Radioactive iodine ablation may not decrease the risk of recurrence in intermediate-risk papillary thyroid carcinoma

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Abstract

The use of radioactive iodine (RAI) ablation in patients with intermediate-risk papillary thyroid carcinoma (PTC) who show microscopic extrathyroidal extension (ETE), regional lymph node (LN) metastasis, tumors with aggressive histology, or vascular invasion has been debated due to the lack of data regarding long-term prognosis in this risk group. Therefore, the purpose of this study was to resolve the controversy surrounding the prognostic benefit of RAI ablation, especially in intermediate-risk PTC patients. We retrospectively reviewed the medical records of 8297 intermediate-risk PTC patients who underwent primary total thyroidectomy with or without neck dissection at the Thyroid Cancer Center, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea, between January 1997 and June 2015. Of these 8297 patients, 7483 (90.2%) received RAI ablation. After adjusting for clinicopathological characteristics, RAI ablation did not significantly decrease the risk of loco-regional recurrence (LRR) (adjusted hazard ratio (HR)=0.852, $P=0.413$). Moreover, RAI ablation did not decrease the risk of LRR even in intermediate-risk PTC patients with aggressive features such as *BRAF* positivity (adjusted HR=0.729, $P=0.137$), tumor size >1 cm (adjusted HR=0.762, $P=0.228$), multifocality (adjusted HR=1.032, $P=0.926$), ETE (adjusted HR=0.870, $P=0.541$), and regional LN metastasis (adjusted HR=0.804, $P=0.349$). Furthermore, high-dose RAI ablation (>100 mCi) did not significantly decrease the risk of LRR (adjusted HR=0.942, $P=0.843$). Therefore, RAI ablation in intermediate-risk PTC patients should be considered on the basis of tailored risk restratification.

Key Words

- ▶ papillary thyroid carcinoma
- ▶ radioactive iodine ablation
- ▶ intermediate-risk
- ▶ recurrence

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Introduction

Papillary thyroid carcinoma (PTC) is the most prevalent thyroid cancer and its incidence has increased rapidly worldwide (Ahn & Park 2009, Siegel et al. 2014). This

increase is likely to be due to earlier detection of small PTCs as a result of widespread use of high-resolution ultrasonography (US) and fine-needle aspiration biopsy

(FNAB) (Davies & Welch 2006). The long-term prognosis of PTC is generally good with early detection, appropriate surgical resection, and radioactive iodine (RAI) ablation (Davies & Welch 2010).

The American Thyroid Association (ATA) Management Guidelines (Cooper *et al.* 2009) recommend RAI ablation for high-risk patients with gross extrathyroidal extension (ETE), distant metastasis, or incomplete tumor resection. RAI ablation is not recommended in low-risk patients without ETE, regional or distant metastasis, vascular invasion, or aggressive histology (e.g. tall cell, insular, columnar cell carcinoma). However, RAI ablation in intermediate-risk PTC patients who show microscopic ETE, regional lymph node (LN) metastasis, tumors with aggressive histology, or vascular invasion has been debated due to the lack of data regarding long-term prognosis in this risk group.

In support of RAI ablation, a number of large retrospective studies have shown a significant reduction in disease recurrence and cause-specific mortality (DeGroot *et al.* 1990, Mazzaferri & Jhiang 1995, Chow *et al.* 2003, Jonklaas *et al.* 2006). Moreover, a recent retrospective study of a large group using the National Cancer Database demonstrated that RAI ablation is associated with improved overall survival in intermediate-risk PTC patients (Ruel *et al.* 2015). However, other studies have failed to show prognostic benefits of RAI ablation (Hay *et al.* 2002, Pelizzo *et al.* 2006, Lundgren *et al.* 2007, Podnos *et al.* 2007), including a report in which RAI ablation did not prevent recurrence in intermediate-risk papillary thyroid microcarcinoma (Kim *et al.* 2013).

To resolve the above controversies surrounding the prognostic benefit of RAI ablation in intermediate-risk PTC patients, we conducted a retrospective analysis using a large group of patients from a single institution. Because the mortality rate is extremely low in PTC (Davies & Welch 2010), we adopted loco-regional recurrence (LRR) as a primary endpoint.

Materials and methods

Patient selection

Between January 1997 and June 2015, a total of 20,030 patients underwent thyroidectomy at the Thyroid Cancer Center of Samsung Medical Center, a tertiary referral center in Korea. Among 20,030 patients, we included a total of 8297 intermediate-risk PTC patients, defined as patients with microscopic ETE, regional LN metastasis, tumor with aggressive histology (e.g. tall cell, insular,

columnar cell carcinoma), or vascular invasion, who underwent primary total thyroidectomy (TT) with or without neck dissection. A total of 11,733 patients with the following conditions were excluded: previous history of thyroidectomy, lobectomy, or sub/near-TT, age <18 years, non-PTC carcinomas (follicular/medullary/anaplastic), mixed-type PTC, high-risk patients (with gross ETE, distant metastasis, or incomplete tumor resection), low-risk patients (without ETE, regional and distant metastasis, vascular invasion, or aggressive histology), or follow-up duration <6 months (residual malignancy or LN detected within 6 months after initial surgery, reoperation within 6 months after initial surgery, or loss to follow-up within 6 months).

Surgical strategy

TT was performed when the primary tumor size was >1 cm, and when multifocality, bilaterality, ETE, or regional LN metastasis was detected during preoperative or intraoperative examination, according to the ATA management guidelines (Cooper *et al.* 2009). In our institution, TT is the standard treatment for PTC, and sub/near-TT is rarely performed. This study included cases with both therapeutic and prophylactic central neck dissection (CND). Therapeutic CND was performed when suspicious central LN metastasis (CLNM) was detected during preoperative or intraoperative examination. Prophylactic CND was performed on PTC patients with clinically uninvolved central neck LNs, in particular for advanced primary tumors (T3/T4) (Cooper *et al.* 2009), or according to the surgeon's preference at the time of operation. CND was performed immediately after the completion of TT and involved the removal of all nodes and fibro-fatty tissue extending vertically from the hyoid bone to the thoracic inlet and laterally from the medial border of the common carotid artery to the midline of the trachea. The recurrent laryngeal nerve was mobilized and skeletonized along its entire cervical course. In our institution, lateral neck dissection (LND) was performed in patients with clinically suspicious lateral LN metastasis (LLNM) confirmed by US, CT, and/or FNAB. LND was defined as excision of the lateral neck LNs, including modified radical neck dissection (MRND) and selective neck dissection (SND) (Robbins *et al.* 2002). MRND referred to the excision of lateral neck LNs, including levels II–V, with preservation of one or more nonlymphatic structures, such as the spinal accessory nerve, internal jugular vein, or sternocleidomastoid muscle. Level I dissection was not

performed unless indicated. SND referred to the excision of suspicious lateral neck LNs with preservation of one or more of the LN groups that are routinely removed in the MRND.

Histopathologic examination of surgical specimens

Surgical specimens were microscopically examined by two or more experienced pathologists, and the following histopathologic factors were assessed: cell type of the main lesion, primary tumor size (measured as the longest diameter of the largest lesion), location, multifocality, ETE, lymphovascular invasion, margin involvement, regional LN metastasis, and underlying conditions of the thyroid, such as chronic lymphocytic thyroiditis (CLT). To distinguish tumor bilaterality from multifocality, we defined multifocality as more than two conventional PTC lesions in one lobe, regardless of the presence of tumor bilaterality.

Postoperative management and follow-up

All patients underwent regular follow-up with clinical evaluations, including physical examinations, US, iodine-131 (¹³¹I) scans, serum thyroglobulin (Tg), and Tg antibodies at 6–12-month intervals. Thyroid-stimulating hormone (TSH) suppression therapy (serum TSH level less than 0.5 mIU/L) by levothyroxine with or without RAI ablation was considered as an initial postoperative therapy. RAI ablation was performed with ¹³¹I according to the ATA guidelines (Cooper et al. 2009). Although RAI ablation was generally proposed for patients classified as high risk for recurrence (e.g. old age, larger tumor size, ETE, LN metastasis, and individual histology), the final decision was made based on the physician or patient preference. The first RAI ablation was performed 2–3 months after surgery when the level of TSH was greater than 30 mIU/L. Levothyroxine was stopped 4 weeks before RAI treatment and switched to liothyronine for 2 weeks, followed by the withdrawal of liothyronine for 2 weeks. Patients consumed a low-iodine diet for 2 weeks before RAI administration. Alternatively, recombinant TSH was used when patients could no longer tolerate levothyroxine withdrawal. The need for subsequent RAI ablation was determined based on serum Tg, anti-Tg antibody, and ¹³¹I scan. RAI administration and cumulative doses of RAI were recorded at follow-up. RAI after recurrence and diagnostic doses of RAI were not included. When RAI treatment was no longer needed for these patients, they received regular follow-up. Loss to follow-up, withdrawal, and deaths were

censored as of the last date of follow-up. When recurrence was suspected, patients underwent US-guided aspiration biopsy with or without measurement of washout Tg levels and/or a thyroid CT or a positron emission tomography/CT. In our study, LRR was defined as the presence of tumor or metastatic LN at least 6 months after the initial surgery.

Statistical analysis

Statistical analysis was performed using SPSS version 22.0 software (Chicago, IL, USA), and statistically significant differences were defined as those with *P*-values less than 0.05. Continuous variables were presented as mean ± standard deviation (s.d.) and categorical variables were presented as the number of cases with the percentage (%) and odds ratio (OR). Chi-squared and Fisher's exact tests were used for categorical variables and the Student's *t*-test was used for continuous variables. Kaplan–Meier methods and the log-rank test were adopted for analysis of time-dependent variables. The adjusted hazard ratio (HR) and 95% confidence intervals (CIs) for LRR were calculated using Cox regression models. To verify the prognostic impact of RAI ablation according to clinicopathological characteristics, several subset analyses were performed.

Results

Clinicopathological characteristics of intermediate-risk PTC patients according to RAI ablation

Of the 8297 intermediate-risk PTC patients, 7483 (90.2%) received RAI ablation and 814 (9.8%) did not (Table 1). Young age ($P < 0.001$), extensive neck dissection ($P < 0.001$), large tumor size ($P < 0.001$), multifocality ($P = 0.026$), ETE ($P = 0.037$), absence of CLT ($P = 0.003$), and regional LN metastasis ($P < 0.001$) were significantly associated with an increased likelihood of receiving RAI ablation. In our institution, *BRAF* mutation analysis was initiated in 2008 and was performed in 2779 intermediate-risk PTC patients. *BRAF* mutation positivity ($P = 0.005$) was significantly associated with an increased likelihood of receiving RAI ablation in intermediate-risk PTC patients. Gender ($P = 0.164$), the type of surgical approach ($P = 0.183$), the variant type of PTC ($P = 0.118$), and bilaterality ($P = 0.116$) were not significantly associated with the likelihood of receiving RAI ablation in intermediate-risk PTC patients. The mean dose of RAI in the ablation group was 101.5 mCi and 2135 (28.5%) patients received more than 100 mCi.

Table 1 Clinicopathological characteristics of intermediate-risk PTC patients according to RAI ablation.

	RAI (–) (n=814)	RAI (+) (n=7483)	OR	P-value
Gender				
Female	656 (80.6)	5873 (78.5)		
Male	158 (19.4)	1610 (21.5)	1.138 (0.949–1.366)	0.164
Age				
Mean ± s.d. (years)	50.8 ± 13.5	46.4 ± 11.7	NA	<0.001
<45 years	282 (34.6)	3427 (45.8)		
≥45 years	532 (65.4)	4056 (54.2)	0.627 (0.539–0.730)	<0.001
Surgical approach				
Open	762 (93.6)	7088 (94.7)		
Minimal invasive	52 (6.4)	395 (5.3)	0.817 (0.606–1.101)	0.183
Neck dissection				
No	131 (16.1)	820 (11.0)		
CND	567 (69.7)	5092 (68.0)		
LND	116 (14.3)	1571 (21.0)	NA	<0.001
BRAF ^a				
Negative	86 (22.3)	396 (16.5)		
Positive	299 (77.7)	1998 (83.5)	1.451 (1.116–1.888)	0.005
Variants of PTC				
Conventional	796 (97.8)	7329 (97.9)		
Follicular	5 (0.6)	72 (1.0)		
Diffuse sclerosing	1 (0.1)	52 (0.7)		
Oncocytic	7 (0.9)	6 (0.1)		
Tall cell	1 (0.1)	7 (0.1)		
Cribiform morular	1 (0.1)	4 (0.1)		
Solid	1 (0.1)	4 (0.1)		
Oxyphilic	2 (0.2)	3 (0.0)		
Columnar	0 (0.0)	3 (0.0)		
Insular	0 (0.0)	2 (0.0)		
Clear	0 (0.0)	1 (0.0)	NA	0.118
Tumor size				
Mean ± s.d. (cm)	1.1 ± 1.0	1.3 ± 0.9	NA	<0.001
≤0.5 cm	176 (21.6)	1071 (14.3)		
0.5–1.0 cm	337 (41.4)	2649 (35.4)		
1.0–2.0 cm	225 (27.6)	2790 (37.3)		
2.0–4.0 cm	62 (7.6)	837 (11.2)		
>4.0 cm	14 (1.7)	136 (1.8)	NA	<0.001
Multifocality				
Absent	620 (76.2)	5427 (72.5)		
Present	194 (23.8)	2056 (27.5)	1.211 (1.022–1.434)	0.026
Bilaterality				
Absent	599 (73.6)	5310 (71.0)		
Present	215 (26.4)	2173 (29.0)	1.140 (0.968–1.343)	0.116
ETE				
Absent	193 (23.7)	1540 (20.6)		
Present	621 (76.3)	5943 (79.4)	1.199 (1.011–1.423)	0.037
CLT				
Absent	577 (70.9)	5592 (74.7)		
Present	237 (29.1)	1891 (25.3)	0.823 (0.702–0.966)	0.017
Regional LN metastasis				
Absent	539 (66.2)	2393 (32.0)		
CLNM	193 (23.7)	3697 (49.4)		
LLNM	82 (10.1)	1393 (18.6)	NA	<0.001
Administered RAI ^b				
Mean ± s.d. (mCi)	0.0	101.5 ± 84.5	NA	<0.001
0 mCi	814 (100.0)	0 (0.0)		
≤30 mCi	0 (0.0)	1532 (20.5)		
30–100 mCi	0 (0.0)	3816 (51.0)		
100–150 mCi	0 (0.0)	930 (12.4)		
>150 mCi	0 (0.0)	1205 (16.1)	NA	<0.001

PTC, papillary thyroid carcinoma; RAI, radioactive iodine; OR, odds ratio; s.d., standard deviation; ETE, extrathyroidal extension; CLT, chronic lymphocytic thyroiditis; LN, lymph node; CLNM, central lymph node metastasis; LLNM, lateral lymph node metastasis; NA, not available.

^aBRAF mutation analysis began in 2008 and was performed in 2779 intermediate-risk PTC patients. ^bCounted by the endpoint of follow-up.

Prognostic impact of RAI ablation on LRR in intermediate-risk PTC patients

The mean follow-up duration for enrolled intermediate-risk PTC patients was 64.8 ± 39.7 months (range: 6.0–219.9). The mean follow-up time was significantly longer in the ablation group than in the no-ablation group (66.7 vs 48.2 months, $P < 0.001$). LRR was observed in 427 patients (5.1%). Recurrence sites included regional LNs in 394 patients (92.3%) and the operation bed in 33 patients (7.7%). The recurrence-free survival (RFS) rates in the no-ablation group were 95.7% (229/252) at 5 years, 89.0% at 10 years, and 89.0% at 15 years. The RFS rates in the ablation group were 94.9% at 5 years, 91.6% at 10 years, and 88.8% at 15 years. There was no significant difference in LRR according to RAI ablation ($P = 0.627$, by log-rank test) (Fig. 1). After adjusting for clinicopathological characteristics using the Cox proportional hazards model (Table 2), RAI ablation did not significantly decrease the risk of LRR in intermediate-risk PTC patients (adjusted HR=0.852, $P = 0.413$). Tumor size per 0.1 cm (adjusted HR=1.325, $P < 0.001$), multifocality (adjusted HR=1.412, $P = 0.002$), ETE (adjusted HR=1.413, $P = 0.011$), CLNM (adjusted HR=2.473, $P < 0.001$), and LLNM (adjusted

HR=4.704, $P < 0.001$) significantly increased the risk of LRR. However, CND (adjusted HR=0.588, $P = 0.002$) significantly decreased the risk of LRR. Male gender (adjusted HR=1.243, $P = 0.054$), age per 10 year (adjusted HR=0.986, $P = 0.711$), minimally invasive surgery (adjusted HR=0.844, $P = 0.621$), bilaterality (adjusted HR=1.130, $P = 0.263$), and CLT (adjusted HR=0.948, $P = 0.659$) did not show any prognostic impact on LRR. On subgroup analyses (Table 3), RAI ablation did not significantly decrease the risk of LRR under any other clinical conditions, even in intermediate-risk PTC patients with aggressive features such as BRAF positivity (adjusted HR=0.729, $P = 0.137$), tumor size >1 cm (adjusted HR=0.762, $P = 0.228$), multifocality (adjusted HR=1.032, $P = 0.926$), ETE (adjusted HR=0.870, $P = 0.541$), and regional LN metastasis (absent (adjusted HR=0.732, $P = 0.416$), CLNM (adjusted HR=1.106, $P = 0.825$), and LLNM (adjusted HR=0.699, $P = 0.194$)). The prognostic impact of RAI ablation was also assessed according to surgical extent; however, there was no significant influence on LRR (TT (adjusted HR=0.768,

Table 2 Cox proportional hazards model for LRR in intermediate-risk PTC patients.

	Adjusted HR (95% CI)	P-value
RAI ablation	0.852 (0.581–1.250)	0.413
Male gender	1.243 (0.996–1.551)	0.054
Patient age (per 10 years)	0.986 (0.915–1.062)	0.711
Surgical approach		
Open (reference)	NA	NA
Minimally invasive	0.844 (0.430–1.654)	0.621
Neck dissection		
No (reference)	NA	NA
CND	0.588 (0.420–0.824)	0.002
LND	0.683 (0.334–1.394)	0.295
Tumor size (per 0.1 cm)	1.325 (1.250–1.404)	<0.001
Multifocality (+)	1.412 (1.134–1.757)	0.002
Bilaterality (+)	1.130 (0.912–1.399)	0.263
ETE (+)	1.413 (1.083–1.843)	0.011
CLT (+)	0.948 (0.746–1.203)	0.659
Regional LN metastasis		
Absent (reference)	NA	NA
CLNM	2.473 (1.823–3.356)	<0.001
LLNM	4.704 (2.326–9.512)	<0.001

Figure 1 Unadjusted RFS for intermediate-risk PTC patients according to RAI ablation. RFS, recurrence-free survival; PTC, papillary thyroid carcinoma; RAI, radioactive iodine. *Calculated using the log-rank test. A full colour version of this figure is available at <http://dx.doi.org/10.1530/ERC-15-0572>.

LRR, loco-regional recurrence; PTC, papillary thyroid carcinoma; HR, hazard ratio; CI, confidence interval; RAI, radioactive iodine; ETE, extrathyroidal extension; CLT, chronic lymphocytic thyroiditis; LN, lymph node; CLNM, central lymph node metastasis; LLNM, lateral lymph node metastasis.

Table 3 Subgroup analysis of the prognostic impact of RAI ablation in intermediate-risk PTC patients.

	Adjusted HR of RAI ablation (95% CI)	P-value
Gender		0.939
Female	0.980 (0.589–1.632)	0.080
Male	0.586 (0.322–1.067)	
Age		
<45 years	0.772 (0.437–1.365)	0.373
≥45 years	0.907 (0.537–1.531)	0.715
BRAF (+) ^a	0.729 (0.480–1.106)	0.137
Conventional PTC	0.845 (0.575–1.241)	0.390
Tumor size		
≤1 cm	0.965 (0.442–2.107)	0.928
>1 cm	0.762 (0.490–1.185)	0.228
Multifocality (+)	1.032 (0.527–2.023)	0.926
ETE (+)	0.870 (0.557–1.359)	0.541
Regional LN metastasis		
Absent	0.732 (0.345–1.554)	0.416
CLNM	1.106 (0.454–2.696)	0.825
LLNM	0.699 (0.407–1.200)	0.194
Surgical extent		
TT	0.768 (0.291–2.029)	0.595
TT+CND	1.160 (0.541–2.488)	0.703
TT+CND+LND	0.708 (0.423–1.185)	0.189
RAI > 100 mCi ^b	0.942 (0.692–1.570)	0.843
LRR at 48 months ^c	0.794 (0.501–1.259)	0.327

LRR, loco-regional recurrence; PTC, papillary thyroid carcinoma; RAI, radioactive iodine; HR, hazards ratio; CI, confidence interval; ETE, extrathyroidal extension; LN, lymph node; TT, total thyroidectomy.

^aBRAF mutation analysis was performed in 2779 intermediate-risk PTC patients and 2394 (86.1%) patients tested positive. ^bComparing the no-ablation group ($n=814$) with the RAI >100mCi group ($n=2135$).

^cBecause the mean follow-up time was significantly longer in the ablation group than in the no-ablation group (66.7 months vs 48.2 months, $P<0.001$), a subgroup analysis was performed to evaluate the prognostic impact of RAI ablation at 48 months after initial surgery, the mean follow-up time in no-ablation group.

$P=0.595$), TT+CND (adjusted HR=1.160, $P=0.703$), and TT+CND+LND (adjusted HR=0.708, $P=0.189$)). Furthermore, even high doses of RAI ablation (>100mCi) did not significantly decrease the risk of LRR (adjusted HR=0.942, $P=0.843$). Because the mean follow-up time was significantly longer in the ablation group than in the no-ablation group (66.7 vs 48.2 months, $P<0.001$), a subgroup analysis was performed to evaluate the prognostic impact of RAI ablation at 48 months after initial surgery, the mean follow-up time in the non-ablation group. However, we did not find a significant

impact of RAI ablation at 48 months after initial surgery (adjusted HR=0.794, $P=0.327$).

Discussion

As a result of a lack of prospective randomized trials (Sawka *et al.* 2008) and retrospective analyses based on current recommendations (Cooper *et al.* 2009), the prognostic benefit of RAI ablation in intermediate-risk PTC patients is unclear (Kim *et al.* 2013, Ruel *et al.* 2015). The purpose of this study was to resolve the controversy surrounding the use of postoperative RAI ablation in intermediate-risk PTC patients.

In this study, increased use of RAI ablation was associated with aggressive features such as large tumor size, multifocality, ETE, and regional LN metastasis, as recommended by ATA guidelines (Cooper *et al.* 2009) (Table 1). Young age and BRAF positivity were also significantly associated with an increased likelihood of receiving RAI ablation. Increased use of RAI ablation in the young age group can be explained by the associations between young age and aggressive features of PTC (Bonnet *et al.* 2009, Roh *et al.* 2011, Ito *et al.* 2014, Alzahrani *et al.* 2015). Likewise, the relationship between BRAF mutation with RAI ablation usage can be explained by its strong association with aggressive features of PTC (Xing *et al.* 2009). Interestingly, RAI ablation was administered less often in PTC patients with CLT. This is supported by previous studies, demonstrating that PTC with coexisting CLT is less often associated with ETE, advanced stage, and regional LN metastasis (Loh *et al.* 1999, Kim *et al.* 2009, Lee *et al.* 2013, Lang *et al.* 2014, Kim *et al.* 2016).

Survival analysis was not performed in this study because cause-specific death was observed in only 22 (0.3%) of 8297 intermediate-risk PTC patients. LRR was observed in 427 patients (5.1%), mostly in regional LNs (92.3%) (Hay *et al.* 2008). Kaplan–Meier survival analysis (Fig. 1) showed no difference in log-rank test results ($P=0.627$) for LRR according to RAI ablation. Furthermore, after adjusting for clinicopathological characteristics by the Cox proportional hazards model (Table 1), RAI ablation did not significantly decrease the risk of LRR in intermediate-risk PTC patients (adjusted HR=0.852, $P=0.413$). These results were consistent with those of a recent study on intermediate-risk papillary thyroid microcarcinoma (Kim *et al.* 2013). However, another large retrospective study demonstrated that RAI ablation is associated with an improved overall survival in intermediate-risk PTC patients (Ruel *et al.* 2015). Several hypotheses could be suggested to explain the lack of prognostic impact of

RAI ablation on LRR in indeterminate-risk PTC patients. First, it is possible that microscopically detectable residual thyroid cancer has little chance of evolving into clinically and prognostically significant disease. However, there is general agreement on the benefit of RAI ablation in high-risk patients with grossly remnant cancer or grossly detectable distant metastasis (Cooper et al. 2009). Second, due to the indolent nature of PTC (Davies & Welch 2010), the follow-up period in our study might be too short to detect a significant difference in LRR.

As shown in Table 2, CND significantly decreased the risk of LRR. In this study, we included both therapeutic and prophylactic CND. Because US is often limited in assessing the deep anatomical spaces of the central neck compartment (Ito et al. 2006, Stulak et al. 2006), it has been generally known that a considerable number of PTC patients are eventually found to have CLNM at the time of surgery or in pathology specimens, up to 90% (Wada et al. 2003, Pereira et al. 2005). From the above factors, for the management central neck area, in addition to therapeutic CND, prophylactic CND was also recommended (Cooper et al. 2009). Thus, because there was a chance to remain undetected CLNM in no CND group, CND group showed better prognosis than no CND group. However, more recent studies have reported that prophylactic LND yields LLNM in 8–23% of patients (Hartl et al. 2012, Ducoudray et al. 2013). Because there was no evidence to indicate that prophylactic LND improves survival or loco-regional control, prophylactic LND was not recommended in the guidelines (Cooper et al. 2009). In our study, LND did not significantly decrease the risk of LRR. This result should not be interpreted as that LND does not show any therapeutic benefit on LRR in PTC patients, but should be interpreted with the concept of 'noninferiority'. Following the guidelines, in our institution, we only performed therapeutic LND in patients with clinically suspicious LLNM. Therefore, there was a little chance to remain undetected LLNMs in no LND group, contrary to central neck compartment. As shown in Table 1, among the 1687 patients who underwent LND, LLNM was found in 1475 (87.4%) patients. Therefore, it is likely that there was no significant difference in prognosis between the patients with and without clinically suspicious LLNM because LLNMs were removed by LND.

Some studies have shown higher recurrence rates in older patients (Lin et al. 1998, Hay et al. 2002). However, in other studies (Mazzaferri & Jhiang 1994, Ito et al. 2012), young age was an independent risk factor for LRR. In contrast to reports from previous studies (Jonklaas et al. 2006, Podnos et al. 2007), suggesting

that RAI ablation may benefit older patients, a recent study showed the survival benefits of RAI ablation in patients younger than 45 years (Ruel et al. 2015). In our study, RAI ablation did not significantly decrease the risk of LRR in either age group (45 and <45 years). *BRAF* mutation has been demonstrated to be associated with aggressive clinicopathological characteristics, such as advanced stage, ETE, LN metastasis, and tumor recurrence (Xing et al. 2009). In subgroup analysis focusing on *BRAF* mutation, there was no prognostic benefit of RAI ablation on LRR in *BRAF*-positive intermediate-risk PTC patients; however, subgroup analysis was not possible in the *BRAF*-negative group because of the small numbers. To make our results more homogeneous, we conducted subgroup analysis in patients with intermediate-risk conventional PTC, a major variant of PTC. We found that RAI ablation did not significantly decrease the risk of LRR in conventional PTC. A previous study by Kim and coworkers focusing on papillary thyroid microcarcinomas yielded results similar to ours (Kim et al. 2013). Therefore, we conducted subgroup analyses in two tumor size groups (≤ 1 and > 1 cm) and found that RAI ablation did not significantly decrease the risk of LRR in either group. The results from this and previous studies (Table 2) showed that multifocality (Hay et al. 2008, Ross et al. 2009), ETE (Byar et al. 1979, Hay et al. 1993), and regional LN metastasis (Chow et al. 2003, Hay et al. 2008, Ross et al. 2009) were independent predictors for LRR. Although we conducted further subgroup analyses in intermediate-risk PTC patients who showed multifocality, ETE, and regional LN metastasis, we did not observe a prognostic benefit of RAI ablation on LRR. To assess the prognostic impact of high-dose RAI ablation, we compared the no-ablation group ($n=814$) with the group that received RAI > 100 mCi ($n=2135$); however, there was no significant reduction of LRR in the RAI > 100 mCi group.

Preparation for RAI ablation requires withdrawal of thyroid hormone or recombinant TSH and a low-iodine diet, which could decrease the quality of life (Duan et al. 2015). In addition, when the patient is treated, precautions have to be taken to reduce the radiation exposure of family members and the public (ATA Taskforce on Radioiodine et al. 2011). Furthermore, the role of RAI ablation has changed with recognition of the complications and the risk of secondary cancers. Complications from RAI therapy have become more prevalent as the incidence of thyroid cancer has increased (2.4-fold increase from 1973 to 2002) (Davies & Welch 2006). A previous study using questionnaires from more than 200 patients after

RAI treatment suggested that immediate (<3 months after treatment) side effects occurred in 76.8% of patients and long-term (>3 months after treatment) complaints were reported by 61% (Alexander *et al.* 1998). It is critical for clinicians to recognize the increased risk for progressive or life-threatening disease associated with repeated ¹³¹I treatments with high iodine uptake, including recurrent sialoadenitis, xerostomia, dental caries, and second primary malignancies such as leukemia (Lee 2010). Therefore, only patients who are expected to have a prognostic benefit should be selected to receive RAI ablation.

Our study has several limitations. First, the inherent limitations of a nonrandomized retrospective cohort study, such as insufficient patient information, were inevitable. Second, although RAI therapy was generally proposed for patients with high-risk features (e.g. old age, larger tumor size, ETE, LN metastasis, and individual histology), the final decision was made based on the physician or patient preference. Therefore, there was a possible selection bias regarding RAI therapy. Third, LRR was more readily detected in patients who underwent RAI with more frequent follow-up visits and evaluation using imaging modalities. Fourth, the follow-up period was relatively short, and we did not conduct survival analysis because of the small number of cause-specific deaths. However, our study has significant strengths. We used medical records from a single institution, rather than a national or multicenter database, with rigorous exclusion and inclusion criteria. Furthermore, we assessed the prognostic impact of RAI ablation in a relatively large group of more than 8000 intermediate-risk PTC patients. The adjusted HR of RAI ablation from the multivariate analysis was verified in all patients as well as in subgroups according to clinically significant characteristics. Given the paucity of data regarding intermediate-risk PTC patients, our results based on a large group of patients with multivariate analysis may have valuable and practical implications for postsurgical management.

In conclusion, postoperative RAI ablation did not significantly decrease the risk of LRR in intermediate-risk PTC patients, even in patients with aggressive features such as BRAF positivity, large tumor size, multifocality, ETE, and LN metastasis. Therefore, RAI ablation in intermediate-risk PTC patients should be considered on the basis of tailored risk restratification. Further, long-term, large-scale, prospective randomized controlled studies will be required to fully elucidate the benefits of RAI ablation in intermediate-risk PTC patients.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution

S K Kim, J-W Woo, J H Lee, and I Park were involved in the review of literature, acquisition of data, and drafting and completing the manuscript. S K Kim, J-H Choe, J-H Kim, and J S Kim conceived the study, participated in the coordination and acquisition of data, and helped to draft the manuscript. All authors read and approved the final manuscript.

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