www.jmscr.igmpublication.org
Impact Factor 5.84
Index Copernicus Value: 83.27
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v5i7.217

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Hurthle Cell Tumours of the Thyroid- Personal Experience with Review of the Literature

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ABSTRACT
Hurthle cell carcinoma represents about 4-5% of differentiated thyroid carcinomas. The prognosis of the malignant type of the tumour is still under debate as some authors have reported that Hurthle cell adenoma very rarely behaves like Hurthle cell carcinoma. Aim of this present study is to evaluate previously reported data and experience on the clinical and pathological features of patients affected by Hurthle cell tumour that may predict disease progression and death. In the literature, the factors potentially associated with decreased survival are: age, disease stage, tumour size, extra-glandular invasion, lymph node invasion, distant metastases, surgery, radioiodine treatment. From 2005 to 2016, we identified 28 patients affected by Hurthle cell tumour, 9 with Hurthle cell adenoma and 19 with Hurthle cell carcinoma. Of these, 22 were females and 6 males. Mean age of patients affected by adenoma was 49.7 years (range 30-72) vs. 49.3 years (range 15-72) in Hurthle cell carcinoma patients. In all the patients, total thyroidectomy was performed. At histology, 9 adenomas, 5 "minimally invasive" and 14 invasive carcinomas were found. Post-operatively, in Hurthle cell carcinoma patients, TNM stage showed 9 patients with stage I, 5 stage II, 4 stage III and one stage IVa. All invasive carcinomas underwent I^{131}therapy (91-585 mCi). One Hurthle cell carcinoma patient received external beam radiation. The mean follow-up period was 62 months (range 6-324). Relapse was not observed in the patients with adenoma. Only 1 Hurthle cell carcinoma patient showed distant lung metastases at 60 months' follow-up. In the conclusion, Hurthle cell carcinoma was not found to present a more aggressive behaviour than follicular carcinoma, when risk factors, including extent of tumour invasion, were taken into account.Patients with Hurthle cell adenoma did not showed a relapse or death caused by the tumour.

Keywords: *Thyroid • Hurthle cell adenoma • Hurthle cell carcinoma.*

INTRODUCTION

Hurthle cell carcinoma (HCC) represents approximately 4-5% of differentiated thyroid carcinomas [1]. Hurthle cell tumour (HCT) is a rare thyroid neoplasm of follicular cell origin, > 70-75% being composed of oncocytes. The entity was first described in 1907, by Langhans [2] the ability to classify each tumour with oncocytic

features as either benign or malignant has been extensively studied. As a consequence, even in recent years several studies have been focused on this topic. HCC accounts for approximately 3-6% of well-differentiated thyroid carcinomas [3]. In fact, small series of patients with HCC have been reported in the literature during the past years. Due to its relative rarity, its pathologic and clinical significance has not been well documented [4-6] and little is known about the long-term survival of patients with this tumour. Some Authors suggested that HCC have a worse prognosis than papillary and follicular thyroid histotypes. Only an estimated 10% of HCC metastases take up radioiodine. HCC more frequently involves regional lymph nodes than does follicular carcinoma, shows a higher mortality rate and a greater tendency to metastasize to distant sites like lungs[7-9] while others have reported a relatively benign course and have shown that patients have survival rates similar to those for follicular carcinoma, when the tumour is treated aggressively by surgery [10 11]. Moreover, much controversy exists in distinguishing benign from malignant Hurthle cell type. The two entities are distinguished based on identification of capsular/ vascular invasion or the presence of metastatic disease [12-14].However, the prognosis of the malignant type of the tumour remains controversial as some Authors reported that patients with benign lesions subsequently developed malignant changes with metastatic disease [15].

Stemming from these differences in experience, much controversy has emerged as to the best treatment approach for HCC. Some Authors recommend conservative management whereas others suggest aggressive treatment[10 11 15 16.]

AIM OF THE STUDY

To evaluate the clinical and pathological features of our patients with Hurthle cell neoplasms, in order to analyse the clinical and pathologic prognostic factors reported in the literature that could be associated with a worst prognosis.

PATIENTS AND METHODS

A total of 28 patients with Hurthle cell tumour followed from 2005 to 2016 at the R L Jalappa Hospital and Research Centre, Tamaka are reviewed retrospectively.

Thyroid hormonal profile

	NORMAL RANGE
TSH (thyroid stimulating hormone)	0.3-3.5 mcIU/ml
Free T3	2.2-5.00 pg/ml
Free T4	8.00-18.50 pg/ml
Thyroglobulin(Tg)	0.2-50 ng/ml
SerumTg antibodies(Tg-Ab)	0-115 U/ml
Thyroperoxidase antibodies(TPO-Ab)	0- 32 U/ml

Ultrasonography of the neck (USG) and scintis can information are obtained for all patients. In all patients a thyroid nodule/neck node fine needle aspiration cytology y (FNAC) was performed. A diagnosis of follicular lesion was considered suspicious for malignancy. Surgery was performed in all patients with a suspicious or certain pathological diagnosis of malignancy. Cervical lymph node dissection was done if lymph node involvement was present at preliminary imaging or at surgery. The tumours are classified as “carcinoma” on the basis of the presence of vascular or capsular invasion and in “adenoma”, in the absence of these features. Information regarding tumour size was obtained mainly from histopathological specimens, imaging reports or clinical examination. The extent of the tumour at presentation was stated according to the TNM staging classification system for thyroid cancer (International Union Against Cancer). Surgery was followed by administration of radioactive iodine (I^{131}) in all invasive carcinomas. External Beam radiotherapy was given in only one patient with HCC. Metastatic tumour was treated with multiple radioactive iodine treatment. After primary treatment, levothyroxine TSH-suppressive therapy was started in all the patients.

RESULTS

The study population comprised of 28 patients (22 female, 6 male) 19 with HCC and 9 with Hurthle cell adenoma (HCA). None had any family history

of thyroid cancer or a personal history of radiation exposure in the past . Mean age of patients affected by adenoma was 49.7 years (range: 30-72) *vs*. 49.3 years (range: 15-72) for patients with HCC. Pre-operatively, thyroid hormonal profiles (TSH, FT3 and FT4) were in the normal range in all patients. Serum Tg levels were elevated in 5 out of 19 patients with HCC (range 110-34,000 ng/ml). Two out of 28 patients had detectable serum Tg and TPO Ab. On ultrasound examination a multi-nodular goitre was found in 21 patients, while a single nodule was found in 7 patients. All nodules resulted "cold" at scintiscan examination. In 16 patients, cytological findings were positive or suspicious for malignancy. A total of 12 patients were subjected to surgery for obstructive symptoms (breathlessness/stridor/ dysphagia). All patients underwent total thyroidectomy, except one who was submitted to hemithyroidectomy. Only one patient was submitted cervical lymph node dissection due to neck node metastases at presentation. The neoplasms ranged in size from 5-58 mm in the maximum diameter. Mean diameter was 28.8 mm in HCA patients and 25.8 mm in HCC patients. At histology, 9 adenomas, 5 "minimally invasive" and 14 invasive carcinomas were found. In 2 patients with HCC, a foci of papillary carcinoma was also detected. In 2 patients with Hurthle cell tumours of thyroid HCC, histological findings revealed chronic inflammation with detectable serum thyroid antibodies. One patient had neck nodes metastases. In 2 patients. HCC was multifocal. After surgery, 6 patients had persistent hypo-parathyroidism with hypocalcemia features and 2 patients had permanent vocal cord palsy. At post-operative TNM staging, 9 patients were stage I, 5 stage II, 4 stage III and 1 patient was stage IVa. A I^{131} whole body scan (WBS) was performed in all invasive carcinomas. Due to evidence of high levels of serum Tg, repeated radioiodine treatments (range of radiation dose 91-585 mCi) were performed. No Hurthle cell invasive carcinoma showed distant metastases at I^{131} WBS examination. In one patient in the HCC group, computed tomography (CT) detected distant lung metastases 60 months after total thyroidectomy; the lesion was confirmed by I^{131} WBS. The patient underwent further radioiodine treatment (cumulative dose 585 mCi) and is still observed at follow-up. The median follow-up period in this series was 62 months (range 6-324). In patients affected by HCA, relapse was not observed.

DISCUSSION

Hurthle cell neoplasms are heterogeneous tumours that may display various clinical entities. These neoplasms arise from follicular cells and are predominantly composed of cells exhibiting oncocytic features, also called oncocytes. Oncocytes are microscopically characterized by an abundant granular cytoplasm.

Electron microscopic studies have shown that the granularity is due to abundant intra-cytoplasmatic mitochondrias[17]. Oncocytic cells have been referred to as Hurthle cells, Askanazy cells and oxyphilic cells. They are usually considered a variant of follicular epithelial cells as sustained by the Tg immuno-reactivity found on cytological or histolopathological specimens and as confirmed by the presence of the functional activity of thyrotropin receptor- adenylate cyclase [18]. The World Health Organization (WHO) Committee prefers to define them as oxyphilic cells [15]. However, the most widely used definition among endocrinologists is "Hurthle cells", although the cells that Hurthle first discovered, in 1894, in a dog's thyroid, were more likely to be C cells [19].

Since Hurthle cells are found in both neoplastic and non-neoplastic thyroid lesions, it is difficult to differentiate benign Hurthle cell hyperplasia from true Hurthle cell neoplasm. There is general agreement that the cutoff parameter useful to distinguish between true HCT and Hurthle cells hyperplasia, is 70-75% of the cell population is made of Hurthle cells.

Usually, as for the follicular type, a HCT can be classified as malignant (HCC) when capsular or vascular invasion is reported or if there is a peri-thyroid infiltration or distant metastases are found [20,21]. At histopathology, HCC is distinguished as

"minimally invasive HCC", if only capsular invasion is reported or "invasive HCC", when both vascular and capsular infiltration are present. Consequently, the findings obtained by means of FNAC do not offer the possibility to differentiate between true follicular and Hurthle cell neoplasms and between the benign and malignant types of HCT [22]. As in the case of the follicular thyroid neoplasms, even intra-operative frozen sections show a low sensitivity and specificity in the detecting Hurthle cell carcinoma [23] [24]. Only histolopathogical analysis can differentiate between adenoma and carcinoma. Therefore some Authors claimed that all thyroid nodular lesions with a cytological finding of more than 50-60% of Hurthle cells should be treated [25].

Nevertheless, a recent report claimed that, despite a high risk of malignancy, clinical features such as size of the nodule, age and sex of the patient should be a part of the decision-making [22]. Hurthle cell neoplasm was first described, in 1907, by Langhans who reported 5 patients with thyroid lesions composed of oncocytes[2]. Although 2 out of the 5 patients died on account of distant metastases, the Authors did not describe any microscopic evidence of malignancy. Twenty years later, Wegelin et al. stated that most of the HCT were benign[25], while in 1941, Harry et al. described these tumours as moderately malignant [26] and Warren et al. classified these lesions as benign tumours which are potentially malignant[27].

In 1951, the American Cancer Association claimed that surgical treatment of Hurthle cell neoplasms should be extensive because of their malignant potential [28]. More recently, some Authors reported that as Hurthle cell thyroid neoplasms are usually aggressive malignant neoplasms and even adenomas can metastasize [29], all Hurthle cell lesions should be subjected to total thyroidectomy. In 1989, McLeod et al. again suggested that treatment of Hurthle cell neoplasms was controversial because of the absence of a clear correlation between the microscopic features and the clinical behaviour of the tumour[30]. Thompson et al. claimed that Hurthle cell tumours should be considered malignant irrespective of size and pathological features and subjected to total thyroidectomy for all such lesions [29].

In 1874 Grant et al. reported that only one out of 271 patients affected by HCA presented evidence of malignancy and no patients died of thyroid carcinoma[31]. In the last 20 years, various studies have been performed in order to detect reliable histopathological and clinical factors in predicting malignancy in patients with Hurthle cell neoplasm [32] [33]. Since HCT may exhibit a follicular or papillary growth pattern, they have often been classified only on the basis of their architecture independently of the presence of Hurthle cells. At present, there is general agreement in considering Hurthle cell tumours as a subset of all differentiated thyroid malignancy, irrespective of the papillary or follicular growth pattern. The WHO Committee considers this tumour the oxyphilic variant of follicular thyroid cancer, while for the Armed Forces Institute of Pathology (AFIP), HCC should be included in a subset of thyroid neoplasms different from true follicular cancers [14] [34].

Recently, in a large series of patients affected by HCC with a papillary growth pattern, the Authors found worse characteristics than in classic papillary thyroid carcinoma, similar to the tall cell variant, in terms of vascular invasion, distant metastases and prognosis [35] [36]. Whether prognosis of patients affected by HCC is worse than those with the follicular variant is still a matter of debate. Some authors consider this neoplasm aggressive , with a mortality rate as high as 25% in 30 years while others find it no more aggressive than similarly staged follicular carcinoma without Hurthle cells [37] [38].

The pathogenesis of these lesions seems related to alterations of mitochondrial DNA (mtDNA) [39]. Systematic analysis of the primary structure of mtDNA in 79 benign and malignant tumours (43 Hurthle and 36 non-Hurthle cell neoplasms) and respective normal parenchyma displayed a relatively high percentage (up to 16%) of mtDNA common deletions (CD) in Hurthle cell tumours, irrespective of the histology of the lesion. The

percentage of deleted mtDNA molecules was significantly higher in tumours with D-loop mutations than in mtDNA stable tumours. The Authors concluded that germline polymorphisms of the ATPase 6 gene are associated with the occurrence of mtDNA CD, the hallmark of Hurthle cell tumours [40].

In 2001, Erickson et al. analysed Hurthle cell neoplasms by inter-phase fluorescence *in situ* hybridization to evaluate the diagnostic and prognostic usefulness of numerical anomalies by DNA fluorescent probes for cyclin D1 and p53 gene loci and chromosomes 5, 7, 11, 12, 17, and 22. They showed that chromosomal imbalances as gains are common in both benign and malignant Hurthle cell neoplasms, but HCC tend to have more chromosome losses than adenomas and that the loss of chromosome 22 may be of prognostic significance in HCC [40].

Musholt PB et al., in 2004, suggested that "the expression of rearranged RET hybrid oncogenes is present in a similar percentage of HCC when compared with the literature on non-oxyphilic papillary thyroid carcinoma", and may play a role in the early tumourigenesis of oncocytic tumours[41].

Recent reports suggested the use of some proliferative cell markers such as PCNA and Ki-67 in the cytological diagnosis of Hurthle cell tumours. Augustynowicz et al. reported a significant difference in all proliferative activity markers between malignant and benign tumours (HCC:HCA $p < 0.01$; HCC:HCM $p < 0.001$) [42].

Despite the fact that HCC is a rare occurrence, prognostic scoring systems have been criticised for not taking into account the possible differences between HCC and follicular cancer with their variable behavior at histopathology. Shaha et al. have shown that there are several differences between HCC and follicular thyroid carcinoma [43].

Patients affected by HCC frequently present an intra-thyroid multifocality (35%), extra-thyroid invasion (37%), lymph node (25%) or distant metastasis (18%). It has been reported that some of these features are increased in HCC patients compared to those affected by follicular carcinoma of thyroid. Patients with HCC are significantly older, have large nodules, higher mortality rates associated with recurrence, and a higher treatment failure rate compared to follicular thyroid neoplasm patients. Cervical lymph node metastases are common in HCC patients, but uncommon in follicular thyroid carcinoma patients.

HCC does not usually take up radioactive iodine whereas most follicular thyroid carcinomas take up radioactive iodine. In some reports on HCC and follicular thyroid carcinoma, it has been stated that an older patient's age, large tumour size, extra-thryoid invasion, all have a negative prognostic significance [44-46].

Aim of the present study was to identify the clinical and pathologic features of HCC that may help to predict disease progression or death. A comparison was made between 19 patients affected by HCC and 9 patients with HCA. None of them had previous exposure to external radiation. In this study, the mean age of the HCC group was younger than that in the reported series [46]. No sex differences were present in either group, nor was there a significant difference in the age of patients or the size of primary tumours.

In the literature, the incidence of males is 20-28%, but there has been a female predominance among HCC patients in most reports [1]. In this study, the male-female ratio among HCC patients was approximately 1:3 *vs*. approximately 1:2 among those with HCA. The multifocality rate, observed in 2 patients with HCC and the extra-thyroid invasion rate, found in 3 HCC patients, were lower than those reported in other series. Vascular invasion was not associated with a poor survival rate. Except one, all our patients underwent total thyroidectomy, so we did not evaluate the impact of surgery on survival. In the absence of prospective trials, due to the rarity of HCC, it is too early to draw any conclusions concerning the effects of the different treatments. The use of radioactive iodine is still controversial since, in most metastases from these tumours, uptake of radioactive iodine is rare [47.] However, if uptake of radioactive iodine is observed, as in our invasive

hurthle cell carcinoma patients, this treatment is advisable, as even low risk patients who have HCC or follicular thyroid carcinoma and invasion of the major blood vessels are at some risk of recurrence and death. This does not apply to patients with minimal capsular invasion alone. In this series, all patients with invasive cancers received radioactive iodine, independently of ^{131}I WBS uptake. They were treated with at least one course of radioiodine, for which the main indication was adjuvant thyroid remnant ablation. The dose of radioiodine ranged between 91-150 mCi. In one patient with HCC, who was treated with radioactive iodine for adjuvant ablation of remnant thyroid tissue (150 mCi), 60 months after primary radioiodine treatment, a HRCT scan showed lung metastasis negative, at ^{131}I WBS, in spite of high serum Tg levels. A series of reports from Cleveland Clinic, Lahey Clinic, and Memorial Sloan-Kettering Cancer Center comparing HCC and follicular thyroid carcinoma often showed that HCC is more aggressive in behaviour with poor patient survival. Carcangiu et al. were also of this opinion, although they did not have a group of follicular thyroid carcinoma patients for comparison [17 32 48 49].

However, in other reports, patients with HCC are considered to have better survival than those with follicular thyroid cancer. In the Memorial Sloan-Kettering Cancer Center series, patients with follicular thyroid cancer had a higher rate of regional lymph node metastases than patients with HCC, but these data are also considerably higher than those generally found in this neoplasm. Data from the Mayo Clinic demonstrated a higher rate of regional lymph node metastasis in HCC than in follicular thyroid cancer[36]. In this study, lymph node dissection was performed in only one patient with extra thyroid invasion, which is much lower than the number reported in other series. In the Memorial Sloan-Kettering Cancer Center series, and the earlier series from the Mayo Clinic, HCC presented a higher rate of distant metastasis than follicular thyroid cancer [36]. Recent reports from the Mayo Clinic stated that the survival of patients with HCC and follicular thyroid cancer patients was similar, while earlier series from the same Institution revealed poorer HCC patient survival [50 51]. Our findings are not in agreement with these data as, in fact, we observed distant metastases in only 4.5% of our cases. In agreement with the results of other authors, recurrence was observed within the first 5 years after surgery. In our series of patients, neither adenoma nor minimally invasive HCC exhibited malignant behaviour. We compared patients with only minimal capsular invasion *vs.* those with blood vessel invasion or major capsular invasion. Recurrence was present only among the patients with invasive HCC. Although in this study population , the follow-up was relatively short, age, sex, tumour size, extra thyroidal invasion, or neck node, at presentation, were not found to be of significant prognostic value in patients affected by HCC. Blood vessel invasion and/or major capsular invasion did not represent a significant risk of death in any of the patients. Of all the risk factors we examined, none were associated with all-cause mortality or disease specific mortality.

CONCLUSION

in this study, HCC was not found to display an aggressive behaviour, unlike those reported by other authors when risk factors, including the extent of tumour invasion were taken into account [51]. None of the patients in this series, affected by HCA, presented relapse or death caused by the disease.

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