex, ETE, multifocality, and cervical LN metastasis after variable selection

[c] Inverse-probability-of-treatment weighted (IPTW) method

for RRA therapy depended on the risk factors related to poor prognosis and recurrence. Median primary tumor size of the RRA group was significantly larger than that of the no-RRA group. ETE and cervical LN metastasis (N1a) also were more frequent in the RRA group. Therefore, we applied the IPTW method which is a type of propensity score analysis to overcome a possible bias by other risk factors.

The DRS system using response to therapy is known to be effective for estimating the risk of recurrence in patients with differentiated thyroid cancer (DTC).[23,25,26] Patients who achieved an excellent response to initial therapy had a very low risk of recurrence.[24] In this study, the proportion of patients with excellent response was lower in the RRA group than in the no-RRA group. No-RRA therapy was significantly associated with excellent response after adjusting for risk factors using IPTW (OR 0.63, 95% CI 0.40–0.95; $P = 0.03$). Diagnostic WBSs were more commonly performed in patients with RRA therapy than in patients without RRA therapy. The proportion of patients with indeterminate response was higher in the RRA group than in the no-RRA group because there was a faint uptake in the thyroid bed on diagnostic WBS.

Adjuvant RRA therapy for patients with DTC could influence quality of life, and there is a possibility of adverse effects. Preparing for RRA is inconvenient for patients, especially for those who are not administered recombinant human TSH. Loss of taste and dry mouth due to salivary gland damage are two of the most common adverse effects. In addition, safety precautions must be implemented to prevent others from being exposed to the radiation. However, its benefit in most patients with PTMC is unclear. There is conflicting evidence of improved disease-specific survival or RFS in patients with PTMC.[11,14–18] In this study, we demonstrated that RRA had no additional benefit to improve RFS or to achieve excellent response for most patients with PTMC.

The purpose of RRA after TT in patients with DTC is not only adjuvant therapy but also remnant ablation to facilitate the detection of recurrent disease using serum Tg measurements or diagnostic WBS.[1,2] However, all recurrences in this study were locoregional and were detected by regular neck US. Serum Tg measurement did not have an important role for detection of recurrent disease. Due to its low sensitivity, diagnostic WBS is not recommended for low- or indeterminate-risk patients with undetectable Tg with negative anti-Tg antibodies and a negative US.[1,27–29]

This study might have the possibility of selection bias due to its retrospective nature and the enrollment of patients only from our single tertiary referral center. In total, 85% of the patients underwent RRA, and the baseline clinicopathological features were different between the no-RRA and RRA groups. However, we could overcome these limitations using the IPTW method, which is a type of propensity score analysis. Moreover, we evaluated the effect of RRA with a large number of PTMC patients without lateral cervical LN metastasis or distant metastasis. We could compare the clinical outcomes of PTMC patients with or without RRA for a relatively long follow-up period.

In conclusion, RRA therapy did not reduce recurrence in patients with PTMC who underwent TT. Surgical treatment without RRA could be applicable for most patients with PTMC if there is no evidence of lateral cervical LN metastasis or distant metastasis. Further prospective research with large numbers of patients and a longer follow-up period is required for RRA therapy in patients with PTMCs.

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DISCLOSURE The authors declare that they have no conflict of interest.

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