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ORIGINAL RESEARCH ARTICLE

Evaluation of response to radioiodine therapy in thyroid oncocytic carcinoma patients: A single center experience from Iran

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ABSTRACT

Introduction: Thyroid oncocytic carcinoma, also known as Hürthle cell carcinoma (HCC), is a rare subtype of thyroid cancer with unique characteristics. Radioiodine therapy, while less effective for HCC due to poor radioiodine accumulation in tumor, has shown improved survival rates for tumors larger than 2 cm. Adjuvant radioiodine therapy is recommended in certain cases, particularly for older patients with a worse prognosis.

Methods: This study reviewed data from 18 HCC cases compared to the overall patient population (OPP) at our center between 2019 and 2022.

Results: The mean age at diagnosis was higher for HCC patients compared to OPP, with varying responses to therapy observed. Assessment of response to therapy after one year revealed 26.7%, 20%, 20%, and 33.3% of HCC patients with excellent, indeterminate, biochemical incomplete, and structural incomplete responses, which were 41.5%, 24.7%, 13%, and 20.7% in OPP, respectively. The Kaplan curve of patient survival showed an average of 100±13.5 months.

Conclusion: Approximately 44% of HCC patients showed excellent survival outcomes after radioiodine therapy, highlighting its importance as a treatment option for HCC. Further research is needed to optimize treatment choices and improve patient outcomes in this less common subtype of thyroid cancer.

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INTRODUCTION

Thyroid cancer is the most common endocrine cancer and the prevalence of thyroid cancer is progressively rising, likely due to improved diagnostic and treatment methods [1]. Differentiated thyroid cancer (DTC) originates from follicular cells and rank as the seventh most common cancer in women [2]. DTC is divided into three main groups; papillary thyroid cancer (most common), follicular thyroid cancer, and Hürthle cell thyroid cancer (HTC). HTC, accounting for 3-5% of DTC, has unique clinical and biological features [3]. Despite the incidence of thyroid cancer declined since 2014, the incidence-based mortality rates are still increasing suggesting the changing pattern of thyroid nodules management did not lead to decrease the high-risk patient's mortality [3]. Compared to other well-differentiated thyroid cancers, Hürthle cell cancer is known to exhibit a more aggressive behavior, leading to a higher incidence of metastasis and a lower rate of survival [4].

While RAI therapy is proved effective for treating papillary and follicular thyroid carcinoma, it faces limitations in its applicability for HCC due to the poor accumulation of RAI in HCC tumors [5]. In contrast to other types of differentiated thyroid cancers, HCC tumors may not respond to RAI treatment, which poses a challenge in managing advanced cases [6]. However, it has been observed that RAI can enhance survival rates in HCCs larger than 2 cm, which needs to be taken into consideration. Also, adjuvant RAI therapy can be considered after total thyroidectomy in cases where HCC is larger than 1 cm, microvascular invasion is present , with positive margins and extra thyroidal extension along with cervical lymph node metastases or elevated postoperative unstimulated thyroglobulin levels more than 1 ng/ml. Research studies have indicated that older age is associated with a poorer prognosis, and therefore, more aggressive management strategies may be necessary for older patients with HCC [6].

Pretreatment risk assessment for patients with differentiated thyroid cancer includes neck-imaging techniques [7]. Ultrasound continues to be the primary imaging technique for assessing thyroid cancer, playing a crucial role in evaluating both the main tumor and the adjacent cervical lymph nodes before surgery [8]. Neck ultrasound plays a key role by providing basic information about the size, location, number of tumors and lymph nodes, and local invasion of surrounding tissues [9]. While preoperative imaging can identify nodal disease in around 30% of patients, post operation pathological series indicate that nodal metastasis is present in 20-50% of patients [10], which leads to modification of surgical plan among two thirds of these cases [11].

Hürthle cell carcinoma (HCC), also known as oncocytic or oxyphilic carcinoma, is defined as a thyroid malignancy consisting of at least 75% Hürthle cells. It can be distinguished of Hürthle cell adenoma (benign) by capsular and/or vascular invasion characteristics [12]. The Hürthle cell lesion remains a matter of ongoing and evolving controversies in various aspects, including nomenclature and treatment [13].

Detection of thyroglobulin immunoreactivity supports the notion that Hürthle cells are derived from thyroid follicular cells [13]. However, the Hürthle cell variant of follicular thyroid carcinoma was reclassified as a separate type by the World Health Organization in 2017, owing to its unique histopathological features that distinguish it from follicular thyroid carcinoma [6].

Several research studies have proposed that HCC could potentially arise from parafollicular cells, owing to its ability to metastasize through the lymphatic system, its resistance to radioactive iodine, and its distinct oncogene expression profile when compared to follicular thyroid cancer [6]. Hürthle cell cancer exhibits a reduced affinity for ^{131}I in comparison to other types of thyroid carcinomas. It has been reported that around 10% of metastases of HCC have the ability to absorb radioiodine [14]. Thus, the effectiveness of radioactive iodide treatment, which is considered the most beneficial non-surgical approach for managing well-differentiated thyroid carcinoma, may not always be applicable for patients with Hürthle cell carcinoma resulting in limited effectiveness of radioactive iodide treatment. This poses challenges in Hürthle cell carcinoma treatment [13].

The ATA recommends RAI postoperatively for HCC tumors >1 cm following total thyroidectomy, and the NCCN selectively recommends RAI for tumors >2 cm or in the presence of vascular invasion, extra-thyroidal extension, lymph node metastases, or elevated postoperative unstimulated thyroglobulin (Tg) levels [15]. The efficacy of radioactive iodine in treating Hürthle cell carcinoma has been confirmed in a limited number of studies [16-18], while other studies have yielded inconclusive results. Therefore, it is necessary to investigate this disagreement with more research so that the survival of these patients can be increased by choosing the preferred treatment approach.

METHODS

In our study, the process of data extraction involved a comprehensive review of all 3287 patients diagnosed with thyroid cancer between 2019 and 2022, who were referred to our center. Following the implementation of exclusion criteria, which focused on individuals who did not return for the necessary follow-up after the radioiodine therapy, a selection was made consisting of 18 cases. The comparison was made between the group of patients diagnosed with Hürthle cell carcinoma and the entire patient's population.

RESULTS

The age at the time of diagnosis ranged from 35 to 74, with an average age of 54.22 (standard deviation=11.8) among the patients. In comparison, the average age of the entire population in the clinic database was 48.8 ± 15.0 years.

Table 1 shows TNM staging of the patients according to 8th AJCC edition.

Staging of the patients according to 8th edition of AJCC were 66.6%, 5.5%, 16.73% and 11.11% 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 47.1 months. There were 10 females, accounting for 55.6% of the total, and 8 males, making up 44.4%. One patient reported family history of differentiated thyroid cancer. Multifocal lesions were detected in four of the patients.

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

Staging		Frequency	Percent
T category	T1a	2	11.1
	T1b	4	22.2
	T2	2	11.1
	T3a	7	38.9
	T3b	2	11.1
	T4a	1	5.6
Nodal involvement	Nx	4	22.2
	N0a	2	11.1
	N0b	4	22.2
	N1a	4	22.2
	N1b	4	22.2
Distant metastasis	M0	15	83.3
	M1	3	16.7

During the follow up two patients passed away.

In the review of the overall patient population in the department data set, supplementary interventions such as repeat radio-iodine therapy, surgical procedures, radiotherapy, and other treatments were administered to 22.3%, 12%, 17.9%, and 0.85% of patients, respectively.

Tables 2, 3, 4 and 5 describe the radioiodine doses and whole-body scan findings of two groups.

Out of the patients who underwent initial ultrasound examination in 6-8 weeks after the surgery (8 patients), only three patients showed abnormal findings indicating thyroid malignancy. Additionally, during the first whole body iodine scan 9 patients showed positive results.

According to the 8th edition of AJCC, one patient was classified as stage I and eight individuals were classified as stage II. Additionally, one patient was categorized as stage III, and two individuals were identified as stage IVB. The TNM examination revealed that only eight out of these patients had lymph node involvement. Furthermore, iodine absorption in the thyroid bed was observed in 14 patients and remnants of developmental thyroid cells were observed outside the thyroid area in only one patient. Three patients had distant metastases, which only two of them were

detected by a whole-body iodine scan demonstrating lung and bone involvement. The third one had distant lymph node involvement that was not detected by the radioiodine scan.

Table 2. Radioiodine doses administered to the patients

Administered dose [mCi]	Frequency [%]	Accumulative dose [mCi]	Frequency [%]
≤30	3[16.7]	0-200	12[66.6]
100	3[16.7]	200-400	2[11.1]
150	8[44.4]	400-600	3[16.7]
175	0[0]	600-800	0[0]
200	1[5]	800-1000	0[0]
Other	3[16.7]	>1000	1[5]

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

Administered dose [mCi]	Frequency [%]	Accumulative dose [mCi]	Frequency [%]
≤30	517 [41.6]	0-200	1475 [83.5]
100	154 [12.4]	200-400	198 [11.2]
150	500 [40.2]	400-600	58 [3.3]
175	9 [0.7]	600-800	14 [0.8]
200	44 [3.5]	800-1000	12 [0.7]
Other	30 [1.7]	>1000	9 [0.5]

Table 4. Whole body radioiodine scan findings of the patients

Whole body Iodine scan findings [diagnostic or post treatment]		Frequency [%]
Thyroid bed uptake		14[77.8]
Lymph node metastasis		8[44.4]
Distant metastasis	Lung	1[5.0]
	Bone	1[5.0]
Negative		6[33.3]
Not available		3[16.7]

Table 5. Whole body radioiodine scan findings of the differentiated thyroid cancer patient's population

Whole body Iodine scan findings [diagnostic or post treatment]		Frequency [%]
Thyroid bed uptake or negative scan		734 [41.5]
Distant metastasis	Lung	37 [2.1]
	Bone	18 [1.0]
Lymph node metastasis		416 [23.6]
Not available		544 [30.8]

Table 6 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.

The last treatment response evaluation performed at the last visit revealed that 44.4% of the patients (8 individuals) displayed an excellent response, while two had an incomplete biochemical response and 8 had structural incomplete response. The Kaplan curve was used to evaluate patient survival, which had an average of 100 months (SD=13.5). Figure 1 illustrates the survival curve of the patients.

DISCUSSION

The study findings show that out of all the available collected data, only 18 individuals have been treated for Hürthle cell carcinoma, indicating a very low prevalence of this disease. Possible factors contributing to this low number may be the difficulty in accurately diagnosis the disease through FNA as well as the misconception of radioiodine absorption deficiency in these tumors, which may lead to failure in referring patients to nuclear medicine departments. Additionally, this highlights the insufficient information and data on this type of cancer, which is similar to previous studies.
In terms of gender, there was no significant difference between Hürthle cell carcinoma patients and the rest of the patients in the department's dataset. In examining the family history of the patients, only a single individual presented a positive family history.
A population cohort study was conducted using data extracted from the surveillance, epidemiology, and end Results database. It was found that being male is linked to a higher risk of late-stage HCC [16].

Table 6. Treatment responses in Hürthle cell carcinoma and overall patient population groups

Kind of response	Response in oncocytic carcinoma patients		Response in original dataset	
	One year response [%]	Final response [%]	One year response [%]	Final response [%]
Excellent	26.7	44.4	41.5	54.2
Indeterminate	20	0	24.7	20
BIR	20	11.2	13	9.5
SIR	33.3	44.4	20.7	16.4

BIR: Biochemical incomplete response, SIR: Structural incomplete response

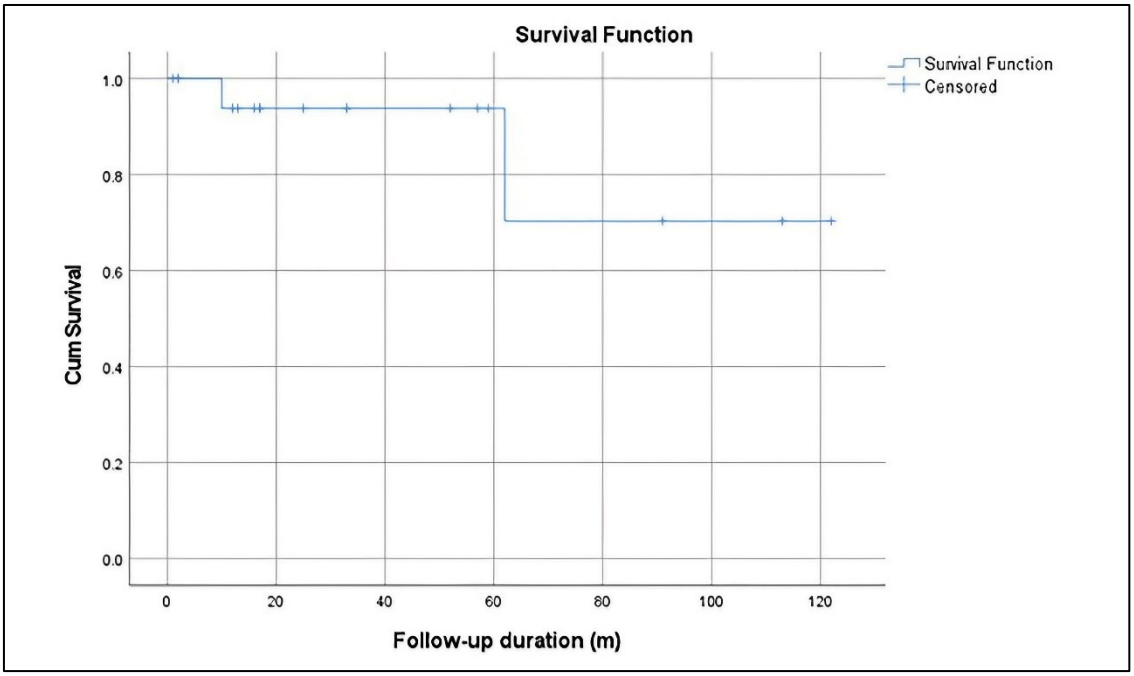

Figure 1. Survival curve of the patients

Typically, Hürthle cell carcinoma manifest after 4th decade of life and exhibit a higher prevalence among females compared to males. Despite the fact that a familial background of thyroid cancer is considered as a risk factor for follicular and Hürthle cell thyroid cancer, a significant proportion of patients do not possess any identifiable risk factors at all.

Almost all patients in the study were treated by radioiodine.

In the initial year, a noteworthy proportion of patients (22%) exhibited an excellent response rate to the treatment, and this number increased to 44% by the end of the study. However, it is worth noting that the patients who displayed a poor response to the treatment primarily attributed it to structural factors.

Among functional assessment, it was noted that the mean TSH level had risen after one year of treatment in comparison to the initial examination, which could be due to successful ablation of the thyroid remnant tissue. Conversely, the levels of serum thyroglobulin and anti-Thyroglobulin were higher during the first examination and had decreased in response to the treatment. The patients were followed up for an average of 40 months, indicating that nearly all received and benefited from adequate follow-up and care.

In 2004, Besic et al. conducted a retrospective study aimed at investigating the use of radioiodine therapy in patients with Hürthle cell carcinoma. They reviewed the medical records of 48 patients who had been treated for HCC including eight metastatic patients, and eight tumor recurrence. The study found that RAI uptake (range 0.1-12%) was confirmed in 11 of 16 patients, leading the researchers to conclude that

whole body scanning with RAI should be performed and that RAI may be effective in treating HCTC [17]. Another study conducted by Ahmadi et al., demonstrated that Hürthle cell carcinoma generally exhibits a more aggressive clinical behavior associated with a higher incidence of distant metastases when compared to other types of differentiated thyroid cancers. On the other hand, minimally invasive HCC demonstrates a significantly less invasive behavior. They concluded that thyroid lobectomy alone, without the use of radioactive iodine (RAI), can effectively treat lesions that are smaller than 4 cm in size. It has been observed that HCC has a lower capacity to absorb iodine in comparison to other differentiated thyroid cancers. However, recent data has indicated that patients with HCC larger than 2 cm, as well as those with nodal and distant metastases, may experience a more favorable prognosis when treated with RAI. For patients with iodine-resistant local disease who are not suitable candidates for an expectant approach, local therapies can be employed as a treatment option. Ultimately, the authors concluded that systemic treatment should be reserved for patients with progressive and metastatic HCC in general [18].

A large database study conducted by Jillard et al., to investigate the impact of iodine therapy on Hürthle's cell carcinoma, revealed that patients who received RAI treatment were generally younger. The 5- and 10-year survival rates were significantly higher for patients who underwent RAI treatment. Additionally, the administration of RAI treatment was associated with a 30% reduction in mortality. This study strongly suggest that RAI treatment improves survival outcomes for HCC patients. Based on the results, it is recommended that RAI treatment be considered for HCC patients with tumors larger than 2 cm, as well as patients who have distant metastases and lymphatic involvement. This treatment approach has shown potential in enhancing survival rates and should be taken into account for these specific patient groups [5].

In another study conducted by Zhu et al., on Hürthle cell carcinoma (HCC), among them, 82.82% (1740 individuals) had localized disease, 11.66% (245 individuals) had regional disease, and 4.24% (89 individuals) had distant involvement. The 5-year and 10-year cancer-specific survival rates were found to be 95.4% and 92.6%, respectively. Notably, the group with distant involvement exhibited a higher proportion of male patients, multifocal tumors, and extensive tumors compared to the group with localized disease. They concluded that male gender, multifocal tumors, and extended tumors are associated with an increased risk of HCC in advanced stages. However, there was no significant difference in survival between total and subtotal thyroidectomy, or between RAI and non-RAI treatment [16].

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 [19].

In our study, the mean age of HCC patients was 54.22 years. This is slightly lower than the average age of 55.9 years reported in other studies, indicating that a significant proportion of patients with this disease are over 50 years of age [20].

Despite the majority of patients were female, this disparity in percentage did not yield any significant findings. Conversely, previous studies have indicated that the prevalence of the disease among females was two to three times greater than that among males. This pattern is also observed in the case of papillary thyroid cancer, where it is more frequently diagnosed in women [21].

The Hürthle cell carcinoma have about 11% mortality within a year. This statistic remains noteworthy.

In a study by Besic et al.'s survival rate was 81% and 60% within five and ten years, respectively, for individuals with distant metastases. In comparison to other forms of differentiated thyroid cancers, Hürthle cell carcinoma generally exhibits a more aggressive nature. Conversely, papillary thyroid cancer is often regarded as a favorable cancer due to its less aggressive nature and effective treatment options. Nonetheless, our study indicated that 44% of patients ultimately achieved an outstanding response to treatment [22-24]. Hürthle cell carcinoma exhibits a more aggressive natural course compared to follicular carcinoma, resulting in higher rate of local recurrence, distant metastases, and mortality [18].

In our research, 44% of the patients exhibited lymph node involvement, while multifocal

involvement was observed in 22% of the patients, which aligns with previous studies. Similar to the findings in Mills et al.'s study, patients often presented with large multifocal tumors, lymph node metastasis, and signs of extra-thyroidal spread. These findings have contributed to the significant occurrence of local recurrence (34%) and distant metastases (27%). Furthermore, distant metastasis was detected in 16.6% of the participants in our study. Additionally, 11% of the patients displayed lymph node involvement based on the pathological examination of the removed lymph nodes [12].

Surgery remains the primary treatment for all differentiated thyroid cancers, including HCC. The completeness of surgical resection is particularly crucial for HCC due to its relatively reduced affinity for RAI and the potential impact of compromised treatment [18]. Two types of surgery are available: total thyroidectomy and subtotal thyroidectomy. In our study, total thyroidectomy was performed on most patients, while two patients underwent subtotal thyroidectomy. Despite surgery being a mainstay treatment for thyroid cancers, extensive surgery has not shown significant improvement in patient prognosis [23, 25]. However, some studies have indicated that radical surgery with complete thyroidectomy in Hürthle cell carcinoma has shown more favorable outcomes [12, 26, 27].

Our patients underwent two different forms of treatment, namely classical and non-classical treatment. In addition to surgery, radiotherapy and iodine therapy were utilized as supplementary treatments. A significant majority, over 90%, of the individuals involved in the study received iodine therapy as an adjunctive treatment with the median initial dose of 150mci. Despite the fact that this particular type of thyroid cancer exhibits low iodine uptake, radioactive iodine therapy may provide a survival advantage when utilized as adjuvant ablation therapy, however, it does not offer the same benefit in the presence of residual disease. Long-term follow-up is conducted to improve specificity. This follow-up should involve the serial measurement of serum thyroglobulin (Tg) level [23].

The effectiveness of radiotherapy has been observed in metastatic patients, especially bone metastases.

Studies have shown that iodine therapy, when used as a complementary treatment, can also be effective in treating thyroid carcinoma, with a significant therapeutic outcome (44%) at the end of the study. However, due to varying opinions among studies, further research is necessary to fully understand the potential of iodine therapy in treating this type of cancer.

Imaging plays a crucial role in the initial stages of the disease. One of the main challenges in promptly treating HCC is our limited ability to establish a preoperative diagnosis using imaging methods or fine-needle aspiration (FNA)-based cytology. When imaging studies do not reveal any signs of invasive or metastatic diseases, it can be difficult to differentiate between a benign Hürthle cell neoplasm and HCC. Consequently, histological evaluation based on a surgical specimen is typically required. Ultrasound alone is insufficient in distinguishing HCC from other histological types, as it can exhibit a range of ultrasound findings from hypoechogenic to hyperechogenic patterns [28]. 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

Based on the findings of this research, approximately 40% of patients show excellent survival rates. Since almost all patients received radioiodine therapy, it can be considered a significant and crucial treatment option for Hürthle cell carcinoma. However, further studies are needed, particularly among the Iranian population. Hürthle cell carcinoma is significant due to its aggressive nature compared to other forms of differentiated thyroid cancer, and the lack of prompt diagnostic and effective treatment method. Furthermore, the number of affected patients is limited, and comprehensive databases in this regard are still needed. This can be achieved by supporting researchers in exploring treatment options for this cancer and gathering data and information from the patients.

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