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Ultrasound requested by general practitioners or for symptoms unrelated to the thyroid gland may explain higher prevalence of thyroid nodules in females

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ABSTRACT

Background: A higher prevalence of thyroid nodules/carcinoma in females is well-known from the literature. The reasons for this difference are not fully explained. We intended to assess gender variation in the referral for ultrasound-guided fine needle aspiration (FNA) of thyroid nodules, to study reasons for gender referral differences, and to assess differences in nodules characteristics between genders.

Methods: Included were 272 consecutive patients, with 290 nodules submitted to FNA. Patients were questioned on the reason why ultrasound (US) examination was required. Electronic medical records were reviewed. Nodules' ultrasound/cytological characteristics were assessed. Variables studied: referral cause; referral pattern (hospital-specialist versus general-practitioner); number of nodules; age, thyroid function; nodule size, TIRADS classification, resistive index, Doppler pattern, Bethesda categorisation. Variables were compared between males and females referred for FNA. Significant variables were assessed with logistic regression.

Results: Of the 272 patients, 215(79%) were women with a female:male referral ratio for FNA of 3.8:1. Non-parametric statistically significant differences ($p < 0.05$) were found between genders in: thyroid function, nodule size, referral pattern and referral cause. Nodule size and thyroid function tests became non-significant in logistic regression. Cause and referral pattern remained significantly associated with gender. Referral by a general-practitioner was associated with a 2.6-fold increase in odds of referring a female. Causes unrelated to the thyroid were associated with a 3.2-fold increase in odds of female reference.

Conclusions: A referral bias might be responsible for the higher rate of thyroid nodules in female patients, both due to referral by general practitioners and due to causes indirectly related to the thyroid gland.

1. Introduction

It is well known, from epidemiologic studies, that thyroid nodules are highly prevalent worldwide. The prevalence is higher in females and increases with age [1–3]. The female: male prevalence ratio in palpable thyroid nodules is 5:1 [1].

The incidentally discovered nodules in imaging examinations performed for a plethora of causes unrelated to the thyroid gland are considered to have greatly contributed to the rising incidence of thyroid differentiated carcinomas [4]. There have been concerns regarding overdiagnosis of thyroid carcinomas, particularly in women (3 to 5 times more frequent than in men) [5], supported by the steady low mortality rate of these tumours as opposed to the rising incidence [6,7].

Data available from Portugal's National Oncologic Registries are similar to the rest of the world: in 2005, the crude thyroid carcinoma incidence was 9.75:100,000 [8]; in 2008 it was 14:100,000 and became the third most-frequent malignant carcinoma in women [9,10]; in 2010, it increased to 15.3:100,000, with a female: male ratio of diagnosed thyroid carcinomas of 3.9:1 [8,11].The mortality/incidence ratio, however, was higher in males than in females (8 and 4%, respectively) [11]. This could be due to a more aggressive behaviour of thyroid carcinomas in males or, alternatively, could reflect an overdiagnosis of microcarcinomas in females, which have an excellent prognosis and do not affect mortality.

The causes for the gender difference in the incidence of thyroid cancer are still not well known. Possible explanations range from the

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higher incidence of benign thyroid pathology in women (and the consequent more frequent thyroid palpation and imaging), to men's tendency to look for medical attention later than women [12], or even to the potential role of sex steroids [13].

Considering that several studies have demonstrated that men and women have different behavioural patterns when attending diagnostic examinations [14], and that baseline characteristics studies performed in thyroid nodules are invariably asymmetric due to the higher number of females with clinical detectable disease [2,15], we thought of the possibility of a referral bias as a reason for the differences in gender prevalence of thyroid nodules and thyroid carcinomas in the clinical practice.

To test this hypothesis, we performed a prospective observational study aiming to assess gender variation in thyroid nodules' referral for FNA, to assess reasons for gender referral differences, and to assess differences in nodule characteristics between men and women.

2. Methods

2.1. Study design

A prospective, observational, descriptive, and analytical study was performed.

2.2. Study population

A sample population was included from a prospective cohort design (work in progress for a PhD thesis aiming to quantify thyroid nodules' echogenicity), including 272 consecutive patients referred to Hospital Professor Doutor Fernando Fonseca (HFF) for ultrasound-guided FNA of 290 nodules, between 2015/01/01 and 2015/12/31.

HFF is a Public General and Teaching Hospital, serving a population of about 600.000 residents, of Amadora and Sintra Municipalities, Lisbon district, Portugal.

A multidisciplinary decision team, comprising radiologists, surgeons, endocrinologists, and internists, meets regularly to discuss thyroid patients.

This study was conducted according to the Declaration of Helsinki.

All patients signed two distinct informed consent forms: one related to the FNA procedure, and the other for participating in the study. The study protocol and the informed consent form were approved by HFF, and Nova-FCM Ethics Committees.

Information concerning thyroid function and referral pattern was gathered from the electronic medical records.

Referral pattern was documented as: 1) by a hospital specialist - endocrinology, surgery, otorhinolaryngology, internal medicine (In Portugal, Internal medicine is a hospital specialty), or 2) by a general practitioner (GP).

Patients were moreover questioned about their reasons for performing Thyroid US.

Answers were included in one of two groups:

1. Related to the thyroid gland, including visible and/or palpable nodules; nodules incidentally detected by a different imaging technique; family history of thyroid carcinomas, and having symptoms of thyroid dysfunction along with altered thyroid function tests;
2. All other reasons were considered unrelated to the thyroid gland (if not associated with thyroid dysfunction and implausible to be related to the nodule found), including weight loss or gain; occasional dysphagia; odynophagia or dyspnoea; sore throat; pregnancy; routine exam; high blood pressure; syncope; anaemia; hair loss; diabetes; choking, neighbours or acquaintances diagnosed with thyroid nodules, and stress-induced hoarseness. Patients unaware or incapable of recalling the cause for referral were also included in this group.

2.3. Ultrasound and FNA

The ultrasound equipment used was a GE Logic E9, with a ML linear probe (6–15 MHz). Two radiologists performed all examinations, one with 4 years and the other with 20 years of experience in thyroid ultrasound.

A gland was considered multinodular if 2 or more nodules > 5 mm were present. Otherwise, it was considered uninodular.

The nodule(s) selected for FNA was (were) classified according to the French TIRADS categorisation of Russ et al. [16].

Size (maximum diameter), Doppler US pattern, and resistive index of the selected nodule were recorded.

FNA was always US guided. Aspiration was performed with a 25 G needle attached to a 10 ml syringe in a metal handle. A cytotechnician was always present to assess specimen adequacy. One to three passes were performed depending on each sample's adequacy, assessed by a fast-staining method (Diff-Quick), on air-dried slide smears, and preserved in 95% alcohol for Papanicolaou staining.

Needle washout fluid was also preserved in a liquid medium (cytolyt®).

The final cytological diagnosis was made by a pathologist and reported according to the Bethesda System [17].

2.4. Statistical analysis

To compare referral between males and females, we tested the distribution of different parameters (thyroid function, reference pattern, reason for referral, number of nodules, nodule size, TIRADS classification, Doppler pattern, resistive index, and Bethesda categorisation) in the two genders. For comparisons between groups, we used the non-parametric Mann-Whitney *U* test for continuous variables, and Fisher exact test for categorical variables. Multivariable analysis was performed with logistic regression.

The statistical analysis was performed with IBM SPSS statistics for Macintosh, version 21; SPSS Chicago, IL. The statistical significance level was set at $p < 0.05$. All values were two-tailed.

3. Results

We included 272 patients, 215 females and 57 males (ratio 3.8:1).

Patients' and nodules' baseline characteristics are summarised in Table 1, and referral causes by gender can be found in Table 2. The main referral cause was a visible or palpable nodule (27%), closely followed by an incidentally detected nodule (24%). CT was the most frequent imaging modality for incidental detection (80%), the others being MRI, Doppler, Ultrasound, and chest X-ray. The most common reasons for performing CT were staging and follow-up of various tumour types.

There was no statistically significant difference between males and females concerning patients age (males median age: 65 years; females median age: 60 years); number of nodules (35% of males and 30% of females had only one nodule); TIRADS categorisation (21% of males nodules and 13% of females nodules were TIRADS 4b or 5); Doppler pattern (67% of males nodules and 61% of females nodules had central or peripheral vascularization); resistive index (median 0.61 in males and median 0.58 in females), and Bethesda cytological classification (12% of males nodules and 6% of females nodules were diagnosed as Bethesda IV, V, or VI).

Despite the median nodule size being the same for both genders (20 mm), the mean ranks were significantly different between genders (male mean rank = 168,46; female mean rank = 139,38. Mann Whitney *U* test; $p = 0.016$), with a tendency for bigger nodules in men (Fig. 1). Altered thyroid function was more prevalent in the female group than in the male patients (32% versus 18%; $p = 0.033$). The percentage of women referred by a GP rather than by a hospital specialist was higher than the percentage of men (78% versus 47%,