Management of thyroid Hurthle cell neoplasms: a single centre experience and literature review

Management delle neoplasie a cellule di Hurthle della tiroide: esperienza di un singolo centro e revisione della letteratura

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Summary

Aim. **We report our experience on the management of Hurthle cell neoplasms (HCNs) of the thyroid and a review of the literature in order to describe the most relevant clinical, diagnostic, biologic and therapeutic aspects.** ***Materials and Methods.*** **We retrospectively reviewed the clinical records of 15 consecutive patients with HCN. The male/female ratio was 1:4 and the mean age was 53.8 years. Fourteen patients underwent total thyroidectomy and one patient lobectomy. Two patients were lost to follow up. The mean follow up time was 54 months.** ***Results.*** **Eleven Hurthle cell adenomas and 4 carcinomas were found. At the time of initial surgical evaluation 9 patients (60%) were symptomatic, with hyperthyroidism and dysphagia being the most frequent manifestations. Only in 6 (40%) cases the diagnosis was obtained by preoperative fine needle aspiration biopsy. Among patients with Hurthle cell adenoma and carcinoma the mean age was 51 and 62 years respectively and the mean lesion size 1.6**

Riassunto

Obiettivo. **Riportiamo in questo articolo la nostra esperienza nel management delle neoplasie a cellule di Hurthle (HCNs) ed una revisione della letteratura allo scopo di sottolineare i più importanti aspetti clinici, diagnostici, biologici e terapeutici.** ***Materiali e metodi.*** **Abbiamo esaminato i dati clinici di 15 pazienti consecutivi con HCN. L'età media dei pazienti era di 53,8 anni e il rapporto maschi/femmine 1:4. Quattordici pazienti sono stati sottoposti a tiroidectomia totale ed uno a lobectomia. Due pazienti sono stati persi al follow up. Il tempo medio di follow up era di 54 mesi.** ***Risultati.*** **Undici pazienti sono stati trovati affetti da adenoma a cellule di Hurthle e 4 da carcinoma. Nove pazienti (60%) erano sintomatici, e solo in 6 (40%) casi la diagnosi è stata ottenuta tramite biopsia con ago aspirato. L'età media dei pazienti affetti da adenoma era 51 anni e di quelli con carcinoma 62. La dimensione media delle lesioni era superiore nei pazienti con carcinoma (3,8 cm verso 1,6 in quelli con adenoma). Non sono stati**

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and 3.8 cm respectively. No cases of death or recurrence were registered. *Conclusions.* Clinical manifestations are similar to those for other differentiated thyroid neoplasms. Patients with Hurthle cell carcinoma presented a mean age and a mean tumor size greater than those with Hurthle cell adenoma. Our data suggest that adenomas have not a malignant potential; nevertheless surgical resection is necessary to obtain a precise evaluation of eventual infiltrative events. Surgical resection is also the treatment of choice for the treatment of carcinomas with total thyroidectomy representing the best surgical option. Eur. J. Oncol., 17 (4), 181-188, 2012

Key words: **thyroid, Hurthle cell, oncocytic, oxyphilic, thyroidectomy**

osservati decessi o recidive. *Conclusioni.* Abbiamo osservato una differenza di età e di dimensione delle lesioni tra i pazienti affetti da adenoma e quelli affetti da carcinoma. I nostri dati suggeriscono che gli adenomi a cellule di Hurthle non hanno potenziale maligno, tuttavia l'asportazione chirurgica è necessaria per la valutazione di eventuali eventi infiltrativi. Il trattamento chirurgico con tiroidectomia totale o resezioni più ampie ove necessario rappresenta il trattamento di scelta per i carcinomi. Eur. J. Oncol., 17 (4), 181-188, 2012

Parole chiave: **tiroide, cellule di Hurthle, oncocitico, ossifilico, tiroidectomia**

Introduction

Hurthle cell neoplasms (HCNs) are rare tumors of the thyroid gland, composed for more than 75% of oncocytic or Hurthle cells and may be benign (adenomas) or malignant (carcinomas). Hurthle cell carcinomas (HCCs) assess for approximately 3-7% of well differentiated thyroid carcinomas (1-5). HCNs are characterized by a broad spectrum of clinical manifestations and the imaging techniques routinely employed for clinical assessment present a low specificity. Fine needle aspiration biopsy (FNAB) is often able to detect oncocytic cells but it is of limited utility in identifying eventual capsular or vascular tumoral invasion. Addictively, several authors sustain that Hurthle cell adenomas (HCAs) may be potentially malignant and capable of local or distant spreading. These features of HCNs may render challenging the diagnosis and the choice of the appropriate treatment. In this article we report our experience on the management of HCNs and a review of the literature in order to describe the most relevant clinical, diagnostic and therapeutic implications.

Materials and methods

In the last 10 years we performed in our institution 640 surgical interventions for thyroid disease. Fifteen cases of HCNs were retrospectively identified, accounting for 2.3% of the overall surgical operations: twelve women and three men (male/female ratio = 1:4) and mean age 53.8 years (range 26-76). Fourteen patients (93.3%) were affected by a single lesion, while one (6.7%) presented two synchronous HCAs (Table 1).

Preoperative assessment was performed through neck ultrasound in all cases and no cervical lymphadenopathy was observed. Computed tomography (CT) scan examination was not employed in this cohort. Eleven patients (73.3%) preoperatively underwent FNAB. Such procedure was not performed in four patients with voluminous multinodular goiter in whom a HCN was occasionally discovered at histopathlogical examination of the surgical specimen.

Fourteen (93.3%) total thyroidectomies (TTs) and one lobectomy (in a young lady with a small lesion) were performed by a senior surgeon with standard open approach, as we reported in the past (6,7). Three cases of early post-operative hypocalcemia and one case of recurrent laryngeal nerve damage were observed. No bleeding or other complications were seen.

Thirteen out of 15 patients were interviewed by phone and clinical and survival data were collected, while two patients with HCA were lost to follow up. The mean follow up time was 54 months (3 - 120).

Results

Table 1 summarizes the principal demographic, clinical, pathological and prognostic findings.

At the time of initial surgical evaluation 6 patients (40%) did not refer any symptom while nine (60%) were symptomatic. The clinical manifestations observed in the latter patients were: hyperthyroidism and dysphagia in four cases (26.7%), hypothyroidism in two cases (13.3%), dyspnea, dysphonia and hypoparathyroidism in one case (6.7%). Nine patients (60%) presented a normal functional thyroid status. The mean time between onset of symptoms and surgery was 38 months (1 - 204).

In nine (60%) cases the diagnosis of a HCN was fortuitous, while in six cases (40%) the diagnosis of a HCN was preoperatively obtained by FNAB. Two of the nine patients who had a fortuitous diagnosis of HCN were affected by a HCC, detected after histopathological examination of the surgical specimen. Totally 11 patients (73.3%) underwent FNAB and among them six (54.5%) had a HCN diagnosis, while four (36.4%) had a diagnosis of colloidal goiter. In one case repeated FNAB resulted non diagnostic.

Eleven patients (73.3%) were found to be affected from a HCA and four patients (26.7%) from HCC. The mean age of patients affected of HCA and HCC was 51 and 62 years respectively. The mean size of HCA lesions was 1.6 cm and that of HCCs was 3.8 cm. Eleven patients (73%) were affected by at least one additional pathological condition: colloidal goiter in ten cases (multinodular goiter is endemic in Sardinia), papillary carcinoma in three cases, chronic thyroiditis in two cases and parathyroid adenoma in one case. Among patients with HCC vascular invasion was present in all cases, while capsular invasion was detected in two cases (50%).

All 13 patients whose telephone number was available were alive and the long term surgical

Table 1 - Demographic, clinical, pathological and prognostic findings

Patient	Age (years)	Sex (M - F)	Hormonal State	FNA	Surgery	Histology	Max dimension (cm)	Histologically found comorbidities	Radioiodine treatment	Follow Up (state - months)
1	43	F	Hypothyroid	No	TT	HCA	0.5	Goiter	No	Not available
2	39	F	Euthyroid	Yes	TT	HCA	3	Goiter	No	Alive - 120
3	55	F	Hyperthyroid	Yes	TT	HCA	3.5	No	No	Alive - 113
4	33	F	Euthyroid	Yes	TT	HCA	0.8 - 1.2	No	No	Alive - 108
5	74	F	Hyperthyroid	Yes	TT	HCC	1.2	No	Yes	Alive - 101
6	43	M	Euthyroid	Yes	TT	HCC	4	Goiter	Yes	Alive - 66
7	50	F	Hyperthyroid	Yes	TT	HCA	0.6	No	No	Alive - 48
8	76	F	Euthyroid	Yes	TT	HCA	2.5	Papillary cancer + Thyroiditis	Yes	Not available
9	75	F	Hyperthyroid	No	TT	HCA	0.6	Goiter	No	Alive - 43
10	47	F	Euthyroid	Yes	TT	HCA	1	Goiter	No	Alive - 30
11	64	F	Euthyroid	No	TT	HCC	6	Goiter	No	Alive - 28
12	26	F	Euthyroid	Yes	Lob	HCA	1	Goiter	No	Alive - 25
13	63	M	Euthyroid	No	TT	HCA	1.2	Goiter + Papillary cancer	Yes	Alive - 12
14	66	M	Euthyroid	Yes	TT	HCC	4	Goiter + Parathyroid adenoma	Yes	Alive - 6
15	51	F	Hypothyroid	Yes	TT	HCA	2.5	Goiter + Papillary cancer + Thyroiditis	Yes	Alive - 3

M: males, F: females, FNA: fine needle aspiration, TT: total thyroidectomy, Lob: lobectomy

complications registered among them were one case of persistent hypoparathyroidism and one case of recurrent laryngeal nerve damage. Three patients with HCC underwent radioiodine treatment after surgery, on the basis of postoperative serum thyroglobulin levels and evidence of residual thyroid tissue at postoperative imaging. Three patients with HCA underwent radioiodine therapy as they were affected also by papillary thyroid cancer. No one of the remaining patients with HCA underwent further treatment after surgery. There were no recurrences or progression of the disease among the 13 patients interviewed.

Discussion

The term "Hurthle Cell" was introduced by Ewing in 1928 (8). He thought that HCN was made of the same cells described by Hurthle in the normal thyroid of dogs in 1894 (9). Although this labelling is inaccurate because the cells defined by Hurthle are likely parafollicular (C cells), it remained in the literature and adopted in the WHO classification of thyroid neoplasms. Other terms are also used to describe the same cell type (oxyphilic, oncocytic, Askanazy) characterized by polygonal and acidophilic granular cytoplasm with abundant mitochondria, ergastoplasm and hypercromatic nuclei.

Thyroid cancer is rare among human malignancies (< 1%) but accounts for over 93% of all cancers of the endocrine system (10). Worldwide frequency of thyroid cancer may widely vary because of age, gender, ethnic, geographic and environmental variations. HCC assess for approximately 3-7% of thyroid carcinomas (1-5), even if some authors report higher incidences, greater than 10% of all thyroid tumors (11). The mean age of peak incidence of HCC is usually 50-60 years, approximately 10 years greater than the age associated with other types of differentiated thyroid cancers, being a disease of adults, whereas papillary and to a lesser extent follicular cancer occur in younger patients (12). Evidence of predominance in females about HCN (male-female ratio reported ranges from 1:3 to 1:5) is present, as for papillary and follicular cancer of the thyroid (2, 12, 13). Male patients exhibit a higher frequency of carcinomas (13). In our series the mean age was 53.8 (range 26 - 76 years), and the male/female ratio was 1:4.

In the suspect of HCC previous illness or head and neck irradiation, recent pregnancy, time of onset and rate of growth of the neck swelling should be assessed. Most patients with thyroid nodules have few or no symptoms and no clear relationship exists between nodule histological type and the reported symptoms. In our experience 9 HCNs (60%) were casually discovered. However, some clinical features may be suggestive of malignancy, as rapid growth over weeks, hoarseness, dysphagia, dyspnea and dysphonia, particularly when observed in the absence of a multinodular goiter. Differentiated thyroid carcinomas rarely cause airway obstruction, vocal cord paralysis, or esophageal symptoms as initial clinical presentation. Hence, the absence of local symptoms does not rule out malignancy. Most patients with HCN are euthyroid, but in some cases signs of thyroid hormonal imbalance may be present. In our experience 60% of the patients presented normal thyroid function, 26.7% hyperthyroidism and 13.3% hypothyroidism.

Most commonly the physical examination reveals a palpable single nodule or multiple neck nodules. If a single nodule is detected it is important to consider the location, the size, the consistence and the mobility in relation to the adjacent deep or superficial anatomic structures; the firmer the nodule, the greater the concern for carcinoma. The examination of the neck includes also the evaluation of eventual lymphadenopathy: large, multiple, firm, or even fixed lymph nodes are suggestive of metastatic carcinoma and may be the first clinical presentation in some cases.

Ultrasonography actually represents the most employed diagnostic tool as it is easy to perform, widely available and without radiation exposure risks and high costs (14). It represents the most sensitive method in the survey of thyroid disease, particularly in detection and description of thyroid neoplasms and cervical nodal metastases (15), and it was the only imaging examination used in our study. Several ultrasonographic findings in the contest of a thyroid nodule may be associated with a higher likelihood of malignancy such as microcalcifications, hypoechogenicity, irregular margins, predominant central flow and a shape taller than the width

measured in the transverse dimension. In spite of its high sensitivity its specificity is low, especially in recognizing HCNs.

^{131}I Scintigraphy is traditionally recommended for nodules greater than 1 cm with indeterminate cytology, even though it is not a routine test for the investigation of thyroid nodules. When a cold or hot nodule is detected, the possibility of malignancy amounts for 38.5% and 2.5%, respectively. Uptake in the nodule indicates its benign nature and spares patients from surgery due to suspicion of malignancy (14). However, scintigraphy does not always permit an unequivocal interpretation. Positron emission tomography (PET) with different radionuclides have similar limitations. The major role of nuclear medicine tests is the detection and treatment with radioactive iodine for residual malignant thyroid tissue and metastatic disease in patients with differentiated thyroid carcinoma after total thyroidectomy (4).

Usually both CT and magnetic resonance imaging (MRI) have a limited role in the initial investigation of a patient presenting with a thyroid nodule. In invasive thyroid malignancy, cross-sectional imaging helps to evaluate extra-thyroid spread of tumor to adjacent anatomical structures and provides evidence of regional or distant metastases in order to decide the best therapeutic strategy (15).

FNAB is safe, cheap, minimally invasive, and highly accurate in the diagnosis of thyroid nodules. It has been shown to have a diagnostic sensitivity of 89% to 98% and a specificity of 92% (16) in detecting thyroid cancer with overall false negative and false positive rates ranging from 0.5% to 11.8% and from 0% to 7.1% respectively (15). The sensitivity and specificity in the identification of HCNs is correspondingly 97% and 100%, but it is substantially incapable of distinguish HCC from HCA. Cytological findings of a Hurthle cell lesion with a high degree of atypia are highly suspicious for malignancy; furthermore HCAs have a broader range of cytological features than carcinomas and may present with an abundant colloid matrix. It is important to consider that Hurthle cells may also be present in a wide range of benign conditions including hyperplasic nodules in Hashimoto thyroiditis and adenomatous - multinodular goiters with Hurthle cell metaplasia. Differential diagnosis is of primary importance in these cases.

A wide set of criteria has been proposed for the cytological diagnosis of HCN including cytoarchitecture, monomorphism, macronucleoli and among all vascular or capsular invasion (17). These last features are certainly better examined in a surgical specimen. For this reason some authors use intraoperative frozen-section (FS) biopsy to confirm the FNAB findings and to guide the extent of thyroidectomy in order to avoid a subsequent completion thyroidectomy (18). However, FS evaluation may miss vascular or capsular invasion because of the limited number of sections and the presence of artefacts. In these cases, final diagnosis is deferred to examination of the entire capsule and a completion procedure may be required. Some authors have not found any difference in sensitivity and specificity between FS and FNAB (19). Such speculations suggest that FNAB is useful in the preoperative evaluation of patients with nodular thyroid disease, but only histological examination of the entire lesion surgically excised is capable to detect the presence of capsular or vascular invasion.

Following the diagnostic uncertainties, it is not easy to asses the appropriate treatment of HCNs on the basis of preoperative findings. Some authors recommend total or near-total thyroidectomy (TT) in all cases, while others suggest a less aggressive approach as lobectomy or isthmusectomy followed by completion thyroidectomy if necessary. TT is also preferred because oxyphilic neoplasms often are found in the context of multinodular goiter or nodular Hashimoto's thyroiditis (20), as it happened in 73% of our patients. It is also recommended if the primary thyroid carcinoma is larger than 1 cm, when contralateral thyroid nodules and regional or distant metastases are present. TT is also indicated when the patient has a head and neck radiation history or a first-degree family history of differentiate thyroid carcinoma. Some authors consider age greater than 45 years a criterion to choose near-total or TT even for small tumors because of the higher recurrence rate in this age group (21). Lobectomy should be considered in low-risk patients with minimally invasive tumors, while isthmusectomy is not recommended. Compartment-oriented lymph node dissection should be performed in cases of clinically and/or intraoperatively evidenced lymph node involvement. Ipsilateral lymph node metastatic

lesions occur in about 25% of patients with HCC (22). With less extensive resection the recurrence rate in the contralateral lobe is approximately 7%, and 50% of patients with recurrent differentiate thyroid carcinoma will eventually die from this disease (23). No one of our patients had evidence of cervical lymphadenopathy, preoperatively or intraoperatively.

The surgical risks of two-stage thyroidectomy (lobectomy followed by completion thyroidectomy) are similar to those of TT and generally consist in recurrent laryngeal nerve damage and permanent hypoparathyroidism. These complications may be reduced in experienced hands, but unilateral resection is clearly associated with fewer complications.

Controversy exists as regards the use of ^{131}I as less than 10% of HCCs take up the radionuclide and does not appear to improve outcomes in patients with HCC. After a partial or subtotal thyroidectomy, radioiodine can be employed for thyroid residue ablation and to detect recurrence. External irradiation should be selectively used in cases of unresectable tumors especially in absence of ^{131}I uptake and for isolated bone metastases after surgical resection (24).

The identification of prognostic factors able to predict the biological and clinical behaviour of HCN may influence the appropriate choice of surgical or adjuvant therapy in order to reduce over treatment. It may also be useful in selecting patients who need a careful follow-up after primary therapy. An association has been observed between older age and HCC. Lopez-Penabad *et al.* and Yi Wei Zhang *et al.* found a clear difference in age in patients with HCA and HCC (3, 25). Our results confirm this trend: the mean age in patients with HCC and HCA was respectively 62 and 51 years.

As regards the correlation between tumor size and malignancy risk, no clear evidence exists. Some studies suggest that HCC has a tendency to present a larger size than HCA at the time of diagnosis (2). In the study of Chen *et al.* HCC exhibited a mean tumor size at presentation of 4.0 cm, whereas HCA had a mean tumor size of 2.4 cm (26), while Sippel *et al.* demonstrated a proportional increase of the risk for malignancy when tumor size raises (27). Nevertheless, Chen *et al*. found a 23% risk of malignancy in lesions 1-4 cm (26) and Giorgadze *et al*. a 45% risk in lesions smaller than 2 cm (28). Even in our study the nodule size was associated with a higher risk of malignancy: HCC had a mean tumor diameter of 3.8 cm and HCA of 1.6 cm. Considering that adenomas are often larger than 2 cm and sometimes overpass 5 cm in diameter, the size of the lesion alone cannot be used as a criterion of malignancy (13). Other evidences suggest that the size of HCCs correlates with the aggressiveness of the tumor (24,29) but no definitive conclusions exist on the topic. Local invasion and extraglandular expansion adversely influence survival as well as lymph node involvement and distant metastases. In particular the occurrence of distant metastases (especially bone and lung metastases) is considered the factor with the worst impact on prognosis (24).

One of the most debated issues regarding HCNs is to predict their clinical behaviour on the basis of pathological criteria. Historical studies demonstrate that there is not always an exact correlation between histological features and oncologic nature of such lesions (30,31). Thompson *et al.* report 11 deaths among 25 patients with HCN and malignant behaviour in 3 out of 4 patients with HCA, concluding that all HCNs must be considered as malignant, irrespective of size (32). This experience seems exceptional, considering that most recent studies exclude any malignant behaviour in benign Hurthle cell lesions. Bondeson *et al.* reported 34 patients with HCA without evidence of clinically malignant evolution (33). Similarly in our experience no one of the patients with HCA presented malignant course, even after several years of follow-up in some cases. However many authors believe that HCNs are to consider always malignant but with a different progress capacity.

Conclusions

HCNs are rare neoplasms of the thyroid gland, amounting in our experience for the 2.3% of the overall surgical operations for thyroid disease. Clinical manifestations are similar to those of other differentiated thyroid neoplasms and the best diagnostic tools in our practice was ultrasound and FNAB. Our data suggest that HCAs have no malignant potential as some authors reported in the past,

but surgical resection is necessary in order to obtain a precise evaluation of eventual infiltrative events. Surgical resection is the treatment of choice for the treatment of HCNs and total thyroidectomy represents in our opinion the best surgical option, while larger interventions have to be considered in cases of advanced disease and lobectomy in low-risk patients with minimally invasive tumors.

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