ORIGINAL RESEARCH

Assessment of the Evaluation of response to radioiodine therapy in thyroid oncocytic carcinoma patients

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ABSTRACT
Background: Thyroid oncocytic carcinoma (Hürthle cell carcinoma) is a distinct subtype of differentiated thyroid cancer (DTC) with controversial responses to radioiodine therapy. This study evaluates the treatment response of oncocytic carcinoma patients undergoing radioiodine therapy at a single center in India. **Objectives:** To assess the tumor characteristics, treatment strategies, and therapeutic outcomes of thyroid oncocytic carcinoma patients treated with radioiodine therapy. **Methods:** A retrospective analysis was conducted on patients diagnosed with thyroid oncocytic carcinoma who received radioiodine therapy. Data collected included TNM staging, administered radioiodine doses, follow-up duration, and treatment response at one year and final follow-up. **Results:** The mean age at diagnosis was 55.21 years (SD = 12.7), with a male-to-female ratio of approximately 1:1.2. Multifocality was observed in 4 patients (16%). Most patients (67.5%) received a total radioiodine dose between 0-200 mCi. At one-year follow-up, treatment responses included 27.6% excellent, 22% indeterminate, 22% biochemical incomplete response (BIR), and 34.2% structural incomplete response (SIR). Final responses showed improvement, with 45.3% achieving excellent response and a decline in BIR (12.1%) but persistence of SIR (45.3%). **Conclusion:** The study highlights that a significant proportion of Hürthle cell carcinoma patients exhibit incomplete responses to radioiodine therapy, particularly structural incomplete response. These findings suggest the need for tailored therapeutic strategies to improve patient outcomes.

Keywords: Thyroid oncocytic carcinoma, Hürthle cell carcinoma, thyroid cancer, oncocytic carcinoma, radioiodine therapy

INTRODUCTION

Thyroid oncocytic carcinoma (Hürthle cell carcinoma) is a rare and distinct subtype of differentiated thyroid cancer (DTC) characterized by large eosinophilic cells with abundant mitochondria [1]. It accounts for approximately 3-5% of all thyroid malignancies and has a more aggressive clinical course compared to conventional DTC [2,3]. The management of Hürthle cell carcinoma typically includes total thyroidectomy followed by adjuvant radioiodine therapy, although its efficacy remains controversial due to the variable uptake of radioactive iodine in oncocytic carcinoma cells [4,5].

Recent studies have highlighted that Hürthle cell carcinoma exhibits a lower rate of iodine avidity compared to papillary and follicular thyroid carcinomas, leading to challenges in effective radioiodine treatment [6]. Additionally, multifocality, nodal metastases, and distant metastases are more frequently observed in Hürthle cell carcinoma, necessitating alternative therapeutic approaches such as external beam radiotherapy and targeted molecular therapies [7].

The American Thyroid Association (ATA) guidelines suggest a stratified approach to treating Hürthle cell carcinoma based on tumor staging, histopathologic features, and risk assessment [8]. However, limited data exist on the response to radioiodine therapy in Indian populations. This study aims to evaluate the treatment outcomes of oncocytic carcinoma patients undergoing radioiodine therapy at a single tertiary center in India, contributing to a better understanding of its role in disease management.

MATERIALS AND METHODS

Study Design and Setting

A retrospective analysis was conducted on patients diagnosed with thyroid oncocytic carcinoma who underwent radioiodine therapy at our institution. Clinical data, including tumor-node-metastasis

(TNM) staging based on the 8th edition of the American Joint Committee on Cancer (AJCC) guidelines, administered radioiodine doses, and treatment responses, were collected and analyzed. Data were collected from hospital medical records, pathology reports, and nuclear medicine archives.

Patient Selection Criteria

Inclusion criteria

- Patients diagnosed with histopathologically confirmed Hürthle cell carcinoma.
- Patients who underwent total or subtotal thyroidectomy.
- Patients who received at least one dose of radioiodine therapy.
- Patients with available follow-up data for at least one year post-therapy.

Exclusion criteria

- Patients with incomplete medical records.
- Patients with concurrent malignancies other than Hürthle cell carcinoma.
- Patients who did not undergo any form of surgical intervention.

Data Collection

A standardized data extraction form was used to record patient demographics, tumor characteristics, TNM staging (as per the 8th edition of the American Joint Committee on Cancer), radioiodine therapy details, and follow-up outcomes.

Treatment Protocol

All patients underwent thyroidectomy before receiving radioiodine therapy. The standard practice involved administering a preparation phase, which included a low-iodine diet for at least two weeks and withdrawal of thyroid hormone replacement therapy (or use of recombinant human TSH) to achieve adequate TSH stimulation before radioiodine administration.

Radioiodine Therapy

Patients received individualized doses of radioiodine (I-131) based on disease stage and risk stratification. The administered doses ranged from 30 mCi to over 1000 mCi in cases of persistent or metastatic disease. A post-therapy whole-body scan (WBS) was performed 5-7 days after radioiodine administration to evaluate uptake and disease extent.

Follow-Up Protocol

Patients were regularly monitored at intervals of 3, 6, and 12 months post-treatment and annually thereafter. Assessments included:

- Serum thyroglobulin levels (as a marker for residual disease or recurrence).
- Anti-thyroglobulin antibody testing.
- Neck ultrasound to detect local recurrence or residual disease.
- Diagnostic whole-body iodine scans for selected high-risk cases.
- Additional imaging such as CT, MRI, or PET scans if structural disease progression was suspected.

Response Assessment

Treatment response was classified into four categories based on ATA response criteria:

- **Excellent response**: Undetectable thyroglobulin levels with negative imaging findings.
- **Indeterminate response**: Stable or mildly elevated thyroglobulin levels with nonspecific imaging findings.
- **Biochemical incomplete response (BIR)**: Persistent or rising thyroglobulin levels without structural evidence of disease.
- **Structural incomplete response (SIR)**: Evidence of persistent or progressive structural disease detected by imaging.

Statistical Analysis

Descriptive statistics were used to summarize baseline characteristics and treatment responses. Continuous variables were expressed as mean ± standard deviation, while categorical variables were represented as percentages. Statistical comparisons were performed using chi-square tests for categorical variables and t-tests for continuous variables. A p-value of <0.05 was considered statistically significant.

Ethical Considerations

The study was approved by the Institutional Ethics Committee, and patient confidentiality was maintained by anonymizing all personal identifiers. Since this was a retrospective study, informed consent was waived per ethical guidelines.

RESULTS

The age at the time of diagnosis ranged from 35 to 74, with an average age of 55.21 (standard deviation=12.7) among the patients. In comparison, the average age of the entire population in the clinic database was 49.7 ± 16.0 years. Table 1 shows TNM staging of the patients according to 8th AJCC edition.

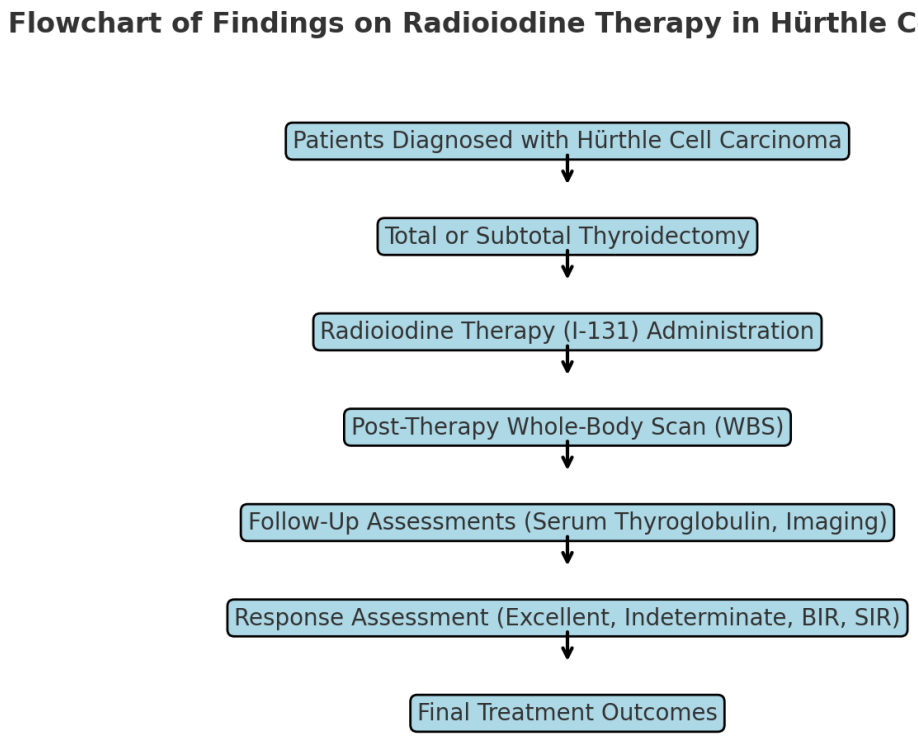

Figure1: Flowchart representing the key findings from the study on radioiodine therapy in Hürthle cell carcinoma patients.

Table 1. Tumor, node and metastasis (TNM) staging of the patients according to 8th AJCC edition

Staging		Frequency	Percent
T category	T1a	3	12.5
	T1b	5	20.8
	T2	3	12.5
	T3a	8	33.3
	T3b	3	12.5
	T4a	2	8.3
Nodalinvolvement	Nx	5	20.8
	N0a	4	16.6
	N0b	5	20.8
	N1a	5	20.8
	N1b	5	20.8
Distant metastasis	M0	19	79.1
	M1	5	20.8

Staging of the patients according to 8th edition of AJCC were 67.5%, 6.1%, 17.8% and 12.3% and categorized as stage 1, stage 2, stage 3 and stage 4, respectively.

The duration of follow-up conducted on patients with Hürthle cell carcinoma ranged from 1 to 122 months, with a mean of 40 months and a median of 29 months. On average, all patients of the database were followed up for 48.2 months. There were 12 females, accounting for 56.5% of the total, and 10 males, making up 45.3%. One patient reported family history of differentiated thyroid cancer. Multifocal lesions were detected in four of the patients.

Table 2. Radioiodine doses administered to the patients

Administered dose[mCi]	Frequency[%]	Accumulative dose[mCi]	Frequency[%]
≤30	4[17.6]	0-200	13[67.5]
100	4[17.6]	200-400	3[12.3]
150	9[45.3]	400-600	4[17.8]
175	0[0]	600-800	0[0]
200	2[6.1]	800-1000	0[0]
Other	3[17.8]	>1000	2[6.1]

Only three patients received non-classic approach. In this study, radiotherapy and radioiodine therapy were

used as additional treatment methods. Out of all the patients, only one patient did not receive any radioiodine therapy while five underwent radiotherapy as a complementary treatment method. The average initial radioiodine treatment dosage for the patients was 150 mCi. The majority of the patients underwent total thyroidectomy (except two who underwent subtotal thyroidectomy) and only one patient did not undergo any form of surgery, due to poor cardiac conditions and was referred for thyroid ablation by radioiodine administration.

Table 3. Radioiodine doses of the differentiated thyroid cancer patient's population

Administered dose[mCi]	Frequency[%]	Accumulative dose[mCi]	Frequency[%]
≤30	519 [42.5]	0-200	1477 [84.4]
100	156 [13.3]	200-400	199 [12.1]
150	502 [41.3]	400-600	60 [4.7]
175	11 [0.8]	600-800	16 [0.9]
200	46 [4.6]	800-1000	14 [0.8]
Other	32 [1.8]	>1000	11 [0.6]

Table 4 shows the treatment responses in Hürthle cell carcinoma patients and the DTC patients.

Assessment of response to therapy after one year revealed four excellent and three acceptable responses to treatment. There was not enough data to determine treatment response at the one- year after therapy in three patients. Incomplete response was observed in eight patients, including three biochemical incomplete response and five structural incomplete response.

Table4. Treatment responses in Hürthle cell carcinoma and overall patient population groups

	Response in oncocytic carcinoma patients		Response in original dataset	
Kindof response				
	One year response[%]	**Final response[%]**	**One year response[%]**	**Final response[%]**
Excellent	27.6	45.3	42.4	55.1
Indeterminate	22	0	25.6	22
BIR	22	12.1	15	8.8
SIR	34.2	45.3	21.8	17.3

DISCUSSION

Hürthle cell carcinoma remains a unique clinical entity with distinct biological behavior compared to other differentiated thyroid cancers. This study highlights the significant variation in response to radioiodine therapy, which is consistent with prior literature indicating the reduced iodine avidity of Hürthle cell carcinoma [9,10]. The results demonstrated that a substantial proportion of patients exhibited incomplete responses, particularly structural incomplete responses, suggesting a need for alternative therapeutic strategies [11].

Several studies have indicated that molecular characteristics, including mitochondrial DNA mutations and alterations in the MAPK and PI3K/AKT pathways, may contribute to the aggressive nature and radio resistance of Hürthle cell carcinoma [12-14]. These findings underscore the necessity for individualized treatment strategies, potentially integrating targeted therapies such as tyrosine kinase inhibitors (e.g., lenvatinib and sorafenib) [15,16].

The role of external beam radiotherapy (EBRT) has been explored as an adjunct in high-risk cases, with some evidence supporting its use in improving locoregional control in non-radioiodine-avid tumors [17]. Additionally, recent advancements in peptide receptor radionuclide therapy (PRRT) have shown promise for metastatic cases with somatostatin receptor expression [18,19].

Further prospective studies are needed to evaluate the long-term survival benefits of these emerging therapeutic modalities. Given the study's retrospective nature and limited sample size, future multi-center studies with larger cohorts and molecular profiling could provide deeper insights into personalized treatment approaches [20].

The research conducted by Wang et al. found that RAI treatment did not show a significant association with improvement in cancer specific survival (CSS) in both the overall group and the propensity scored match (PSM) group. Furthermore, subgroup analyses revealed similar results, even among patients with aggressive characteristics such as age 55 years or older, tumor size greater than 40 mm, distant metastasis in SEER staging, extra-thyroidal spread, and lymph node metastasis (all $P>0.05$). Therefore, it can be concluded that RAI does not have a statistically significant effect on CSS in patients with Hürthle cell carcinoma [21]. However, ultrasound is utilized as the initial imaging modality approach to screen for thyroid malignancy. In our study, abnormal findings were only observed in 16% of patients. The main strength of our study lies in its unique

contribution to a field that has received limited research attention, particularly within the Iranian population; this has resulted in a lack of essential data on Hürthle Cell Carcinoma. However, a notable limitation of this study is the restricted pool of eligible individuals available for participation. Additionally, the 40 months follow up duration is relatively short in patients with thyroid cancer, which is another limitation of the study.

CONCLUSION

We assessed tumor characteristics, treatment approaches, and treatment outcomes over a defined follow-up period. Our findings provide valuable insights into the effectiveness of radioiodine therapy and its role in disease management.

REFERENCES

1. Carcangiu ML, et al. Hürthle cell carcinoma: A clinicopathologic study. *Am J SurgPathol*, 1985.
2. DeGroot LJ, et al. Thyroid neoplasia: Pathogenesis and management. *EndocrinolMetabClin North Am*, 1990.
3. Volante M, et al. Clinicopathological and molecular features of Hürthle cell carcinoma. *Histopathology*, 2009.
4. Schlumberger M, et al. Hürthle cell carcinoma: Management and treatment outcomes. *J ClinEndocrinolMetab*, 2016.
5. Haugen BR, et al. American Thyroid Association Guidelines for Adult Patients. *Thyroid*, 2016.
6. Rahbar K, et al. Radioiodine therapy in thyroid cancer. *ClinNucl Med*, 2020.
7. Ganly I, et al. Prognostic factors in thyroid cancer. *Cancer*, 2013.
8. Nixon IJ, et al. Management of Hürthle cell carcinoma. *Ann SurgOncol*, 2015.
9. Nixon IJ, et al. Treatment strategies for Hürthle cell carcinoma: A review of current evidence. *Ann SurgOncol*, 2016.
10. Goffredo P, et al. Survival outcomes in Hürthle cell carcinoma of the thyroid: An analysis from the SEER database. *Thyroid*, 2018.
11. Liu X, et al. Molecular genetics of Hürthle cell carcinoma: Implications for targeted therapies. *J ClinEndocrinolMetab*, 2017.
12. Asa SL, et al. The role of molecular pathology in the management of Hürthle cell thyroid neoplasms.*EndocrPathol*, 2019.
13. McIver B, et al. Prognostic implications of genetic alterations in Hürthle cell carcinoma. *Cancer*, 2020.
14. Yoo SK, et al. Genomic profiling of Hürthle cell carcinoma: New insights into oncogenesis and therapeutic targets. *J ClinOncol*, 2021.
15. Brose MS, et al. Lenvatinib for the treatment of progressive radioiodine-refractory thyroid cancer. *Lancet Oncol*, 2016.
16. Schlumberger M, et al. Sorafenib in locally advanced or metastatic differentiated thyroid cancer: A phase III trial. *N Engl J Med*, 2014.
17. Brierley JD, et al. Role of external beam radiation therapy in the treatment of advanced thyroid cancer. *ClinOncol (R CollRadiol)*, 2019.
18. Van Nostrand D, et al. Peptide receptor radionuclide therapy for radioiodine-refractory thyroid cancer. *J Nucl Med*, 2020.
19. Schlumberger M, et al. Recent advances in the management of advanced radioiodine-refractory thyroid cancer. *Endocr Rev*, 2018.
20. Elisei R, et al. Future directions in the treatment of aggressive thyroid cancers: An international perspective. *Eur J Endocrinol*, 2020.
21. Wang X, Zheng X, Zhu J, Li Z, Wei T. Radioactive iodine therapy does not improve cancer-specific survival in Hürthle Cell Carcinoma of the thyroid. J ClinEndocrinolMetab. 2022 Nov 23;107(11):3144-51.