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Comparing High and Low-Dose Radio-Iodine Therapy in Thyroid Remnant Ablation Among Intermediate and Low-Risk Papillary Thyroid Carcinoma Patients—Single Centre Experience

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Abstract

The role of Iodine-131 therapy is well established as an adjuvant therapy and for thyroid remnant ablation in differentiated thyroid cancer (DTC); however controversy still exists regarding its appropriate dose. Purpose of this study was to compare the effectiveness of low-dose and high-dose Iodine-131 ablation therapies in low- and intermediate-risk PTC patients. Eighty-four patients were divided equally into Group I: Ablated with high dose of Iodine-131 and Group II: Ablated with low dose of Iodine-131. Iodine-131 WBS, serum *TG* levels and USG neck of all patients were performed at first presentation, 6 months, 1 year, and 2 years follow up. Results are as follows: Group I: 64%, 72%, and 76% intermediate-risk patients were disease free at the follow up intervals of 6 months, 1 year, and 2 years, respectively. Similarly 70%, 82%, and 82% low-risk patients were disease free at above mentioned intervals. Group II: 56%, 60%, and 64% were disease free among intermediate-risk patients while percentage of disease free low-risk patients was 70%, 76%, and 76% at follow up intervals. Low dose of radioactive Iodine-131 was found as effective as high dose in thyroid remnant ablation of PTC patients.

Keywords

intermediate-risk differentiated thyroid cancer, low-risk differentiated thyroid cancer, papillary thyroid carcinoma, radio-iodine-131 ablation therapy, low versus high dose, radio-iodine effectiveness

Introduction

The incidence of thyroid carcinoma is estimated at approximately 40 cases per million people per year in the USA.[1] Although the 10-year survival rate in cases of distant metastasis is approximately 25-40%,[2,3] the 10-year overall cause-specific survival for differentiated thyroid cancer (DTC) patients as a whole is estimated as approximately 85%.[4,5] DTC includes papillary and follicular histology which demonstrate better prognosis with multimodal management options. Papillary thyroid carcinoma (PTC) accounts for 80-85% while follicular thyroid cancer (FTC) is almost 10-15% of thyroid malignancies.[6] PTC prognosis depends upon the presence of aggressive factors including extra-capsular and vascular invasion, larger tumor size, and distant metastasis.[7,8] Despite

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significant biological differences both are treated on the same line. Surgery is the main-stay of treatment followed by radioactive-iodine (RAI) therapy.

It is mandatory to do risk stratification depending upon patient age, tumor size, histology, extra-thyroidal extension, completeness of primary tumor resection, nodal disease, and distant metastasis prior to deciding Iodine-131 ablative dose.[9] Basically radio-iodine therapy holds 2 main purposes in post thyroidectomy DTC patients, principal adjuvant therapy is mostly considered in patients with high-risk of loco-regional recurrence and metastatic disease[10] while ablative dose of Iodine-131 is administered to destroy existing remnant thyroid tissue. Conventional dose for thyroid remnant ablation is 1110 MBq, however it is higher (2590 MBq to 3700 MBq) when administered as adjuvant therapy. Appropriate dose for thyroid remnant ablation as well as adjuvant therapy is still a debate in low- and intermediate-risk DTC patients[11] however low-dose is found equally effective as high dose in terms of recurrence rate in a recently conducted meta-analysis[12] by Vardarli I, Weidemann F et al. At our tertiary care hospital we have been treating DTC with high-dose of radioactive iodine therapy however shift towards new strategies has begun although at slower pace. This clinical research study is conducted to evaluate the efficacy of low-dose Iodine-131 in low- and intermediate-risk differentiated (papillary) thyroid cancer patients.

Objective

To compare the effectiveness of low-dose Iodine-131 therapy against high-dose radio-iodine therapy in thyroid remnant ablation of intermediate- and low-risk PTC patients.

Methods

A significant number of PTC patients present to nuclear medicine and oncology OPD at our hospital for thyroid remnant ablation annually for example 3.8% patients of thyroid cancer were registered between 1984 till 2014 among total of 80,390.[13] In this research study, the effect of low- and high-dose radio-iodine therapy in eighty-four PTC patients was recorded prospectively from 2016 to 2019, study was approved by Institute of Nuclear Medicine and Oncology Lahore (INMOL) Ethical Review Board with Reference Number 03-11/21. Following NCCN 2016 and ATA 2015 guidelines these patients were identified as low- or intermediate-risk and divided into Group I (those who underwent high-dose ablation) and Group II (who were ablated with low-dose Iodine 131). High-dose was ≥3700 MBq and low-dose was ≤1110 MBq. It is double armed randomized observational study, high- and low-doses were administered on alternate weeks, patients (both intermediate- and low-risk) presenting in first week of the month were treated with high-dose while those presenting in second week were given low-dose radio-iodine and same sequence was repeated in third and fourth weeks of the month. Patient's age, gender, physical health condition, thyroid function levels, stimulated serum thyroglobulin (*TG*) and anti-thyroglobulin (ATG) levels, ultrasound (USG)/CT/MRI of neck, and whole body Iodine-131 scan findings were recorded prior to and at 6-months, 1-year, and 2-years intervals after radio-ablation. Successful thyroid remnant ablation, disease progression, and recurrence were also recorded. A definite criterion (serum thyroglobulin (*TG*) level ≤2.0 ng, ultrasound (USG) neck negative for residual thyroid tissue or suspicious cervical lymph nodes and no Iodine-131 avid lesion detected on whole body scan (WBS)) was set to label patient as disease-free.

Whole Body Scan

Iodine-131 whole body diagnostic scan (WBSdx) was performed 3 weeks off thyroxin. Radio-iodine (74-148 MBq) was administered orally after 5 to 6 hours of fasting followed by WBS on Siemens dual head gamma camera by using high energy collimator, setting of 256X 1024 matrix at speed of 10-15 cm/min. Post therapy whole body scan was done at 10th day of therapeutic dose administration on same gamma camera. Scan images were reviewed by 2 consultant nuclear physicians before reporting.

Ultrasound Neck

Neck ultrasonography (USG) was performed on Aplio500 TOSHIBA by 2 consultant radiologists.

Thyroglobulin Levels

Thyroglobulin and anti-thyroglobulin levels were recorded by IRMA (immune-radiometric assay) technique using THYRO kits by "Cisbio Bioassays".

Inclusion Criteria

(1) Intermediate- and low-risk PTC patients with age limit of 15 to 60 years.
(2) Intermediate- and low-risk PTC patients undergoing RAI ablation.
(3) Intermediate- and low-risk PTC patients who agreed for follow up till 2 years at an interval of at least 6 months.

Exclusion Criteria

(1) High-risk PTC patients.
(2) PTC patients with distant metastasis.
(3) Female PTC patients with pregnancy/lactation.

Results

This study included total eighty-four histologically proven papillary thyroid cancer (PTC) patients sixty-four were females and twenty males with mean age of 42 ± 5.5 years.

Before being referred for thyroid remnant ablation all histologically proven patients of PTC had to undergo total or near total thyroidectomy with lymph node removal from neck. Radio-iodine dose ablation was planned 6-12 weeks after surgery. 1-2 weeks prior to ablation all patients had TSH ≥30 IU and significant thyroid remnant on whole body Iodine-131 scan. After first dose ablation all patients were put on TSH suppression however at every follow up visit above mentioned set of investigations were recorded 03-04 weeks off thyroxin.

Group I. High Dose Ablation

Forty-two patients of PTC were enrolled in this group with 32 classic types, 09 follicular variant, and 1 case of micro-papillary carcinoma. Prior to ablation 48% (20/42) had evidence of residual thyroid nodule or suspicious looking regional lymph nodes and 69% (29/42) had high serum *TG* levels. These patients were classified into intermediate- and low-risk PTC.

Intermediate-risk PTC patients. Twenty-five patients of intermediate-risk PTC were ablated with high dose of RAI. 16 patients were disease-free at 6-months, 64% (16/25) had *TG* levels within normal limits, 76% (19/25) had theirs USG neck normal, and 72% (18/25) Iodine-131 WBSdx were unremarkable. At 1-year follow up number of disease-free patients increased to 18 with almost same 72% (18/25) having normal *TG* levels and 76% (19/25) with normal WBSdx while USG neck was unremarkable in 84% (21/25) cases. 76% (19/25) were disease-free at 2-year follow up, 80% (20/25) achieved required serum TG level, 88% (22/25) and 80% (20/25) with unremarkable ultrasound and WBSdx, respectively.

Low-risk PTC patients. Seventeen patients of low-risk PTC were ablated with high radio-iodine dose. Six-month follow-up revealed 70% (12/17) patients with *TG* levels <2.0 ng, 82% (14/17) had normal ultrasound neck and whole body scan was negative for radio-iodine avid lesion in 76% (13/17) cases. 70% (12/17) patients were declared disease-free at the end of 6 months. At 1-year follow up 82% (14/17) patients were disease-free following above mentioned criteria; same number of cases had no evidence of Iodine-131 avid remnant. Serum *TG* levels were within defined limits in 76% (13/17) and unremarkable ultrasound in 88% (15/17) cases. Numbers of disease-free patients were again 82% (14/17); 88% (15/17) patients with normal serum *TG* levels, normal USG in 88% (15/17), and 82% (14/17) with unremarkable WBSdx at the end of 2-years.

Group II. Low Dose Ablation

This group also included forty-two patients; 26 classic type, 13 follicular variant, 1 mixed (classic-follicular), 1 columnar type, and 1 micro-papillary carcinoma. Prior to radio-ablation 61% (26/42) had evidence of residual thyroid nodule or suspicious looking regional lymph nodes and 60% (25/42) had their serum *TG* levels >2.0 ng. These were further divided into 2 groups:

Intermediate-risk PTC patients. Twenty-five patients of intermediate-risk PTC were ablated with low-dose RAI. Six-months follow up revealed 14 disease-free patients following above mentioned criteria. 64% (16/25) patients had normal serum *TG* and 72% (18/25) ultrasound negative for suspicious findings. 56% (14/25) revealed no evidence of Iodine-131 avid lesion. One-year follow-up demonstrated 60% (15/25) patients as disease-free and same percentage of patients had their WBSdx scan negative for any iodine avid lesion. 72% (18/25) and 76% (19/25) had serum *TG* levels <2.0 ng and USG negative for any residual/suspicious node, respectively. After 2-years, 16 patients were disease-free. 64% (16/25) had whole body radio-iodine scan negative for any iodine avid lesion. Percentage of patients with normal serum *TG* was 68% (17/25) while patients with desired ultrasound findings remained same as in 1-year follow-up. Successful ablation among male and female was same as that of intermediate-risk patients in first group.

Low-Risk PTC Patients. Rest of the seventeen patients of low-risk PTC were treated with low dose of RAI and first follow-up revealed 12 disease-free patients. 70% (12/17) patients had WBSdx unremarkable, USG neck and serum *TG* levels were normal in 82% (14/17) cases. At the end of 1-year, further 1 patient was added in successful ablation with 76% (13/17) patients depicting unremarkable WBSdx, 88% (15/22) and 94% (16/17) patients had normal serum *TG* and ultrasound at the end of 1-year. Finally at 2-years follow-up 76% 13 (13/17) patients were disease-free, 82% (14/17) revealed normal WBSdx while percentage of patients with serum *TG* levels <2.0 ng and unremarkable ultrasound were same as at 1-year follow-up. 94% female and 94% male patients were ablated successfully in this group Figure 1.

Above mentioned number of disease-free patients were achieved by administration of single low-dose 1110 MBq. Rest of the patients in both risk groups who did not meet up the criteria were further ablated with low and high-doses at their next follow-up.

Among disease-positive patients at the end of 2 years, different kinds of responses were observed, in case of intermediate-risk patients ablated with high-dose of radio-iodine therapy 12% patients revealed some-response to therapy, 06% did not show any response to therapy, and disease-progression was noted in 06% cases however there was no disease-recurrence reported in these patients. In low-dose ablation 13% revealed some-response, 11% did not show any response to therapy, progression was seen in 09% patients, and disease-recurrence was noted in 03% of cases. In case of

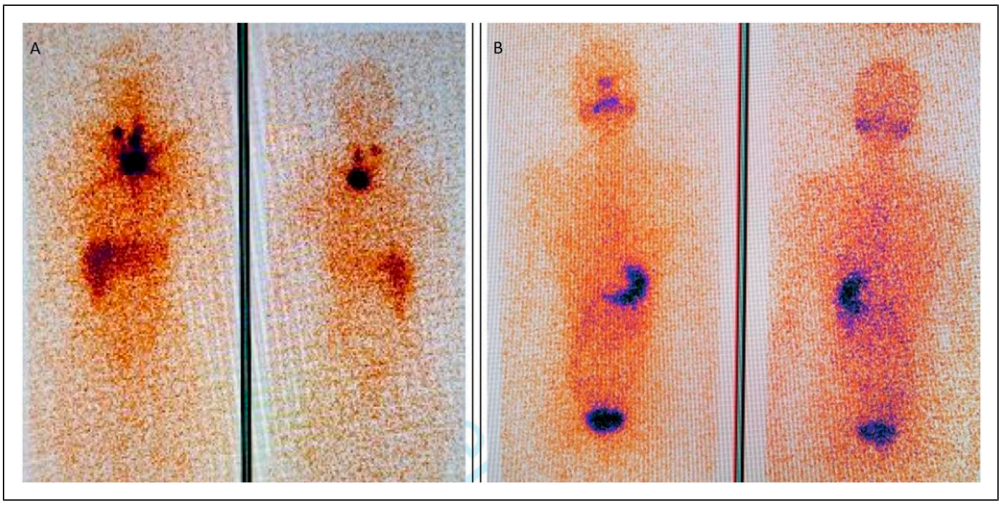

Figure 1. Radio-iodine ablation effects; A: Iodine -131whole body scan image reveal tracer avid residual disease in neck, B: complete ablation of thyroid residual in neck one year after low dose Iodine 131 therapy.

Table 1. Percentage of patients with normal response indicators and disease free status at different intervals in both groups.

		High-dose group			Low-dose group		
Risk groups	Response indicators	06 months (%)	12 months (%)	24 months (%)	06 months (%)	12 months (%)	24 months (%)
Intermediate Risk	WBS	72	76	80	56	60	64
	USG	76	84	88	72	76	76
	Tg	64	72	80	64	72	68
	Disease free	64	72	**76**	56	60	**64**
	"r" at $P < .001$	.947	.759	**.823**	.947	.759	**.823**
Low risk	WBS	76	82	82	70	76	82
	USG	82	88	88	82	94	94
	Tg	70	76	88	82	88	88
	Disease free	70	82	82	70	76	76
	"r" at $P < .001$	.945	.911	1.00	.945	.911	1.00

WBS = Whole body scan (diagnostic), USG = Ultrasound (neck), Tg = Thyroglobulin, r = Spearman correlation coefficient.

low-risk patients receiving high-dose of radio-iodine 14% patients showed some or no response to therapy, disease-progression, and recurrence was appreciated in equal number of cases (02%). Among low-risk patients with low-dose ablation, 12% developed some-response, 06% did not show any response to therapy, disease-recurrence was noted in 02%, and disease-progression in 4% of cases.

Statistical Analysis (SPSS 20): In intermediate-risk patients correlation between high and low-dose ablation was strong and significantly high applying spearman correlation-coefficient at the intervals of 6-months (r = .947 at $P < .001$), 1-year (r = .759 at $P < .001$), and 2-years (r = .823 at $P < .001$). Similarly strong correlation was established among high and low-dose ablations in low-risk patients with spearman correlation-coefficient calculated to be (r = .945 at $P < .001$) at 6-months, (r = .911 at $P < .001$) at 1-year, and (r = 1.00 at $P < .001$) at the end of 2-years. The difference among disease-positive patients in both high and low-dose ablation was statistically-insignificant in intermediate-risk patients (chi square $P = .450$), same was true for high and low-dose ablations in low-risk patients (chi square $P = .671$) as well (Table 1 and Figure 2).

Discussion

The incidence of DTC has steadily increased globally and in developed countries such as South Korea, France, Italy, and the United States during the last 3 decades,[14] however no substantial data on its prevalence is available in our country due to lack of clinical trials on a larger scale. A dramatic change in RAI management of DTC was noted in developed world after the introduction of ATA guidelines 2015 with new recommendations of low-dose radio-iodine ablation in intermediate-risk and no need for radio-iodine treatment in low-risk patients. This paradigm shift is not yet widely accepted in our country where a significant number of PTC patients present to NM and oncology OPD for thyroid remnant

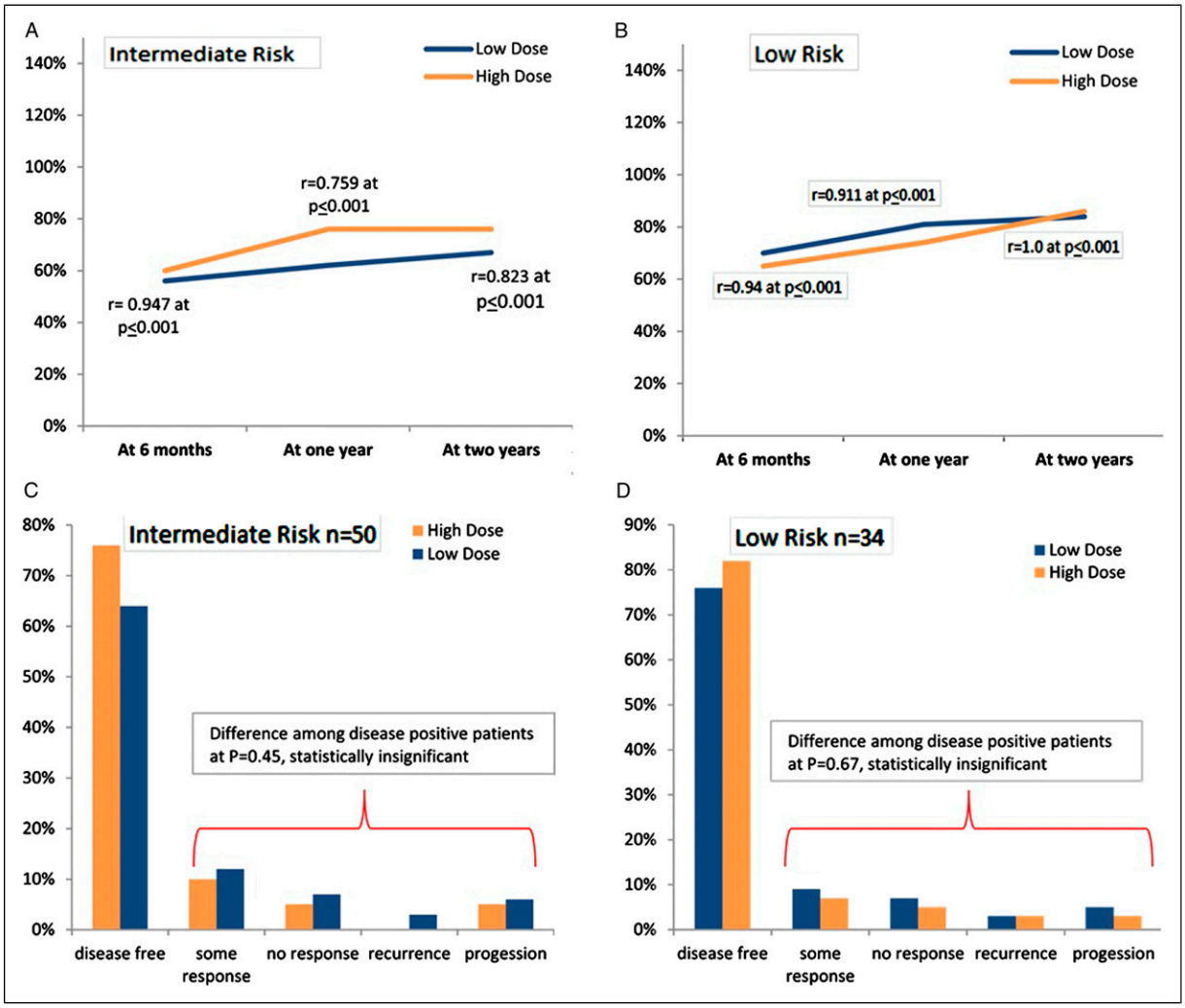

Figure 2. Treatment outcome in PTC patients; (A): trend lines showing the percentage of disease-free patients at 3 intervals in intermediate patients, (B): trend lines revealing the percentage of disease-free patients at 3 intervals in low-risk patients, (C): percentage of disease-free and disease positive patients at the end of 2 years in intermediate-risk patients, (D): percentage of disease-free and disease positive patients at the end of 2 years in low-risk patients.

ablation and they are treated aggressively with high Iodine-131 dose. Some of the treating physicians have shifted to low radio-iodine ablation therapy in low and intermediate-risk PTC patients however keeping in view the aggressive behavior of disease and possibility of non-compliance of patients, a large number of physicians have been in favor of high-dose regimen. Therefore it was considered as need of the time to collect some data and demonstrate the outcome of low-dose iodine-131 therapy in our PTC patients and compare its effectiveness with that of routinely utilized high-dose ablation therapy. Previously it was considered that high-dose of Iodine-131 is appropriate for complete ablation of micro-metastasis and low-dose may not sufficiently serve the purpose however multiple research studies conducted in last 2 decades to assess the role of low-dose RAI in successful ablation have concluded that there was not much difference in successful ablation with low-dose in comparison to high-dose treatment, moreover low-dose was associated with low prevalence of adverse effects.[15] A clinical research study by Muzzaferi and Kloos in 2001[4] revealed that there was no difference in recurrence rates (4 and 6%, respectively at $P = .1$) between low-activity (1037-1850 MBq) and high-activity (1887-7400 MBq) Iodine-131 remnant ablation group. Although low recurrence rate is reported with high RAI dose yet low-dose therapy is associated with additional benefits of short hospital-stay, less adverse effects, and cost-effectiveness. In our study recurrence rate was comparable in both groups, in intermediate-risk patients ablated with high and low-dose the recurrence rate was 0% and 03%, respectively ($P = .45$), in case of low-risk patients it was exactly the same in both groups 02% ($P = .67$). Two clinical research studies[16,17] in 2016 demonstrated equal effectiveness of low- versus high-dose radio-iodine ablation.

In an ongoing debate on appropriate dose of radioiodine in DTC patient almost a decade ago Hackshaw A, Harmer C

et al[18] compared the outcome of low- and high-dose Iodine-131 ablation in DTC, though successful ablation was 10% less in low-dose group still they failed to clearly demonstrate the superiority of high-dose and results were equivocal. Similarly large multicenter controlled randomized trials[19-21] also demonstrated that low-dose of Iodine 131 is as effective as high-dose in thyroid remnant ablation in low-risk and non-metastatic DTC patients after thyroidectomy. Our study results are quite similar to that of above mentioned trials with comparable effectiveness of high and low-dose in DTC patients.

Iodine-131 WBS is performed for residual tissue avidity while post therapy Iodine-131 WBS for restaging and confirmation of proper dose delivery. Specificity of WBSdx is quite high (99%) in detection of distant metastasis.[22] In this research study WBS was considered independent variable for assessment of successful ablation in 6 (12%) patients at the end of 2 year follow up. Highly sensitive assays utilized to detect serum thyroglobulin are quite helpful in prediction of recurrence in intermediate-risk patients. A continuous falling trend of serum *TG* levels was observed in >80% cases in both groups after RAI ablation reaching baseline set point of <2.0 ng however in <20% cases either serum *TG* levels were rising or did not touch baseline of <2.0 ng demonstrated residual/recurrent disease. In majority of our patients' serum *TG* levels were quite consistent with pattern of successful ablation. These results were in concordance with that of a previous study[23] which demonstrated pre-ablation serum *TG* level as good predictor of successful ablation. In this study only 03 patients had their anti *TG* antibody levels above normal and at the end of 2-year follow-up serum anti *TG* antibody levels dropped to normal in almost 97% of cases.

Size and focality of lesion has a significant impact on successful ablation, a uniform pattern of complete ablation was noted at 6-months and 1-year in patients with initially small size lesion (1-3 cm) while larger or multifocal lesions were either difficult to ablate or demonstrated incomplete ablation at the end of 2 years. Two cases of micro-carcinoma were ablated with high- and low-dose of RAI resulting into complete ablation at 6-months and 1-year, respectively. Although British thyroid association,[24] European association of nuclear medicine,[25] and ATA guidelines[26] do not recommend RAI ablation in micro-carcinoma free of risk factors however both of our patients had multifocal disease and also there was risk of non-compliance.

Successful ablation rate in our study in intermediate-risk patients ablated with high-dose was 76% while in patients ablated with low-dose of Iodine-131 it was 64%, in case of low-risk patients ablated with high and low RAI dose successful ablation rate was found to be 82% and 76%, respectively. Although statistically insignificant the difference of disease-free intermediate-risk patients is >10% and possible explanation of this difference includes larger primary lesion size, multi-focality, and extra/peri thyroidal extension as it was observed that comparatively larger number of patients ablated with low-dose manifested above mentioned factors when compared with those ablated with high-dose. In case of low-risk patients, the difference of disease-free patients was almost negligible in both groups hence selection of low-dose of Iodine-131 was more appropriate for low-risk patients as it also adds benefits of less adverse effects and short/no hospital stay. This inference also further strengthens our concept of radio-ablation (if needed) in low-risk patients with low dose of Iodine-131 by ATA guidelines 2015.

Limitations

This study may have following limitations;

(1) PTC patients were followed for disease evaluation till the end of 2 years after radio-iodine therapy, extending this period may have some positive impact on results/treatment outcome.
(2) Patients presenting to our center for thyroid remnant ablation may not be the true depiction of disease prevalence in our country as we lack substantial data on this issue.
(3) Only papillary thyroid carcinoma patients were included in study because follicular cancer patients are less common.
(4) The small sample size is probably due to less common presentation of intermediate- and low-risk PTC patients, 28 low-risk DTC patients presented in 2018 in NM and Oncology OPD.[13] In order to improve validity of study results we intend to further continue follow up of these patients and conduct a similar research in multiple centers of country and collect data from other countries of our region with collaboration of different research groups of same field.

Conclusions

It was concluded that high and low-doses of radioactive Iodine-131 are equally effective therapeutic doses for thyroid remnant ablation in intermediate- and low-risk papillary thyroid carcinoma. Furthermore, chances of local disease recurrence are almost same for both doses in our population.

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Declaration of Conflicting Interests

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