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ORIGINAL SCIENTIFIC REPORT

High-Dose RAI Therapy Justified by Pathological N1a Disease Revealed by Prophylactic Central Neck Dissection for cN0 Papillary Thyroid Cancer Patients: Is it Superior to Low-Dose RAI Therapy?

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Abstract

Objective One of the presumed advantages of prophylactic central neck dissection (pCND) is offering staging basis for more aggressive radioactive iodine (RAI) therapy, which postulates the necessity of high dose for treatment efficacy. The present study aims to compare the effectiveness between low-dose and high-dose RAI in a select cohort of cN0 papillary thyroid cancer (PTC) patients with pathological N1a (pN1a) disease revealed by pCND in terms of ablation rate and response to therapy. The frequency of short-term adverse effects between the two groups was also compared.

Patients and Methods From January 2014 to April 2016, cN0 PTC patients with pN1a disease revealed by pCND in our hospital were retrospectively reviewed. Patients with other indications for high-dose RAI, such as the presence of extrathyroidal extension, vascular invasion or suspicions of distant metastasis, were excluded. For the included patients, high dose (3700 MBq) was administered between January 2014 and August 2015 and low dose (1110 MBq) between August 2015 and April 2016. Ablation assessment was performed 6 months after RAI therapy. Response evaluation after RAI therapy was performed after 46.3 ± 9.5 months for high-dose group and 29.1 ± 2.6 months for low-dose group. All patients were also evaluated for short-term adverse effects 24 and 72 hours after RAI administration.

Results A total of 84 patients were enrolled. Among them, 42 were in the high-dose group and the other 42 in the low-dose group. There was no significant difference in ablation rate (P = 0.7707) and response to RAI therapy (P = 0.6454) between the two groups. Twenty-four hours after RAI administration, neck pain and swelling (33.3% VS. 11.9%; P = 0.0372) and gastrointestinal discomfort (45.2% vs. 21.4%; P = 0.0373) were significantly more frequent in the high-dose group.

Conclusion High-dose RAI therapy, with higher frequency of short-term adverse effects, appears to be not superior to low-dose RAI therapy for cN0 PTC patients with pN1a disease revealed by pCND to achieve better response to therapy. Further randomized studies with larger series of patients and longer follow-up duration, especially with the low-dose group, are needed to validate our results.

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Introduction

Prophylactic central neck dissection (pCND) is the dissection of clinically uninvolved cervical lymph nodes of the central compartment, which requires the removal of apparently normal cervical lymph nodes because of the high probability of microscopic infiltration [1, 2]. While the implementation of pCND is still controversial in cN0 papillary thyroid cancer (PTC) patients due to high incidence of complications and uncertainty of improved oncological outcome [3, 4], supporters argue that because pCND is the only way to identify microscopic central neck metastatic lymph nodes, it would allow for more accurate N stage information and patients with pathological N1a (pN1a) disease could benefit from more aggressive radioactive iodine (RAI) therapy [5, 6]. However, this idea postulates the necessity of high-dose therapy for treatment efficacy, which is not in agreement with the current trends of the following less aggressive strategies in the management of thyroid cancer.

In our department, the prescribed RAI dose experienced a drastic change for cN0-pN1a PTC patients without other adverse pathological indications. Before August 2015, we administered fixed high dose (3700 MBq) because pN1a was considered as with intermediate risk in the 2009 ATA guidelines. From August 2015 on, as we began to lower the dose for non-high-risk PTC patients, fixed low-dose RAI (1110 MBq) was administered to such patients after this time point. This scenario gives us an opportunity to contemplate on the necessity of high-dose therapy and its implications on controversy over the application of pCND as mentioned above.

In the present study, we reviewed the data of a select cohort of cN0 PTC patients with pN1a disease revealed by pCND who received RAI therapy between January 2014 and April 2016 in our department. Among these patients, we compared the efficacy of low-dose and high-dose therapy according to ablation rate and response to therapy system recommended by the 2015 American Thyroid Association (ATA) guidelines. The frequency of short-term adverse effects between the two groups was also compared.

Materials and methods

Patients' inclusion

This study was approved by the Ethics Committee of China-Japan Union Hospital of Jilin University. Between January 2014 and April 2016, cN0 PTC patients with pN1a disease revealed by pCND in our department were retrospectively reviewed. The inclusion criteria were: (1) No clinically positive central lymph node was detected preoperatively with ultrasound or palpation, (2) any pathologically confirmed metastatic lymph nodes revealed by pCND, (3) complete information in hospital database and (4) at least 18 years of age. The exclusion criteria were: (1) histology types other than PTC, (2) patients with other indications for high-dose RAI, such as the presence of extrathyroidal extension, vascular invasion or suspicion of distant metastases due to elevated serum thyroglobulin (Tg) level, radiological findings including whole-body scintigraphy (DxWBS), chest CT or PET/CT or histopathological biopsy and (3) elevated serum Tg antibody level (TgAb >115 IU/ml).

Surgical treatment

Extracapsular TT was performed for all patients. The recurrent laryngeal nerves were exposed until they were inserted into the larynx, and the parathyroid glands were always preserved. pCND included the removal of prelaryngeal, pretracheal and both the right and the left paratracheal nodal basins according to the indications of the ATA Working Group [7]. The addition of pCND at the time of operation was at the discretion of the attending surgeon.

RAI therapy

Within 1–4 month after total thyroidectomy in combination with pCND, patients were prepared by levothyroxine (LT4) withdrawal together with a strict low-iodine diet for at least 2–4 weeks, with the goal of attaining a TSH level above 30 mIU/L. Between January 2014 and August 2015, fixed high-dose RAI (3700 MBq) was administered to the included patients. Between August 2015 and April 2016, low-dose RAI (1110 MBq) was administered. All patients were hospitalized in isolation wards for radiation protection and possible short-term side effects. Patients can be discharged only when the remaining whole-body radioiodine activity was less than 400 MBq and their clinical conditions were stable.

Ablation assessment

The ablation assessment was performed 6 months after RAI therapy by DxWBS and Tg level. Ablation success was defined as the disappearance of any visible ^{131}I thyroid bed uptake or stimulated Tg levels $\leq$1 ng/mL in the absence of TgAb. Faint uptake in the thyroid bed with a stimulated Tg level $\leq$1 ng/mL was also considered to be ablation success.

Response evaluation

Response evaluation after RAI therapy was performed after 46.3 $\pm$ 9.5 months for high-dose group and 29.1 $\pm$ 2.6

months for low-dose group. Follow-up data included suppressed and stimulated Tg, TgAb, DxWBS and cervical ultrasound, chest CT and bone scintigraphic imaging. Based on these data, response to therapy was categorized as excellent, indeterminate, biochemical incomplete and structural incomplete according to the 2015 ATA guidelines [8]. Patients were considered to have an excellent response (ER) to therapy if they had negative imaging and either a suppressed Tg of less than 0.2 ng/ml or a stimulated Tg of less than 1.0 ng/mL. Patients with non-specific imaging findings, faint uptake in the thyroid bed on RAI scanning, suppressed Tg detectable but less than 1.0 ng/ml, stimulated Tg detectable but less than 10.0 ng/ml or TgAb stable or declining in the absence of structural or functional disease were considered to have an indeterminate response. Patients with negative imaging and a suppressed Tg of more than 1.0 ng/ml or a stimulated Tg of more than 10.0 ng/mL or increasing TgAb levels were considered to have a biochemical incomplete response. Patients with structural or functional evidence of disease with any Tg and TgAb level were considered to have a structural incomplete response.

Serological assays

Serological examinations included Tg, TgAb and TSH which were measured before RAI therapy as well as during follow-up. Tg, TgAb and TSH levels were determined using an electrochemiluminescence immunoassay (provided by Roche Diagnostics GmbH, Mannheim, Germany). The measurement ranges were 0.04 to 500 ng/mL, 10 to 4,000 IU/mL and 0.005 to 100 μIU/mL, respectively.

Statistical analysis

Statistical analysis was performed using MedCalc software (version 17.4.4; Mariakerke, Belgium). Comparisons of categorical variables were made with either Chi-squared test or Fisher's exact test as appropriate. Student's t test was used for normally distributed continuous variables, and the Mann–Whitney *U* test was used for non-normally distributed continuous variables. Logistic regression was used in multivariate analysis. $P < 0.05$ was considered with statistical significance.

Results

Patients

Between January 2014 and April 2016, a total of 1793 patients underwent RAI therapy for PTC in our department. Among them, eighty-four cN0 patients were identified according to the inclusion and exclusion criteria mentioned above. There were 23 males and 61 females aged 18–76 years (median 48 years). Between January 2014 and August 2015, high-dose (3700 MBq) RAI was administered for forty-two patients (27 with low risk and 15 intermediate risk). Between August 2015 and April 2016, low-dose (3700 MBq) RAI was administered for forty-two patients (25 with low risk and 17 intermediate risk). Patient characteristics are presented in Table 1. There were no significant differences in all these characteristics between the two groups (all $P > 0.05$).

Ablation assessment and response to RAI therapy

For ablation assessment, 83.33% (70/84) patients achieved ablation success after one RAI treatment. In total, 80.95% (36/42) received low-dose and 85.71% (34/42) received high-dose RAI. For response evaluation, 76.19% (64/84) patients achieved ER after one RAI treatment. In total, 73.81% (31/42) received low-dose and 78.57% (33/42) received high-dose RAI. In all patients, there was no significant difference in ablation rate ($P = 0.7707$) and response to RAI therapy ($P = 0.6454$) between the two groups. In subgroup analysis, we still found no significant difference between the two groups either in patients with tumor size < 1 cm with a mean size of 0.52 ± 0.22 cm ($P = 0.6681$ for ablation and $P = 0.3743$ for response) and patients with tumor size ≥ 1 cm with a mean size of 1.75 ± 0.79 cm ($P = 1.0000$ for ablation and $P = 0.9513$ for response), or in patients with low risk ($P = 1.0000$ for ablation and $P = 0.9162$ for response) and patients with intermediate risk ($P = 0.6911$ for ablation and $P = 0.5380$ for response) (Tables 2, 3).

Analysis of factors associated with ablation success and ER

We identified no significantly different factors between ablation success and ablation failure patients in univariate analysis. For response analysis, we identified that the ratio of metastatic lymph nodes in ER group was significantly higher than that of non-ER group ($P = 0.0271$) (Table 4). However, in multivariate analysis, all the factors including RAI dose, age at diagnosis, sex, tumor size, multifocality, number of metastatic lymph nodes, ratio of metastatic lymph nodes, metastatic lymph nodes size, TNM stage and ps-Tg were not significant in predicting ER (all $P > 0.05$).

Short-term adverse side effects

Twenty-four hours after RAI administration, neck pain and swelling (33.3% vs. 11.9%; $P = 0.0372$) and gastrointestinal discomfort (45.2% vs. 21.4%; $P = 0.0373$) were more frequent among the patients who received high-dose RAI. Seventy-two hours after RAI administration, all the

Table 1 Patient characteristics

	High dose (n = 42)	Low dose (n = 42)	P
Age at diagnosis [n (%)] (years)			0.8272
< 45	23 (54.76%)	21 (50.00%)	
≥ 45	19 (45.24%)	21 (50.00%)	
Sex [n (%)]			0.6252
Male	10 (23.81%)	13 (30.95%)	
Female	32 (76.19%)	29 (69.05%)	
Tumor size [n (%)] (cm)			0.6627
< 1	19 (45.24%)	22 (52.38%)	
≥ 1	23 (54.76%)	20 (47.62%)	
Multifocality [n (%)]			0.6620
Yes	21 (50.00%)	24 (57.14%)	
No	21 (50.00%)	18 (42.86%)	
Number of retrieved lymph node (n) (mean ± SD)	7.86 ± 3.32	8.10 ± 3.39	0.7019
Number of metastatic lymph nodes (n) (mean ± SD)	3.36 ± 2.39	3.93 ± 2.64	0.3026
Ratio of metastatic lymph nodes (%) (mean ± SD)	42.18 ± 24.08	49.89 ± 33.82	0.2322
Size of metastatic lymph nodes (cm) (mean ± SD)	0.22 ± 0.19	0.25 ± 0.21	0.5160
TNM stage [n (%)]			0.8482
I	23 (54.76%)	21 (50.00%)	
III	17(40.48%)	17 (40.48%)	
IV	2 (4.76%)	4 (9.52%)	
Recurrence risk [n (%)]			0.8225
Low	27 (64.29%)	25 (59.52%)	
Intermediate	15 (35.71%)	17 (40.48%)	
Ps-Tg	3.13 ± 3.54	3.40 ± 2.89	0.4862

Table 2 Ablation assessment and response evaluation to high-dose and low-dose RAI therapy according to tumor size

	All pN1a patients		P	Tumor size < 1		P	Tumor size ≥ 1		P
	High dose (n = 42)	Low dose (n = 42)		High dose (n = 19)	Low dose (n = 22)		High dose (n = 23)	Low dose (n = 20)	
Ablation assessment [n (%)]			0.7707			0.6681			1.0000
Success	36 (85.71%)	34 (80.95%)		17 (89.47%)	18 (81.82%)		19 (82.61%)	16 (80.00%)	
Failure	6 (14.29%)	8 (19.05%)		2 (10.53%)	4 (18.18%)		4 (17.39%)	4 (20.00%)	
Response evaluation [n (%)]			0.6454			0.3743			0.9513
Excellent response	33 (78.57%)	31(73.81%)		16 (84.21%)	17 (72.73%)		17 (73.91%)	14 (70.00%)	
Intermediate response	5 (11.91%)	6 (14.29%)		2 (10.53%)	2 (13.64%)		3 (13.04%)	4 (20.00%)	
Biochemical incomplete response	3 (7.14%)	3 (7.14%)		1 (5.26%)	2 (9.09%)		2 (8.70%)	1 (5.00%)	
Structural incomplete response	1 (2.38%)	2 (4.76%)		0 (0.00%)	1 (4.54%)		1 (4.35%)	1 (5.00%)	

symptoms reached to a low frequency and there was no significant difference for all of them between the high-dose group and the low-dose group (all P>0.05) (Fig. 1).

Discussion

cN0 PTC patients with any pathologically confirmed metastatic lymph nodes revealed by pCND were previously considered to be with intermediate risk of recurrence

Table 3 Ablation assessment and response evaluation to high-dose and low-dose RAI therapy according to occurrence risk

	Low-risk patients		*P*	Intermediate-risk patients		*P*
	High dose (n = 27)	Low dose (n = 25)		High dose (n = 15)	Low dose (n = 17)	
Ablation assessment [n (%)]			1.0000			0.6911
Success	24 (88.89%)	22 (88.00%)		12 (80.00%)	12 (70.59%)	
Failure	3 (11.11%)	3 (12.00%)		3 (20.00%)	5 (29.41%)	
Response evaluation [n (%)]			0.9162			0.5380
Excellent response	23 (85.19%)	21(84.00%)		10 (66.67%)	10 (58.82%)	
Intermediate response	2 (7.41%)	2 (8.00%)		3 (20.00%)	4 (23.53%)	
Biochemical incomplete response	1 (3.70%)	1 (4.00%)		2 (13.33%)	2 (11.77%)	
Structural incomplete response	1 (3.70%)	1 (4.00%)		0 (0.00%)	1 (5.88%)	

Table 4 Analysis of factors associated with ablation success and excellent response

	Ablation		*P*	Response		*P*
	Success (n = 70)	Failure (n = 14)		ER (n = 64)	Non-ER (n = 20)	
Age at diagnosis [n (%)] (years)			0.5605			0.6087
< 45	38 (54.29%)	6 (42.86%)		35 (54.69%)	9 (45.00%)	
≥ 45	32 (45.71%)	8 (57.14%)		29 (45.31%)	11 (55.00%)	
Sex [n (%)]			0.3312			0.2500
Male	21 (30.00%)	2 (16.67%)		20 (31.25%)	3 (15.00%)	
Female	49 (70.00%)	12 (83.33%)		44 (68.75%)	17 (85.00%)	
Tumor size [n (%)] (cm)			0.1433			0.4461
< 1	37 (52.86%)	4 (28.57%)		33 (51.56%)	8 (40.00%)	
≥ 1	33 (47.14%)	10 (71.43%)		31 (48.44%)	12 (60.00%)	
Multifocality [n (%)]			0.7784			0.4459
Yes	38 (54.29%)	7 (50.00%)		36 (56.25%)	9 (45.00%)	
No	32 (45.71%)	7 (50.00%)		28 (43.75%)	11 (55.00%)	
Number of retrieved lymph nodes (n) (mean ± SD)	8.03 ± 3.34	7.86 ± 3.32	0.6623	8.19 ± 3.42	7.40 ± 3.00	0.3567
Number of metastatic lymph nodes (n) (mean ± SD)	3.50 ± 2.37	4.21 ± 3.17	0.3375	3.41 ± 2.24	4.40 ± 2.74	0.1061
Ratio of metastatic lymph nodes (%) (mean ± SD)	43.83 ± 26.07	52.29 ± 31.02	0.2862	42.09 ± 29.15	58.66 ± 27.32	0.0271
Size of metastatic lymph nodes (cm) (mean ± SD)	0.23 ± 0.21	0.22 ± 0.16	0.8353	0.25 ± 0.22	0.19 ± 0.13	0.2771
TNM stage [n (%)]			0.5322			0.4013
I	38 (54.29%)	6 (42.86%)		35 (54.69%)	9 (45.00%)	
II	27 (38.57%)	7 (50.00%)		25 (39.06%)	9 (45.00%)	
IV	5 (7.14%)	1 (7.14%)		4 (6.25%)	2 (10.00%)	
RAI dose [n (%)]			0.7706			0.7983
Low	34 (48.57%)	8 (57.14%)		31 (48.44%)	11 (55.00%)	
High	36 (51.43%)	6 (42.86%)		33 (51.56%)	9 (45.00%)	
Ps-Tg	2.94 ± 3.00	4.08 ± 4.14	0.2243	2.82 ± 3.06	4.18 ± 4.00	0.1117

according to the 2009 ATA guidelines, and as such, many institutions administered high-dose RAI to destroy suspected metastatic lymph nodes with the intention of reducing risk of recurrence in these patients [9]. However, high dose is thought to be associated with dysfunctions in non-thyroidal organs (such as salivary gland, lachrymal and stomach) that express sodium iodide symporter and long-term effects such as second primary cancer [10–12]. Moreover, plenty of studies have demonstrated that low dose is as effective as high dose in controlling disease recurrence and improving overall survival in various PTC patient groups with low to intermediate risk [12–16]. Thus,

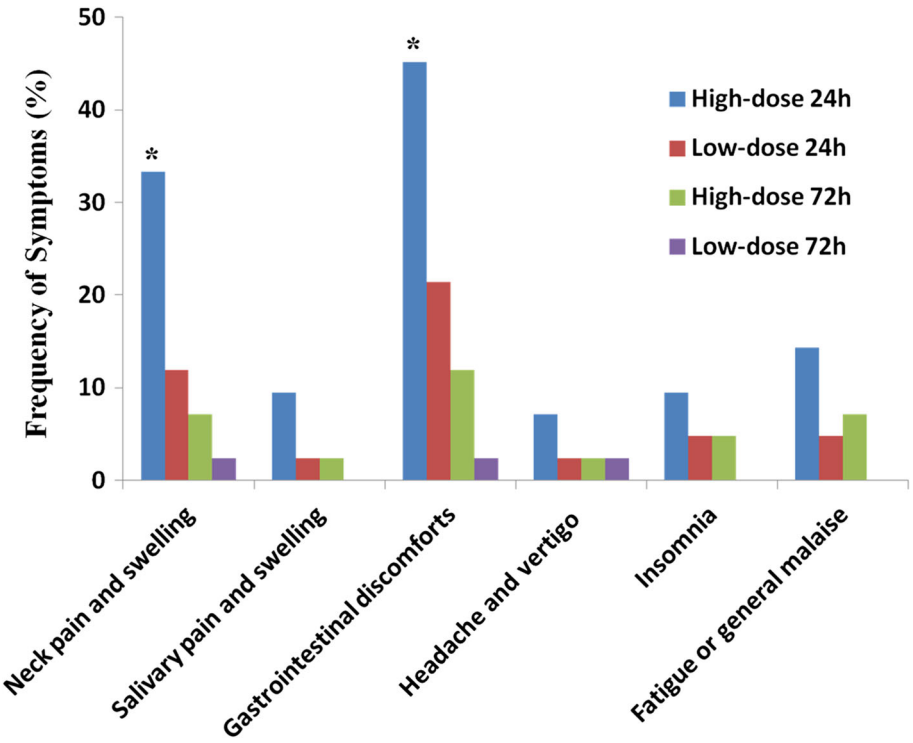

Fig. 1 Frequency of short-term side effects 24 and 72 hours after patients received high-dose and low-dose RAI therapy

we hypothesized that high dose holds no more advantage over low dose in terms of clinical outcome in cN0 patients with pN1a disease revealed by pCND.

In the present study, by using the response to therapy system, which was able to objectively predict real-time risk of recurrence and disease-specific death, we found that there was no significant difference in terms of clinical outcome between the high-dose group and low-dose group ($P = 0.6454$) in patients with pN1a disease or even in patients classified as indeterminate risk (above five lymph node metastases) according to the 2015 ATA guideline. This implies that high-dose RAI therapy may not be necessary in pN1a disease revealed by pCND for treatment efficacy. In other words, although the implementation of pCND might allow for more accurate nodal staging information, the additional pN1a information offered by pCND still could not serve as a justification for high-dose RAI to have a better clinical outcome. Taken into account the lack of clinical benefits and high incidence of hypoparathyroidism reported in numerous previous publications [3, 4, 7, 17, 18], the implementation of pCND is further challenged for its usage in helping RAI dosing based on our results.

Numerous studies have described lymph node characteristics such as size, number and ratio of metastatic lymph nodes and extranodal extension to be predictive of unfavorable clinical outcome [2, 19–21], but few have particularly evaluated the lymph nodes revealed by pCND in this regard. In cN0 PTC patients, Ryu et al. [22] and Zheng at al. [23] found that ratio of metastatic lymph nodes revealed by pCND was significantly related to recurrence both in univariate and in multivariate analysis. As far as we know, we are the first to evaluate the relationship between these lymph node characteristics and the new response to therapy system in such patients. However, in our study, although ratio of metastatic lymph nodes was found to be associated with excellent response in univariate analysis, none of the aforementioned lymph node characteristics was predictive of non-excellent response in multivariate analysis. This implies that the lymph node characteristics revealed by pCND may not serve as prognostic factors or even be used to decide postoperative strategies in cN0 PTC patients.

Moreover, we compared the short-term adverse side effects between the high-dose group and low-dose group 24 and 72 hours after RAI administration in these patients. Compared with the low-dose group, patients in the high-dose group experienced more neck pain and swelling and gastrointestinal discomforts 24 hours after RAI administration. This result further reinforces our assumption that high-dose RAI therapy may not be necessary.

It should be noted that there are several limitations to this study. Firstly, in our study, 61.9% (52/84) CN0 PTC patients were classified as low risk because pCND revealed no more than five lymph node metastases. For such patients, although the most recent ATA guideline does not recommend RAI therapy, the treatment was given on the basis of patients' preference and the role of RAI such as facilitating the detection of recurrence disease was fully

explained to them. Secondly, even though we selected an unique group of patients from a single institution and used strict exclusion/inclusion criteria to try to perform a clear analysis, this study is of retrospective nature and two small patient groups with relatively favorable prognosis were recruited from different time period. These may cause selection bias and a limited statistical validity. Therefore, further randomized studies with larger series of patients are needed to confirm our result. Lastly, the follow-up duration in our study, especially for the low-dose group, is relatively short. To finally clarify the necessity of high-dose therapy in cN0 PTC patients with pN1a disease revealed by pCND, long-term follow-up outcomes including parameters such as progression-free survival and overall survival are also needed.

Conclusion

High-dose RAI therapy, with higher frequency of short-term adverse effects, appears to be not superior to low-dose RAI therapy for cN0 PTC patients with pN1a disease revealed by pCND to achieve better response to therapy. Further randomized studies with larger series of patients and longer follow-up duration, especially with the low-dose group, are needed to validate our results.

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Compliance with ethical standards

Conflict of interest The author declares that they have no conflict of interest.

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