

Age Related Clinical Outcome After Radioiodine Ablation Therapy in Patients with Papillary Thyroid Carcinoma with Lymph Node Metastases

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ABSTRACT

Cervical lymph node metastasis (CLNM) is frequently observed in differentiated thyroid carcinoma (DTC). After thyroidectomy, radioiodine (¹³¹I) treatment is advised to destroy any remaining thyroid tissue. It is still unknown how ¹³¹I therapy may affect the prognosis of DTC in CLNM patients. Our objectives were to examine the correlation between the ages of diagnosis and the results of ¹³¹I administration in individuals with DTC and CLNM and to examine the variables that might have an impact on clinical results. From 2004 to 2010, a total of 290 patients with PTC who received ¹³¹I administration following a near total or total thyroidectomy were recruited from the National Institute of Nuclear Medicine and Allied Sciences (NINMAS) and analyzed retrospectively. The selected patients were divided into two groups according to age: Group A (<18 years) and Group B (>18 years) with the presence of pre- or post-surgical and post-ablative lymph node metastases. The clinical outcomes are categorized as excellent response, indeterminate response and incomplete response. In Group A, out of 31, excellent responses had 16 (51.6%), indeterminate responses had 7 (22.6%), and incomplete responses had 8 (25.6%). In group B, out of 259, excellent responses had 99 (41.4%), indeterminate responses had 101 (42.3%), and incomplete responses had 39 (16.3%). Papillary thyroid cancer lymph node metastases are a potential predictor of prognosis. They are significant for the disease's recurrence. Compared to adult patients, younger PTC patients with lymph node metastases exhibit a better response.

Keywords: Papillary thyroid carcinoma, cervical lymph node metastases, response

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INTRODUCTION

Differentiated thyroid cancer (DTC) is the most common subtype among different types of thyroid carcinoma. It has a relatively good prognosis, with 10-year survival rates of

92–98% (1). Papillary thyroid cancer (PTC) is more likely to occur in younger people. Almost 53% of DTC patients show cervical lymph node metastasis (CLNM) at the time of surgery, which is not common in most other carcinomas (2). Lymph node metastases may be present even when the primary tumor is contained within the thyroid (3). CLNM is considered a risk factor for poor clinical outcomes (4). Increased mortality rates and decreased survival have been demonstrated among patients with DTC with lymph node metastasis (5). Patients' age, histological grade, distant metastases, extracapsular tumor extension, tumor size, and stage of disease are considered prognostic factors. Lymph node metastases are a debatable prognostic factor, having relevance in the recurrence of disease but having no relevance in the survival rate of patients (6). Lymphatic metastases are more common in PTC, and the usual sites are recurrent, jugular, supraclavicular, and upper and middle mediastinal lymph nodes. The frequency of metastasis in the lower mediastinal lymph nodes is less (7). The objective of this study was to analyze the relationship between age at diagnosis and the outcome of patients with DTC and CLNM according to ¹³¹I administration.

PATIENTS AND METHODS

Study type: Retrospective study approved by the Medical Research Ethics Committee of NINMAS.

Study subjects: A total of 290 registered PTC patients with lymph node metastases who received ¹³¹I administration following subtotal or total thyroidectomy were recruited

from National Institute of Nuclear Medicine & Allied Sciences (NINMAS) and analyzed retrospectively from January 2001 to December 2010. All patients were classified according to the American Joint Committee of Cancer (AJCC) risk stratification system (8), and the American Thyroid Association staging system was designed to assess the risk of recurrence in PTC (9).

The selected patients were divided into two groups according to age (Group A = <18 years) and (Group B = >18 years) with presence of pre or post-surgical and post ablative lymph nodes metastases. It must be said that, above all for past cases, it was not possible to assess the extent of lymphectomy and/or the involvement of different LN level.

Follow-Up Strategy: After the primary treatment, all patients received Levothyroxine (L-T4) at TSH-suppressive doses and were periodically followed up, undergoing physical examinations, serum Tg measurements, and neck ultrasonography every 3–12 months. Diagnostic WBS and stimulated Tg after L-T4 withdrawal were performed in all patients at least once. Patients clinically suspected of local recurrence or distant metastasis were assessed using CT scans, diagnostic SPECT/CT, 18F-fluorodeoxyglucose positron emission tomography, and/or fine-needle aspiration (FNA)/surgery. The clinical, pathologic, and incidence of RAI-avid metastatic LN on Rx SPECT/CT were reviewed, and risk factors related to persistent/recurrent disease were analyzed. Data regarding the most recent follow-up period was taken as well. Clinical outcome after RAI ablation therapy was categorized as excellent response, indeterminate response, and incomplete response.

Excellent response: no clinical, biochemical, or structural evidence of disease

Biochemical incomplete response: abnormal Tg or rising anti-Tg antibody levels in the absence of localizable disease.

Structural incomplete response: persistent or newly identified loco-regional or distant metastases.

Indeterminate response: nonspecific biochemical or structural findings that cannot be confidently classified as either benign or malignant. This includes patients with stable or declining anti-Tg antibody levels without definitive structural evidence of disease.

Statistical Analysis: Continuous data are presented as medians and ranges or means and standard deviations, as

appropriate for each variable. Chi-square tests were performed for categorical comparisons, and the Mann–Whitney U test for continuous variables. Statistical analyses were carried out using the Statistical Package for Social Sciences version 26.0 for Windows (SPSS Inc., Chicago, Illinois, USA). Variables are expressed in number, mean, and percentages. For age and Tg level analysis t-test; for other variables Chi square test and the Fisher exact test were applied. P value 0.05 was considered as statistically significant.

Recurrence-free survival was estimated using the Kaplan–Meier method. Factors associated with the risk of persistent/recurrent disease were analyzed using Cox proportional hazard regression analysis. The following characteristics were included: age, gender, TSH, Tg before and after ablation, and post-RAI ablation avidity. Hazard ratios (HRs) and confidence intervals (CIs) were calculated in the model. Statistical analyses were carried out using the Statistical Package for Social Sciences version 25.0 for Windows (SPSS Inc., Chicago, Illinois, USA). Variables are expressed in number, mean, and percentages. P value 0.05 was considered as statistically significant.

RESULTS

A total of 290 PTC patients were enrolled in this study; twenty patients were lost to follow-up; this study was done on the rest of the 270 patients. Among them, 180 (66.7%) females and 90 (33.3%) males, F:M: 2.0:1. The average age of the study population was 34.19± 13.8 years, with a range of 10–70 years. The study population was divided into two groups according to age: Group A is up to 18 years old, and Group B is above 18 years old. In group A, the total number of patients was 31 (11.5%), whereas in group B, it was 239 (88.5%). In group A, the mean age was 15.39 ± 2.4 years and ranged from 10–18, with females at 21 (62.7%) and males at 10 (32.3%). In group B, the mean age was 36.6±12.8 years, ranging from 19 to 70 years, with females 159 (66.5%) and males 80 (33.5%). In Group A type of surgery, total thyroidectomy occurred in 19 (61.3%) and total thyroidectomy with modified neck dissection occurred in 12 (38.7%); in Group B type of surgery, total thyroidectomy occurred in 149 (62.3%), total thyroidectomy with central clearance occurred in 5 (2.1%), and total thyroidectomy with modified neck dissection occurred in 85 (35.6%). Histopathologically, papillary thyroid carcinoma 25 (80.6%)

in group A, 192 (80.3%) in group B, FVPCT in group A 6 (19.4%) and in group B 47 (19.7%); unifocal 12/31, multifocal 19/31 in group A, group B 106/239 unifocal, and 133/239 multifocal. All patients got radio-iodine ablation therapy. Single dose in A group: 16 (51.6%); multiple doses: 15 (48.4%). The mean dose is 217.8 ± 140 mCi (maximum 575 mCi, minimum 30 mCi). In Group B, the single dose was 145 (60.7%), the multiple doses were 94 (39.3%), and the mean dose was 300 ± 144 mCi (maximum 625 mCi, minimum 75 mCi). Average follow-up period is 8 ± 1.5 years with an interval of four to six months. In group A, mean initial Tg 15.5 ± 14.9 ng/ml ranged from (0.9–53 ng/ml),

mean initial TSH 64.6 ± 29.8 ; in group B, mean initial TSH 13.8 ± 18.5 ng/ml ranged from (0.2–101.6 ng/ml), mean initial TSH 58.2 ± 26.5 . Initial lymph node metastases were found in group A 22 and in group B 107. Lymph node metastases develop during follow-up in Groups A, 9, and 132 in Group B. In Group A, out of 31, excellent responses had 16 (51.6%), indeterminate responses had 7 (22.6%), and incomplete responses had 8 (25.6%). In group B, out of 259, excellent responses had 99 (41.4%), indeterminate responses had 101 (42.3%), and incomplete responses had 39 (16.3%). A statistically significant response (p-value < 0.5) was not found between the two groups.

Table-1: Comparison of clinical characteristics of child and adult patients of papillary thyroid carcinoma with lymph node metastases:

Characteristics	Child	Adult	p-value
Age	10-18	19-70	
Gender: Male	10	80	0.5
Female	21	159	
Surgery: Total Thyroidectomy	19	149	0.79
Total Thyroidectomy with M.N.D	12	85	
Total Thyroidectomy with C.Clearance		05	
Histopathology: PTC	25	192	0.09
FVPTC	06	47	
Focality: Unifocal	12/31	106/239	
Multifocal	19/31	133/239	
Initial S.Tg	15.5 ± 14.9	13.8 ± 18.5	
Initial TSH	64.6 ± 29.8	58.2 ± 26.5	
Time of LN Mets: Before RAIA	22	107	
During Follow up	09	132	
Number of doses: Single	15	145	
Multiple (mean \pm SD)	217 ± 140 mCi	213 ± 118 mCi	
	16	94	
	mean- 306 ± 144 mCi	(mean 319.7 ± 128.2 mCi)	
Therapy Response: Excellent Response	16	99	0.5
Indeterminate Response	07	101	
Incomplete Response	08	39	

RAIA-radioactive iodine ablation

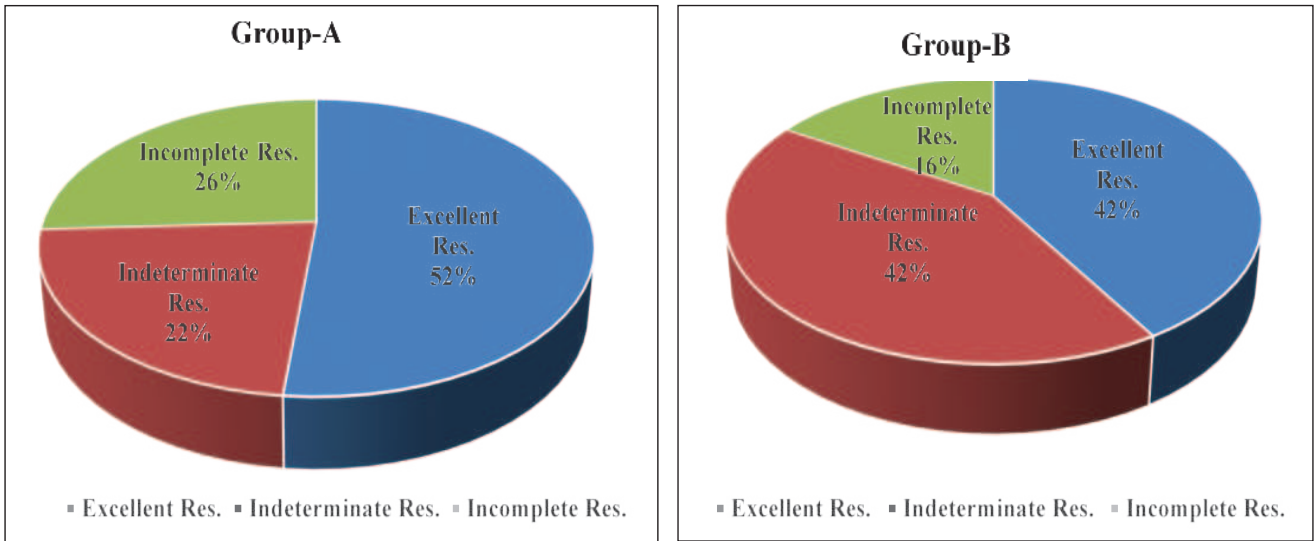


Figure-1: Chart showing significantly higher excellent response in Group-A than group-B; suggesting pediatric PTC patients with lymph nodes metastases show better outcome than adult patient after radioiodine ablation therapy.

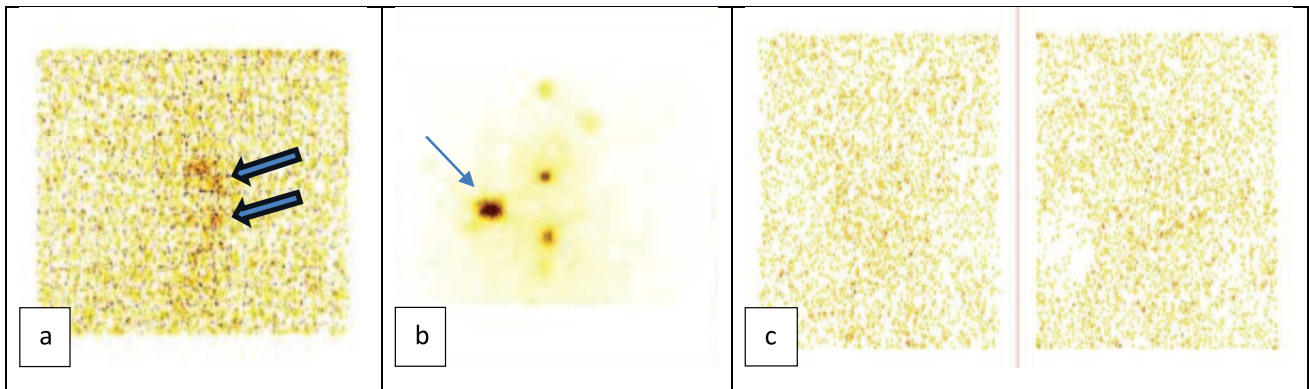


Figure-2: Post therapy scan (RxWBS) showing RAI uptake in left side of neck (a) and right side of neck (b) suggesting iodine avid metastatic lymph node. Diagnostic whole-body scan (DxWBS) showing no radiotracer uptake in neck or elsewhere in the body suggesting excellent therapy response (c).

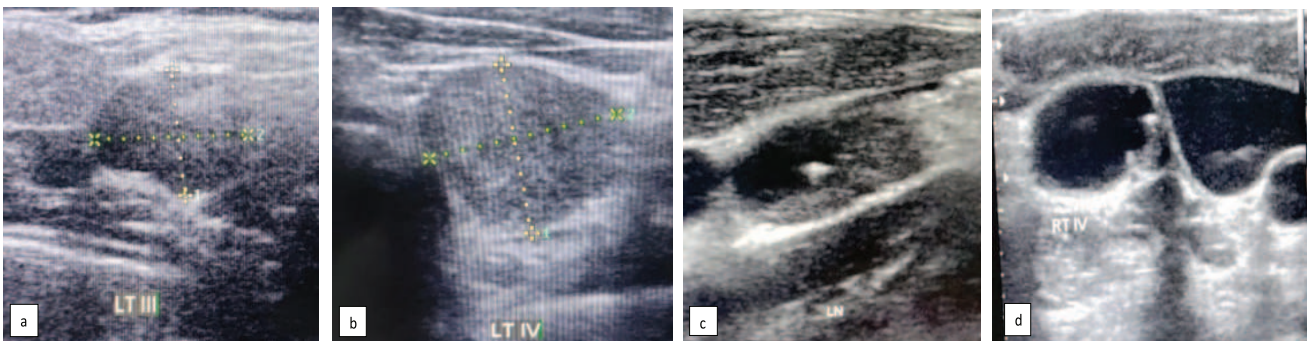


Figure-3: High resolution grey scale ultrasonogram of neck showing enlarged metastatic cervical lymph node with loss of nodal architecture and hilar fat plane with resemblance of thyroid tissue (a,b). Metastatic lymph node with calcification (c) and liquefactive necrosis (d) are also showed in this figure.

DISCUSSION

CLNM is common in DTC, with a frequency of 30–90% (11) and has been demonstrated to be closely associated with higher recurrence and poorer survival rates in patients with DTC (12). The majority of metastatic sites are located in central compartment lymph nodes, and complete central lymph node dissection has been identified to reduce the incidence of disease persistence, recurrence, and mortality (13).

Previous studies have demonstrated that remnant ablation is an independent variable that reduces loco-regional recurrence, distant metastases, and cancer-associated mortality (14). However, no single group achieved 100% ablation following remnant ablation (15). The majority of patients with DTC with CLNM require repetitive I treatments (16). Therefore, the present retrospective study of 270 patients with PTC with CLNM was performed to investigate the rate of successful ablation and to analyze the effects of possible prognostic factors affecting successful ablation, including age, serum Tg, tumor size, number of nodules, and TNM stage.

In the present study, several patients who received multiple doses of ^{131}I did not achieve successful ablation. These results indicated that the diminution of remnant lymph node tissues following remnant ablation and the different iodine activity were not only associated with the outcome of ablation. For this reason, associated factors responsible for the successful ablation of DTC patients with CLNM were investigated. Due to a large disparity in the number of patients receiving 2, 3, and 4 doses of iodine, the present study concentrated on those receiving multiple doses of iodine. It was identified that tumor size, number of nodules, and TNM stage were the independent risk factors affecting successful ablation in patients with DTC and CLNM who received multiple doses of ^{131}I therapy.

The significance of microcalcifications, cystic changes, vascularity, and volume changes in distinguishing CLNM from non-CLNM was demonstrated by long-term, numerous ultrasound follow-ups of ambiguous LNs following PTC ablation. As the cancer spreads, the LN experiences liquefied necrosis, coagulative necrosis, hemorrhage, and calcium deposition from the rapid growth of vascular and fibrous tissues brought on by tumor cell infiltration (17). These symptoms appear as microcalcifications and cystic changes on ultrasonography. One study found that, ≥ 5

microcalcifications and cystic changes are independent predictors for PTC CLNM (18, 19). This study shows microcalcifications in most of the CLNM, and a few show liquefactive necrosis (Figure 3). In cases of incomplete response, some patients show aggressively enlarged lymph nodes and discharging sinuses.

The risk of an incomplete response was not related to the activity of RAI ablation, which was in accordance with the findings of previous studies (including two randomized multicenter trials, three reviews, 21 and five observational studies). This study also shows that the activity of RAI is not statistically significant in relation to response.

Few studies demonstrate that near total or total thyroidectomy and complete lymph node management—that is, modified neck dissection in all cases of lymph node metastasis, whether diagnosed preoperatively or by intraoperative lymph node biopsy—significantly lower the recurrence rate in children with DTC (23). In this study, total thyroidectomy with neck dissection was done in both the child (38.7%) and adult groups (37.7%) due to lymph node metastases.

Age was significantly associated with complete ablation in the univariate analysis, particularly in patients aged ≤ 18 years. The study population was divided into two groups: pediatric (Group A) and adult (Group B). Excellent response was 51.6% in group A, and 41.4% in group B. From this study, excellent responses were found to have a higher percentage than indeterminate or incomplete responses in younger patients, and indeterminate responses were slightly higher in adult patients but not statistically significant (p-value -0.5).

The prognostic value of serum Tg was evaluated in several studies. It showed that patients with RAI-avid but sTg-negative nodes have a better prognosis than those who revealed RAI-avid and sTg-positive nodes ($p = 0.017$). The ^{131}I -detectable metastatic LN with negative sTg had a significantly better chance of being eliminated by initial RAI (24). While RAI-avid nodes with elevated sTg had a higher chance of harboring tumor cells demonstrating heterogeneous radiosensitivity, this might be an origin for future recurrence (25). In this study, both iodine-avid and non-avid lymph nodes were found. At the same time, sTg was raised in most cases.

In clinical practice, patients who fail to achieve complete ablation following remnant ablation should receive a second administration of ^{131}I to achieve successful ablation (26). In the current study, several patients received multiple treatments. In group A, 51.6% of patients got multiple therapies; among them, 37.5% showed excellent response, 18.8% had an indeterminate response, and 43.8% showed an incomplete response, whereas in group B, 39.3% of patients got multiple therapies, and 33% showed excellent response, 37.2% had an indeterminate response, and 29.8% showed an incomplete response. The overall response after RAIT in this study delineates In Group A, out of 31, excellent responses had 16 (51.6%), indeterminate responses had 7 (22.6%), and incomplete responses had 8 (25.6%). In group B, out of 259, excellent responses had 99 (41.4%), indeterminate responses had 101 (42.3%), and incomplete responses had 39 (16.3%). There were several limitations of this study. Ultrasound and CT scan of neck was not available in all patients. Histopathological findings were often inadequate. Additionally, as there was a large variation in the numbers of patients included in two groups, the analysis between the patients with PTC who received 2nd, 3rd and 4th doses of ^{131}I treatment was not completely evaluated. A larger number of patients should have been recruited. Finally, as the trial was only performed in a single center, all conclusions should be verified in a multi-center, large-scale cohort.

CONCLUSION

The study demonstrated that iodine administration is a useful therapy to eradicate remnant thyroid tissue and cervical lymph node metastasis in patients with papillary thyroid cancer, and that age and lymph node metastases were independent risk factors affecting successful ablation in patients with PTC. From this study, excellent responses were found to have a higher percentage than indeterminate or incomplete responses in younger patients, and indeterminate responses were higher in adult patients.

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