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Gender-specific correlation of intranodular chronic lymphocytic thyroiditis with thyroid nodule size, echogenicity, and histologically-verified cytological class of malignancy risk

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ABSTRACT

No data are available on the cytologically and histologically demonstrated presence of intranodular chronic lymphocytic thyroiditis (ICLT) and on the ICLT relationship with thyroid nodule characteristics such as size, echotexture and nature (benign or malignant). We wished to fill this gap by analyzing data in a gender-specific fashion. We studied 408 thyroid nodules from 408 consecutive persons (325 females and 83 males). Nodules were isoechoic (n = 268) or hypoechoic (n = 140), ICLT +ve (n = 113 [27.7%]) or ICLT −ve (n = 295), cytologically low-risk (n = 197) or high-risk (n = 211), histologically benign (n = 263) or malignant (n = 145). ICLT prevailed in females (97/113) and in hypoechoic nodules (58/140 [41.4%] *vs* 55/268 [20.5%], P < 0.0001). Compared to males, females had (i) smaller nodules (18.5 ± 9.4 *vs* 23.3 ± 13.4 mm, P = 0.0002), a difference due to the isoechoic nodules (21.1 ± 9.8 *vs* 26.6 ± 14.1 mm, P = 0.0006), (ii) lower rates of high-risk nodules (161/325 [49.5%] *vs* 50/83 [60.2%], P = 0.082) and malignant nodules (110/325 [33.8%] *vs* 35/83 [42.2%] P = 0.16). ICLT +ve nodules were smaller than the ICLT −ve ones (15.4 ± 6.9 *vs* 20.9 ± 11.2 mm, P < 0.0001), a difference due to the isoechoic nodules (17.5 ± 6.5 *vs* 23.6 ± 11.7 mm, P = 0.0003). The smallest nodules were hypoechoic, cancerous and ICLT +ve nodules in males (9.5 ± 4.0 mm); the largest were isoechoic, cytologically risky and ICLT −ve in males (29.1 ± 13.2 mm). Compared to ICLT −ve nodules, malignancy prevailed in ICLT +ve nodules (55/113 [48.7%] *vs* 90/295 [30.5%], P = 0.0006), both in hypoechoic (37/58 [63.8%] *vs* 41/82 [50.0%]) and isoechoic nodules (18/55 [32.7%] *vs* 49/213 [23.0%]). ICLT +ve hypoechoic nodules of females and ICLT −ve hypoechoic nodules of males had the greatest rate of malignancy (67% both), while ICLT −ve isoechoic nodules of females had the lowest (19%).

In conclusion, presence/absence of ICLT is associated with some sexually dimorphic characteristics of thyroid nodules. Adding the specification of ICLT positivity/negativity in cytological reports may help improving the risk of malignancy at least in some groups of thyroid nodules.

Introduction

Hashimoto's thyroiditis (HT), also known as chronic lymphocytic thyroiditis (CLT)], is not only the most frequent thyroid inflammation and cause of thyroid dysfunction, but also the most frequent autoimmune thyroid disorder [1–5]. The incidence of HT has increased over the years in several geographical areas [2] including our island [1,6–8], and so has the incidence of differentiated thyroid cancer (DTC), particularly papillary thyroid cancer (PTC) of subcentimetric size (microPTC) [7,9–19]. Indeed, the association in the same thyroid of HT/CLT and DTC, especially PTC, appears to be not a random one [2,20–26].

Presentation of HT is heterogeneous, including two indices (thyroid size and nodularity) that are quantifiable at ultrasonography (US). As reported in a study conducted by one of us on 4064 consecutive HT patients observed at a single institution in north-eastern Sicily [1], the

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thyroid gland can have various size (decreased, normal or increased) and various nodularity (absent or present, and if present consisting of one or more lesions). Moreover, like patients without HT, nodules can have various size and echotexture (anechogenous, isoechogenous, hypoechogenous or hyperechogenous). Finally, when nodules of HT patients are evaluated by fine-needle aspiration cytology (FNAC), their nature also varies, from one frankly benign with minimal risk of true cancer at thyroidectomy [colloid or cystic nodules] to one frankly malignant (PTC, most frequently) [2]. Regardless of cytological class of risk, numerous lymphocytes may or may not be detected in the punctured nodule.

To the best of our knowledge, there are no studies that have correlated the detection of CLT at the cytological interrogation of a thyroid nodule with other nodule characteristics, such as size, echotexture and nature (benign or malignant). To fill this gap, we conducted the study reported here.

Materials and methods

The study group consisted of 408 isoechoic or hypoechoic thyroid nodules from 408 consecutive persons (325 females and 83 males) living in southeastern Sicily and who were thyroidectomized during the years 2010 through 2016. Prior to thyroidectomy, nodules were evaluated by US-assisted FNAC, which was performed by the same operator (S.A.). S.A. was unaware of the serum thyroid autoantibody status. Cytology reading was also performed by S.A. Reasons for thyroidectomy were cytological diagnoses of malignancy, suspicious malignancy or probable malignancy (see below for diagnoses). For FNAC classes with lower malignancy risk, reasons were large thyroid size, presence/worsening of compressive symptoms or patient's decision.

In addition to echotexture (isoechoic *vs* hypoechoic), the other nodule characteristics that we considered, were: [i] size (maximum diameter in millimeters); [ii] FNAC category, with formation of two classes of risk of malignancy (low risk *vs* high risk); [iii] cytological picture consistent with chronic lymphocytic thyroiditis (CLT present *vs* CLT absent) regardless of FNAC category; [iv] histological diagnosis [benign *vs* malignant lesion]. All characteristics were analyzed in the background of gender (males *vs* females). Exclusion criteria were anechoic nodules, pseudonodules and nondiagnostic/unsatisfactory cytology

Ultrasonography-assisted fine needle aspiration cytology (FNAC)

Each nodule was aspirated at least twice using a 23-gauge needle. Smears were prepared and stained with hematoxylin and eosin (Papanicolau method). Nodules were classified according to class (or category) of risk and presence/absence of CLT in the smears. As it is common in Italy, we followed the classification of the British Thyroid Association/American Association of Clinical Endocrinologists/Associazione Medici Endocrinologi (BTA/AACE/AME) [27,28]. Because a revised Italian classification was published in the year 2014 [29] and our cohort spanned the years 2014–2016, all 408 cytological diagnoses adhered to the new classification [29]. This classification [29] considers six categories, from TIR1 (inadequate) to TIR5 (malignant), with the TIR3 category subdivided in two subcategories (TIR3A [indeterminate lesion of low risk] and TIR3B [indeterminate lesion of high risk]) that have different risk of malignancy (< 10% and 15–30%, respectively). In the equivalent six-category Bethesda system from category I ("Nondiagnostic or Unsatisfactory") through category VI ("Malignant"), TIR3A corresponds to "atypia of undetermined significance or follicular lesion of undetermined significance (AUS/FLUS), and TIR3B to "follicular neoplasm or suspicious for a follicular neoplasm (FN/SN), with corresponding risk of malignancy of ~5–15% and 15–30%, respectively [30]. Inadequate cases (TIR1) were not included in our study.

For purposes of simplicity, data will be analyzed contrasting two, instead of five, categories of FNAC: the low risk (LR) and the high risk (HR) of malignancy. The low-risk group includes the TIR2 and TIR3A categories, while the high-risk group includes the TIR3B, TIR4 and TIR5 categories.

Intranodular CLT (ICLT) was diagnosed based on the typical features of a diffuse presence of lymphocytes in the background and/or infiltrating thyroid follicles with marked signs of inflammation and moderate amounts of colloid. Additional findings that could or could not be present were follicular atrophy, plasma cells, multinucleated giant cells, epithelioid cell clusters, intralobular fibrosis and Hurtle-cell metaplasia [6]. This metaplasia may display some chromatin clearing, nuclear atypia, nuclear grooves and prominent nucleoli sometimes overlapping with malignant lesions [31]. Cytological presence of ICLT was always confirmed at histology, and it was associated with serum positivity for thyroglobulin autoantibodies (TgAb) and/or thyroperoxidase autoantibodies (TPOAb) in approximately 80% of cases [data not shown], in agreement with a previous study [6].

Statistics

Data are presented as mean ± SD. We compared continuous variables using the two-tailed Student's *t* test, and compared categorical variables using the chi-square test (χ^2) or Fisher's exact test, as appropriate.

Results

Results are summarized in Tables 1–4 and illustrated in Figs. 1 and 2.

Table 1
Characteristics of thyroid nodules in the 408 patients as a whole or stratified by gender.*

	All, n = 408	Females, n = 325	Males, n = 83	F:M ratio	Statistics
Number of nodules	408	325	83	3.9:1	N/A
Isoechoic	268 [65.7%]	209 (78%) [64.3%]	59 (22%) [71.1%]	3.5:1	$\chi^2 = 1.35$, P = 0.25
Hypoechoic	140 [34.3%]	116 (82.9%) [35.7%]	24 (17.1%) [28.9%]	4.8:1	
ICLT −ve	295 [72.3%]	228 (77.3%) [70.2%]	67 (22.7%) [80.7%]	3.4:1	$\chi^2 = 3.69$, ***P = 0.055***
ICLT +ve	113 [27.7%]	97 (85.8%) [29.8%]	16 (14.2%) [19.3%]	6.1:1	
FNAC, low risk	197 [48.3%]	164 (83.2%) [50.5%]	33 (16.8%) [39.8%]	5.0:1	$\chi^2 = 3.03$, ***P = 0.082***
FNAC, high risk	211 [51.7%]	161 (76.3%) [49.5%]	50 (23.7%) [60.2%]	3.2:1	
Histology, benign	263 [64.5%]	215 (81.7%) [66.2%]	48 (18.3%) [57.8%]	4.5:1	$\chi^2 = 2.0$, P = 0.16
Histology, malignant	145 [35.5%]	110 (75.9%) [33.8%]	35 (24.1%) [42.2%]	3.1:1	
Maximum diam, mm	19.5 ± 10.5 [16]	18.5 ± 9.4 [12]	23.3 ± 13.4 [12]	N/A	**P = 0.0002**

The intergender significant difference in maximum diameter was accounted for by the isoechoic nodules (21.1 ± 9.8 mm [19] in females *vs* 26.6 ± 14.1 [23] in males *vs* **P = 0.0006**), not the hypoechoic nodules (13.9 ± 6.2 [12] in females *vs* 15.1 ± 5.9 [12], P = 0.36.

* N/A = Not applicable. In parentheses or in brackets are percentages of column or raw, respectively. For the maximum diameter of the nodules, as determined at ultrasonography, data are mean ± SD with median given in brackets. P values written **boldface** are statistically significant (P < 0.05 or lower), while P values written ***boldface italics*** are borderline significant (*viz*, comprised between 0.10 and 0.05).

Table 2
Characteristics of thyroid nodules in the 408 patients as a whole or stratified based on their echotexture.

	All, n = 408	Isoechoic, n = 268	Hypoechoic, n = 140	Statistics
Females (F)	325 [79.7%]	209 (64.3%) [78%]	116 (35.7%) [82.9%]	$\chi^2 = 1.35$
Males (M)	83 [20.3%]	59 (71.1%) [22%]	24 (28.9%) [17.1%]	P = 0.25
ICLT −ve	295 [72.3%]	213 (72.2%) [79.5%]	82 (27.8%) [58.6%]	$\chi^2 = 20.07$
ICLT +ve	113 [27.7%]	55 (48.7%) [20.5%]	58 (51.3%) [41.4%]	**P < 0.0001**
ICLT −ve, F	228 [70.2%]	161 (70.6%) [75.6%]	67 (29.4%) [81.7%]	$\chi^2 = 1.26$
M	67 [80.7%]	52 (77.6%) [24.4%]	15 (22.4%) [18.3%]	P = 0.26
ICLT +ve, F	97 [29.8%]	48 (49.5%) [87.3%]	49 (50.5%) [84.5%]	$\chi^2 = 0.18$
, M	16 [19.3%]	7 (43.8%) [12.7%]	9 (56.2%) [15.5%]	P = 0.67
FNAC, low risk	197 [48.3%]	152 (77.2%) [56.7%]	45 (22.8%) [32.1%]	$\chi^2 = 44.04$
FNAC, high risk	211 [51.7%]	95 (45%) [43.3%]	116 (55%) [67.9%]	**P < 0.0001**
FNAC, low risk, F	164 [50.5%]	126 (76.8%) [82.9%]	38 (23.2%) [84.4%]	$\chi^2 = 0.06$
M	33 [39.8%]	26 (78.8%) [17.1%]	7 (21.2%) [15.6%]	P = 0.81
FNAC, high risk, F	161 [49.5%]	83 (51.6%) [87.4%]	78 (48.4%) [67.2%]	$\chi^2 = 3.22$
M	50 [60.2%]	33 (66.0%) [28.5%]	17 (34.0%) [17.9%]	***P = 0.07***
Histology, benign	263 [64.5%]	201 (76.4%) [75%]	62 (23.6%) [44.3%]	$\chi^2 = 37.87$
Histology, malignant	145 [35.5%]	67 (46.2%) [25%]	78 (53.8%) [55.7%]	**P < 0.0001**
Histology, benign, F	215 [66.2%]	163 (75.8%) [81.1%]	52 (24.2%) [83.9%]	$\chi^2 = 0.24$
M	48 [57.8%]	38 (79.2%) [18.9%]	10 (20.8%) [16.1%]	P = 0.62
Histology, malignant, F	110 [33.8%]	46 (41.8%) [68.7%]	64 (58.2%) [82.1%]	$\chi^2 = 3.53$
M	35 [42.2%]	21 (60%) [31.3%]	14 (40%) [17.9%]	***P = 0.06***
Maximum diam, mm	19.5 ± 10.5 [16]	22.3 ± 16.1 [17]	14.1 ± 16.2 [12]	**P < 0.0001**
F	18.5 ± 9.4 [12]	21.1 ± 9.8 [19]	13.9 ± 6.2 [12]	**P < 0.0001**
M	23.3 ± 13.4 [12]	26.6 ± 14.1 [23]	15.1 ± 5.9 [12]	**P = 0.0002**

In parentheses or in brackets are percentages of column or raw, respectively. In the intergender comparison concerning the maximum diameter, such diameter of isoechoic nodules in females was different from that of males (21.1 ± 9.8 *vs* 26.6 ± 14.1 mm, P = 0.0006), whereas the corresponding comparison for the ICLT −ve nodules was similar (13.9 ± 6.2 *vs* 15.1 ± 5.9 mm, P = 0.36).

Differences in gender

As said under Materials and Methods, the nodule we will refer to is the one that, in each patient, was considered worthy of FNAC, with subsequent thyroidectomy providing the final diagnosis. We will use interchangeably the terms “size” and “maximum diameter” of such nodule.

Of the 408 nodules, 325 were in females and 83 in males (F:M ratio = 3.9:1), and 113 (27.7%) had cytological and histological evidence of ICLT (Table 1). Because 97/113 and 16/113 ICLT +ve nodules belonged to females and males, respectively, in contrast to the corresponding proportions of 228/295 and 67/295 ICLT −ve nodules, the F:M ratio in the ICLT +ve nodules differed, though borderline significantly, from the F:M ratio in the CLT −ve nodules (6.1:1 *vs* 3.4:1, P = 0.055). Overall, 263 nodules were histologically benign (F = 215, M = 48), while 145 were histologically malignant (F = 110, M = 35), with the corresponding F:M ratios being statistically similar (4.5:1 *vs* 3.1:1, P = 0.16). If this separation on the nature of nodules is operated cytologically, then 197 were low-risk (F = 164, M = 33) and 211 high-risk (F = 161, M = 50), with the corresponding F:M ratios being borderline significantly different (5.0:1 *vs* 3.2:1, P = 0.082).

Gender distribution was also evaluated based on the echotexture of

Table 3
Characteristics of thyroid nodules in the 408 patients as a whole or stratified based on intranodular chronic lymphocytic thyroiditis (ICLT).

	All, n = 408	ICLT +ve, n = 113	ICLT −ve, n = 295	Statistics
Females (F)	325 [79.7%]	97 (29.8%) [85.8%]	228 (70.2%) [77.3%]	$\chi^2 = 3.69$
Males (M)	83 [20.3%]	16 (19.3%) [14.2%]	67 (80.7%) [22.7%]	***P = 0.055***
Isoechoic	268 [65.7%]	55 (20.5%) [48.7%]	213 (79.5%) [72.2%]	$\chi^2 = 20.07$
Hypoechoic	140 [34.3%]	58 (41.4%) [51.3%]	82 (58.6%) [27.8%]	**P < 0.0001**
Isoechoic, F	209 [64.3%]	48 (23%) [87.3%]	161 (77%) [75.6%]	$\chi^2 = 3.48$
M	59 [71.1%]	7 (11.9%) [12.7%]	52 (88.1%) [24.4%]	***P = 0.062***
Hypoechoic, F	116 [35.7%]	49 (42.2%) [84.5%]	67 (57.8%) [81.7%]	$\chi^2 = 0.18$
M	24 [28.9%]	9 (37.5%) [15.5%]	15 (62.5%) [18.3%]	P = 0.67
FNAC, low risk	197 [48.3%]	42 (21.3%) [37.2%]	155 (78.7%) [52.5%]	$\chi^2 = 7.73$
FNAC, high risk	211 [51.7%]	71 (33.6%) [62.8%]	140 (66.4%) [47.5%]	**P = 0.0054**
FNAC, low risk, F	164 [50.5%]	36 (22%) [85.7%]	128 (78%) [82.6%]	$\chi^2 = 0.23$
M	33 [39.8%]	6 (18.2%) [14.3%]	27 (81.8%) [17.4%]	P = 0.63
FNAC, high risk, F	161 [49.5%]	61 (37.9%) [85.9%]	100 (62.1%) [71.4%]	$\chi^2 = 5.47$
M	50 [60.2%]	10 (20%) [14.1%]	40 (80%) [28.6%]	**P = 0.019**
Histology, benign	263 [64.5%]	58 (22%) [51.3%]	205 (78%) [69.5%]	$\chi^2 = 11.77$
Histology, malignant	145 [35.5%]	55 (37.9%) [48.7%]	90 (62.1%) [30.5%]	**P = 0.0006**
Histology, benign, F	215 [66.2%]	48 (22.3%) [82.8%]	167 (77.7%) [81.5%]	$\chi^2 = 0.05$
M	48 [57.8%]	10 (20.8%) [17.2%]	38 (79.2%) [18.5%]	P = 0.82
Histology, malignant, F	110 [33.8%]	49 (44.5%) [89.1%]	61 (55.5%) [67.8%]	$\chi^2 = 8.47$
M	35 [42.2%]	6 (17.1%) [10.9%]	29 (82.9%) [32.2%]	**P = 0.0036**
Maximum diam, mm	19.5 ± 10.5 [16]	15.4 ± 6.9 [14]	20.9 ± 11.2 [18]	**P < 0.0001**
F	18.5 ± 9.4 [12]	15.6 ± 6.8 [14]	19.8 ± 10.0 [17]	**P = 0.0002**
M	23.3 ± 13.4 [12]	15.4 ± 6.4 [15]	25.2 ± 13.9 [22]	**P = 0.007**

In parentheses or in brackets are percentages of column or raw, respectively. In the intergender comparison concerning the maximum diameter of ICLT +ve nodules, such diameter in females was similar to that in males (15.6 ± 6.8 *vs* 15.4 ± 6.4 mm, P = 0.93), whereas the corresponding comparison for the ICLT −ve nodules was significantly different (19.8 ± 10.0 *vs* 25.2 ± 13.9 mm, **P = 0.0004**).

Table 4
Cytological and histological risk of malignancy in thyroid nodules taking into account ecotexture, intranodular chronic lymphocitic thyroiditis (ICLT) and gender.

Echotexture and ICLT status				
	Isoechog	Isoechog	Hypoechog	Hypoechog
	ICLT −ve	ICLT +ve	ICLT −ve	ICLT +ve
All (n = 408)	213 (52.2%)	55 (13.5%)	82 (20.1%)	58 (14.2%)
FNAC risk, low (n = 197)	124 (63.0%) [58.2%]	28 (14.2%) [50.9%]	31 (15.7%) [37.8%]	14 (7.1%) [24.1%]
high (n = 211)	89 (42.2%) [41.8%]	27 (12.8%) [49.1%]	51 (24.2%) [62.2%]	44 (20.8%) [75.9%]
Histology, benign (n = 263)	164 (62.3%) [77.0%]	37 (14.1%) [67.3%]	41 (15.6%) [50.0%]	21 (8.0%) [36.2%]
malignant (n = 145)	49 (33.8%) [23.0%]	18 (12.4%) [32.7%]	41 (28.3%) [50.0%]	37 (25.5%) [63.8%]
Females (n = 325)	161 (49.5%)	48 (14.8%)	67 (20.6%)	49 (15.1%)
FNAC risk, low (n = 164)	102 (62.2%) [63.4%]	24 (14.6%) [50%]	26 (15.9%) [38.8%]	12 (7.3%) [24.5%]
high (n = 161)	59 (36.6%) [36.6%]	24 (14.9%) [50%]	41 (25.5%) [61.2%]	37 (23.0%) [75.5%]
Histology, benign (n = 215)	131 (60.9%) [81.4%]	32 (14.9%) [66.7%]	36 (16.7%) [53.7%]	16 (7.5%) [32.6%]
malignant (n = 110)	30 (27.3%) [18.6%]	16 (14.5%) [33.3%]	31 (28.2%) [46.3%]	33 (30%) [67.3%]
Males (n = 83)	52 (62.7%)	7 (8.4%)	15 (18.1%)	9 (10.8%)
FNAC risk, low (n = 33)	22 (66.7%) [42.3%]	4 (12.1%) [57.1%]	5 (15.1%) [33.3%]	2 (6.1%) [22.2%]
high (n = 50)	30 (60.0%) [57.7%]	3 (6.0%) [42.9%]	10 (20.0%) [66.7%]	7 (14.0%) [77.8%]
Histology, benign (n = 48)	33 (68.8%) [63.5%]	5 (10.4%) [71.4%]	5 (10.4%) [33.3%]	5 (10.4%) [55.6%]
malignant (n = 35)	19 (54.3%) [36.5%]	2 (5.7%) [28.6%]	10 (28.6%) [66.7%]	4 (11.4%) [44.4%]

In parentheses or in brackets are percentages of column or raw, respectively.
Not to complicate the body of the Table, reported as a footnote are the intergender comparison of frequencies of malignancy in low risk nodules (6/164 [3.7%] in females, *vs* 1/33 [3.0%] in males, P = 0.25] and high risk nodules (104/161 [64.6%] in females *vs* 34/50 [68.0%] in males, P = 0. 66].

the nodule. Of the 268 isoechoic nodules, 209 belonged to females and 59 to males, whereas of the 140 hypoechoic nodules, 116 belonged to females and 24 to males, with the corresponding F:M ratios being statistically similar (3.5:1 *vs* 4.8:1, P = 0.25). The US-measured maximum diameter of the nodule was also sexually dimorphic. Indeed, this diameter was approximately 5 mm larger in males than in females

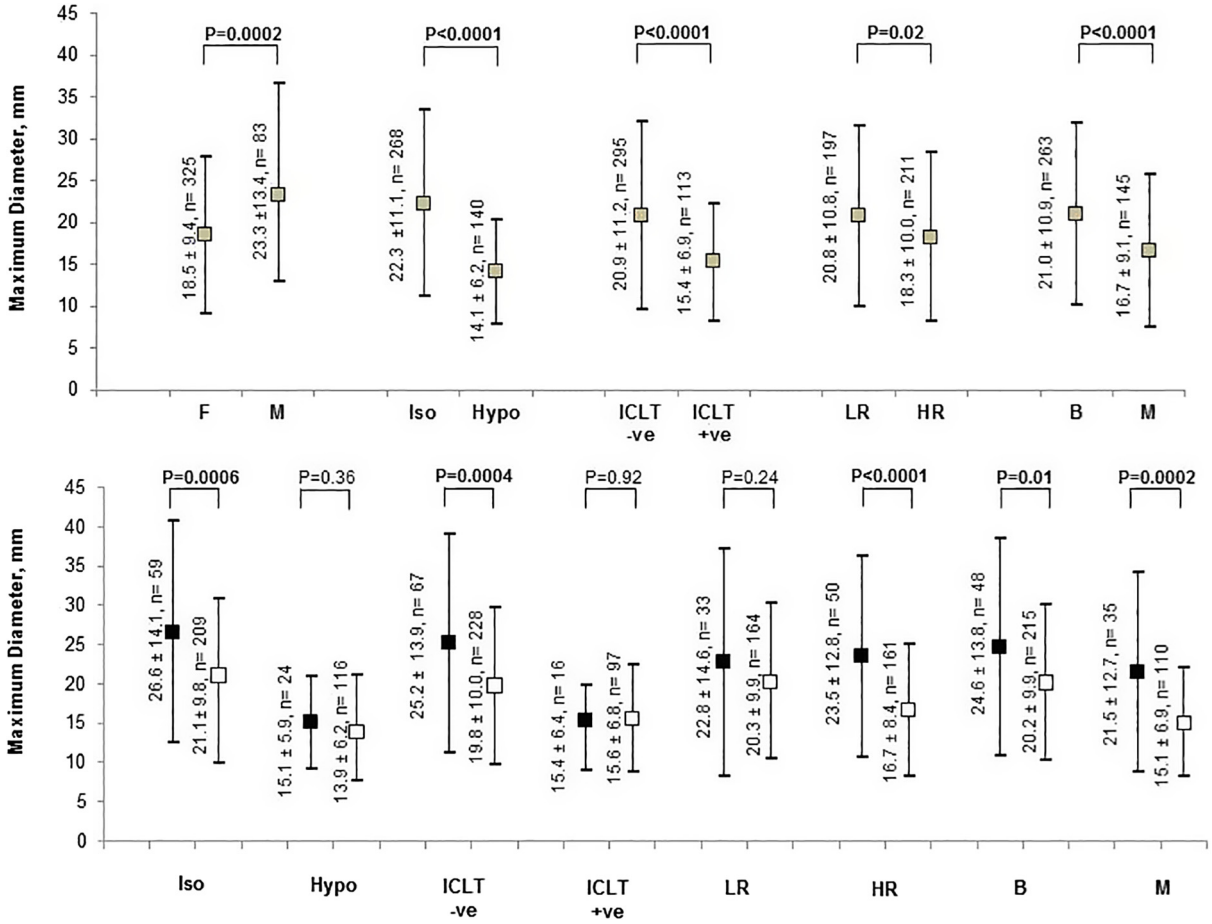

Fig. 1. Maximum diameter in millimeters of nodules (mean ± SD) depending on combinations of the specified variables. Legend: Iso = Isoechoic; Hypo = Hypoehoic; ICLT −ve = Absent; ICLT +ve = Present; LR = Low risk; HR = High risk at FNAc; B = Benign; M = Malignant at histology; ■ = Males □ = Females.

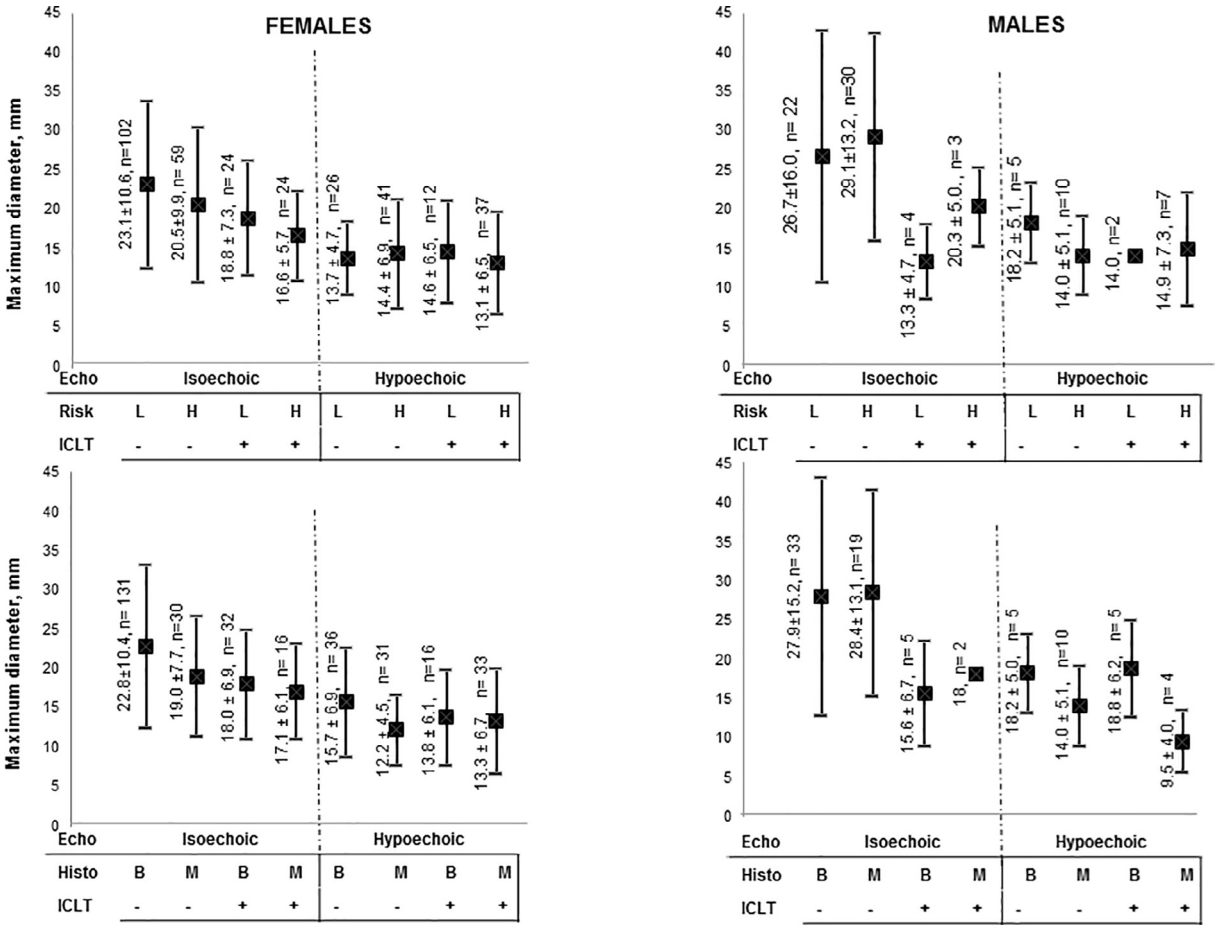

Fig. 2. Maximum diameter in millimeters of nodules (mean ± SD) depending on combinations of the specified variables. Legend: Risk [L = Low risk; H = High risk]; ICLT[− = Absent; + = Present]; Histo [Histology B = Benign; M = Malignant].

(23.3 ± 13.4 [median = 12] *vs* 18.5 ± 9.4 mm [median = 12], P = 0.0002), this difference being accounted for by the isoechoic nodules (Table 1, footnote).

In brief, compared to males, females had (i) an insignificantly greater likelihood of having nodules that are hypoeochoic (35.7% *vs* 28.9%, P = 0.25); (ii, iii) a borderline significantly lower or an insignificantly lower likelihood of having nodules with high-risk of malignancy at FNAC (49.5% *vs* 60.2%, P = 0.082) or conclusively malignant at histology (33.8% *vs* 42.2%, P = 0.16); (iv) a borderline statistically greater likelihood of having nodules that are ICLT +ve (29.8% *vs* 19.3%, P = 0.055). Not shown in Table 1 is that ICLT positivity is the greatest in hypoechoic nodules of females (49/116 [42.2%]) and the smallest in isoechoic nodules of males (7/59 [11.9%]), with a significantly high difference between these two proportions ($\chi^2 = 16.58$, P < 0.001).

A greater rate of malignancy in ICLT +ve nodules compared to ICLT −ve nodules is observed only in females (49/97 [50.5%] *vs* 61/228 (26.8%), $\chi^2 = 17.16$, P < 0.0001), in sharp contrast with the similar corresponding rates in males (6/16 [37.5%] *vs* 29/67 [43.3%], $\chi^2 = 0.17$, P = 0.67). This 2-fold difference in rate for females becomes a 4-fold difference upon comparing the ICLT +ve hypoechoic nodules of females with the ICLT −ve isoechoic nodules of females (33/49 [67.3%] *vs* 30/161 [18.6%], $\chi^2 = 16.58$, P < 0.001; Table 4). Again, the corresponding comparison for males, namely the rates of malignancy in the ICLT +ve hypoechoic nodules and in the ICLT −ve isoechoic nodules were statistically similar (4/9 [44.4%) *vs* 19/52 [36.5%], $\chi^2 = 0.20$, P = 0.65; Table 4).

Relationship of the sonographic nature of the nodules with their cytological or histological nature taking into account ICLT

Of the 408 nodules, 140 (34.3%) were hypoechoic and 268 (65.7%) isoechoic; 113 (27.7%) were ICLT +ve and 295 (70.3%) ICLT −ve, 197 (48.2%) were low-risk and 211 (51.8%) high-risk, 263 (64.5%) benign and 145 (35.3%) malignant (Table 1). Of the 145 histologically malignant nodules, 78 (53.8%) were hypoechoic and 67 isoechoic (46.2%, P < 0.0001; Table 2), 55 (37.9%) were ICLT +ve and 90 ICLT −ve (62.1%, P = 0.0006; Table 3). Of the 113 ICLT +ve nodules, 58 (51.3%) were hypoechoic and 55 isoechoic (48.7%), in sharp contrast with the 295 ICLT −ve nodules, in which approximately one-fourth were hypoechoic and three-fourths were isoechoic (82 [27.8%] and 213 [72.2%], P < 0.0001; Table 3). Approximately half of the same 113 ICLT +ve nodules were malignant (55 [48.7%]) as opposed to approximately one-thirds of the 295 ICLT −ve nodules (90 [30.5%], P = 0.0006; Table 3).

The frequency of histological malignancy was, as expected, greater in the hypoechoic nodules compared to the isoechoic nodules (55.7% *vs* 25.0%, $P = 7.6 \times 10^{-10}$, OR = 3.8 [2.4–5.8]; Table 2); it was also greater in ICLT +ve nodules compared to the ICLT −ve ones (48.7% *vs* 30.5%, P = 0.0006, OR = 2.16 [1.4–3.4], Table 3). The cytological and histological risks of malignancy based on combinations of two characteristics (echotexture and ICLT) are shown in Table 4. Hypoechoic ICLT +ve nodules had the greatest cytological risk and the isoechoic ICLT −ve nodules the lowest risk (44/58 [75.9%] *vs* 89/213 [41.8%], $\chi^2 = 21.2$, $P = 4.2 \times 10^{-6}$, OR = 4.4 [2.3–8.5]). This pattern was confirmed at histology, since the rates of malignancy in the hypoechoic ICLT +ve and isoechoic ICLT −ve groups were 37/58 (63.8%) and 49/

213 (23.0%, $\chi^2 = 35.0$, $P = 3.3 \times 10^{-9}$, OR = 5.9 [3.2–11.0]; Table 4). In turn, the said 75.9% frequency was greater than the 49.1% frequency (27/55) of the high-risk category in the isoechoic ICLT +ve nodules ($\chi^2 = 8.7$, P = 0.0032, OR = 3.3 [1.5–7.3]), and so was the said 63.8% frequency of histological malignancy compared to the equivalent frequency (32.7% [18/55]) in the isoechoic ICLT +ve nodules ($\chi^2 = 10.9$, P = 0.001, OR = 3.6 [1.7–7.9]).

When the comparison is made within the same echotexture, the frequency of high cytological risk in ICLT +ve hypoechoic nodules was borderline significantly greater than in ICLT −ve hypoechoic nodules (44/58 [75.9%] *vs* 51/82 [62.2%], $\chi^2 = 2.91$, P = 0.088, OR = 1.9 [0.9–4.0]), and so was the corresponding frequency of histological malignancy (63.8% [37/58] *vs* 41/82 [50%], $\chi^2 = 2.62$, P = 0.10, OR = 1.8 [0.9–3.5]). In contrast, within the isoechoic nodules, the frequency of high cytological risk was statistically similar in the ICLT +ve nodules compared to the ICLT −ve nodules (49.1% [27/55] *vs* 41.8% [89/213], $\chi^2 = 0.95$, P = 0.33, OR = 1.3 [0.7–1.4], and so was the corresponding frequency of histological malignancy (32.7% [18/55] *vs* 23.0% [49/213], $\chi^2 = 2.20$, P = 0.14, OR = 1.6 [0.8–3.1]).

Noteworthy, when the four categories of nodules in Table 4 are evaluated for concordance between FNAC and histology upon reading from left to right, then this concordance is progressively greater moving from the isoechogenous and ICLT −ve nodules to the hypoechogenous and ICLT +ve ones (49/89 [55.0%] to 37/44 [84.0%]), with a significant difference between these two proportions ($\chi^2 = 10.86$, P = 0.001, OR = 0.23 [0.1–0.6]). Keeping in mind that an intergender comparison is complicated by the small size of the male group with $n < 10$ in two categories, it seems that the said progressively greater rate of concordance is much clearer in females (30/59 [50.8%] to 33/37 [89.2%]) than in males (19/30 [63.3%] to 4/7 [57.1%]). In males, the category of nodules hypoechogenous and ICLT −ve stand out because of the 100% rate of concordance, with 10 out of 10 nodules cytologically at high risk proving to be histologically malignant (Table 4).

Relationship of the size of the nodules with their cytological or histological nature taking into account ICLT

The maximum diameter of the nodule differed, based on gender, echogenicity, absence/presence of ICLT, cytological diagnosis, and histological diagnosis (Fig. 1). Based on combinations of these variables, the average maximum diameter varied greatly (Fig. 2).

The mean size of nodules was almost 5 mm greater in males than females (23.3 ± 13.4 *vs* 18.5 ± 9.4 mm, P = 0.0002), 8.2 mm greater in isoechoic than hypoechoic nodules (22.3 ± 11.1 mm *vs* 14.1 ± 6.2 mm, $P < 0.0001$), this gap being wider in males (11.5 mm) compared to females (7.2 mm). The mean size was 5.5 mm greater in ICLT −ve compared to ICLT +ve nodules ($P < 0.0001$), again with an intergender difference (9.8 mm greater in males compared to 4.2 mm in females). The mean size was 2.5 mm greater in the cytologically low-risk compared to high-risk nodules (P = 0.02) and 4.3 mm greater in the histologically benign compared to the malignant nodules ($P < 0.0001$). Intergender differences were evident because the maximum diameter was consistently greater among males compared with females (2.5 mm in low-risk nodules [P = 0.24], 6.8 mm in high-risk [$P < 0.001$], 4.4 mm in benign [P = 0.01], and 6.4 mm [P = 0.0002] in malignant nodules) (Fig. 1).

Taking into account the small representation of males in the ICLT +ve group, the smallest nodules belonged to males with hypoechoic, cancerous and ICLT +ve nodules (9.5 ± 4.0 mm [median = 10 mm], whereas the largest nodules belonged to males with isoechoic, cytologically risky and ICLT −ve nodules (29.1 ± 13.2 mm [median = 27]). Considering histology rather than cytology, the largest size (28.4 ± 13.1 mm [median = 24]) is confirmed in the group of males/isoechoic nodules/histologically malignant/ICLT −ve.

Discussion

Here we report that the nodule size was smaller in females and hypoechoic nodules. Plausible explanations could be genetic factors for the gender issue and diagnostic bias for the echotexture issue, because of a lower threshold of maximum diameter for FNA biopsy of hypoechoic nodules [32], Most importantly, considering lack of data in the literature, we also report that the presence or absence of ICLT is associated with a number of different characteristics of thyroid nodules. First, presence of ICLT is twice more common in hypoechoic nodules than isoechoic nodules (41% *vs* 20%). As a result, the ratio of hypoechoic: isoechoic nodules in the ICLT +ve group is 1:1, but 0.4:1 in the ICLT −ve group. Second, ICLT +ve nodules are approximately 5 mm smaller than ICLT −ve nodules, but only in the isoechoic nodules. Third, the presence of ICLT appears to exert, depending on sex, a protective or non-protective action toward the nodule having a histologically confirmed malignant nature.

Because of a 2-fold larger representation of the hypoechoic feature in the ICLT +ve nodules compared to the ICLT −ve nodules (51% *vs* 28%), one would have expected a similar 2-fold difference in rates of malignancy. However, the difference was only 1.3-fold (64% *vs* 50%), and with a striking intergender pattern (1.5-fold in females [67% *vs* 46%] but 0.7-fold in males [44% *vs* 67%]).

In the present work on persons living in southeastern Sicily, upon studying a consecutive cohort of thyroid nodules interrogated by US-assisted FNA and the defined histologically, we found that the combination of gender, echotexture and presence/absence of ICLT may influence not only the maximum diameter but also the cytological and histological nature of the thyroid nodule. One implication of our findings is the predictive usefulness of adding the presence or absence of ICLT in the cytological description of a thyroid nodule. One other implication is that predictivity has to take gender into account. For instance, as shown in Table 4, among the same category of nodules (*e.g.*, hypoechoic and ICLT +ve) the risk of histologically verified malignancy is two-thirds in females (67.3%) but just below one-half in males (44.4%), while among another category of nodules (isoechoic and ICLT +ve) the risk is reversed (18.6% in females but 36.5% in males).

Strengths of our study are that, to the best of our knowledge, a correlation study such as ours is unprecedented in the literature. In addition, patients come from the same geographical area (province of Siracusa, southeastern Sicily), and US-FNAC and cytological readings were performed by the same operator. There are limitations in the study, which we believe are difficult to address in subsequent investigations. As explained under Materials and Methods, our study is based on a series of patients who were thyroidectomized for cytological diagnoses of malignancy, suspicious malignancy or probable malignancy or, if the cytological category was low-risk, for mechanical reasons. This may introduce a bias in our study, because for the nodules of patients who were not operated we lack the information that we have for the nodules of patients who were thyroidectomized. Moreover, we cannot establish a cause-to-effect relationship between ICLT and the nodule characteristics. In other terms, we cannot state whether it is the initial appearance of CLT that determines the subsequent characteristics (size, echotexture, benign/malignant nature) or if it is some intrinsic characteristic of the nodule associated with any of the three said characteristics that determines the subsequent presence/absence of CLT. An answer would require a study based on frequent US and FNAC monitoring of persons who, at baseline have no thyroid nodules and no FNAC evidence of CLT, but then start developing nodules and CLT at different times.

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Declaration of interest

The authors declare that there is no conflict of interest that can be perceived as prejudicing the impartiality of the research reported.

References

[1] Benvenga S, Trimarchi F. Changed presentation of Hashimoto's thyroiditis in North-Eastern Sicily and Calabria (Southern Italy) based on a 31-year experience. Thyroid 2008;18:429–41. https://doi.org/10.1089/thy.2007.0234.

[2] Caturegli P, De Remigis A, Chuang K, Dembele M, Iwama A, Iwama S. Hashimoto's thyroiditis: celebrating the centennial through the lens of the Johns Hopkins hospital surgical pathology records. Thyroid 2013;23:142–50. https://doi.org/10.1089/thy.2012.0554.

[3] McLeod DS, Cooper DS. The incidence and prevalence of thyroid autoimmunity. Endocrine 2012;42:252–65. https://doi.org/10.1007/s12020-012-9703-2.

[4] Ott J, Meusel M, Schultheis A, Promberger R, Pallikunnel SJ, Neuhold N, et al. The incidence of lymphocytic thyroid infiltration and Hashimoto's thyroiditis increased in patients operated for benign goiter over a 31-year period. Virchows Arch 2011;459:277–81. https://doi.org/10.1007/s00428-011-1130-x.

[5] Zdraveska N, Kocova M. Hashimoto thyroiditis in childhood– Review of the epidemiology, genetic susceptibility and clinical aspects of the disease. Maced J Med Sci 2012;5:336–45. https://doi.org/10.3889/mjms.1857-5773.2012.0247.

[6] Rizzo M, Rossi RT, Bonaffini O, Scisca C, Altavilla G, Calbo L, et al. Increased annual frequency of Hashimoto's thyroiditis between years 1988 and 2007 at a cytological unit of Sicily. Ann Endocrinol (Paris) 2010;71:525–34. https://doi.org/10.1016/j.ando.2010.06.006.

[7] Latina A, Gullo D, Trimarchi F, Benvenga S. Hashimoto's thyroiditis: similar and dissimilar characteristics in neighboring areas. Possible implications for the epidemiology of thyroid cancer. PLoS One 2013;8(3). https://doi.org/10.1371/journal.pone.0055450. e55450.

[8] Arena S, Latina A, Baratta R, Burgio G, Gullo D, Benvenga S. Chronic lymphocytic thyroiditis: could it be influenced by a petrochemical complex? Data from a cytological study in South-Eastern Sicily. Eur J Endocrinol 2015;172:383–9. https://doi.org/10.1530/EJE-14-0864.

[9] Rizzo M, Sindoni A, Talamo Rossi R, Bonaffini O, Panetta S, Scisca C, et al. Annual increase in the frequency of papillary thyroid carcinoma as diagnosed by fine-needle aspiration at a cytology unit in Sicily. Hormones (Athens) 2013;12:46–57.

[10] Romei C, Fugazzola L, Puxeddu E, Frasca F, Viola D, Muzza M, et al. Modifications in the papillary thyroid cancer gene profile over the last 15 years. J Clin Endocrinol Metab 2012;97:E1758–65. https://doi.org/10.1210/jc.2012-1269.

[11] Vigneri R, Malandrino P, Vigneri P. The changing epidemiology of thyroid cancer: why is incidence increasing? Curr Opin Oncol 2015;27:1–7. https://doi.org/10.1097/CCO.0000000000000148.

[12] Blomberg M, Feldt-Rasmussen U, Andersen KK, Kjaer SK. Thyroid cancer in Denmark 1943–2008, before and after iodine supplementation. Int J Cancer 2012;131:2360–6. https://doi.org/10.1002/ijc.27497.

[13] Kweon SS, Shin MH, Chung IJ, Kim YJ, Choi JS. Thyroid cancer is the most common cancer in women, based on the data from population-based cancer registries, South Korea. Jpn J Clin Oncol 2013;43:1039–46. https://doi.org/10.1093/jjco/hyt102.

[14] James BC, Mitchell JM, Jeon HD, Vasilottos N, Grogan RH, Aschebrook-Kilfoy B. An update in international trends in incidence rates of thyroid cancer, 1973–2007. Cancer Causes Control 2018;29:465–73. https://doi.org/10.1007/s10552-018-1023-2.

[15] Shulin JH, Aizhen J, Kuo SM, Tan WB, Ngiam KY, Parameswaran R. Rising incidence of thyroid cancer in Singapore not solely due to micropapillary subtype. Ann R Coll Surg Engl 2018;100:295–300. https://doi.org/10.1308/rcsann.2018.0004.

[16] Hussain F, Iqbal S, Mehmood A, Bazarbashi S, ElHassan T, Chaudhri N. Incidence of thyroid cancer in the Kingdom of Saudi Arabia, 2000–2010. Hematol Oncol Stem Cell Ther 2013;6:58–64. https://doi.org/10.1016/j.hemonc.2013.05.004.

[17] Sierra MS, Soerjomataram I, Forman D. Thyroid cancer burden in Central and South America. Cancer Epidemiol 2016;44(Suppl. 1):S150–7. https://doi.org/10.1016/j.canep.2016.07.017.

[18] Jayarajah U, Fernando A, Prabashani S, Fernando EA, Seneviratne SA. Incidence and histological patterns of thyroid cancer in Sri Lanka 2001–2010: an analysis of national cancer registry data. BMC Cancer 2018;18:163. https://doi.org/10.1186/s12885-018-4083-5.

[19] Stojanović M, Stojanović D, Rančić N, Ignjatović A, Antic Z, Miljkovic S, et al. Trends in thyroid cancer incidence and mortality in Central Serbia, 1999–2014. Ann Ist Super Sanita 2017;53:299–304. https://doi.org/10.4415/ANN_17_04_05.

[20] Resende de Paiva C, Grønhøj C. Feldt-Rasmussen U, von Buchwald C. Association between Hashimoto's thyroiditis and thyroid Cancer in 64,628 patients. Front Oncol 2017;7:53. https://doi.org/10.3389/fonc.2017.00053.

[21] Lai X, Xia Y, Zhang B, Li J, Jiang Y. A meta-analysis of Hashimoto's thyroiditis and papillary thyroid carcinoma risk. Oncotarget 2017;8:62414–24. https://doi.org/10.18632/oncotarget.18620.

[22] Lee JH, Kim Y, Choi JW, Kim YS. The association between papillary thyroid carcinoma and histologically proven Hashimoto's thyroiditis: a meta-analysis. Eur J Endocrinol 2013;168:343–9. https://doi.org/10.1530/EJE-12-0903.

[23] Ahn D, Heo SJ, Park JH, Kim JH, Sohn JH, Park JY, et al. Clinical relationship between Hashimoto's thyroiditis and papillary thyroid cancer. Acta Oncol 2011;50:1228–34. https://doi.org/10.3109/0284186X.2011.602109.

[24] Anand A, Singh KR, Kushwaha JK, Hussain N, Sonkar AA. Papillary thyroid cancer and hashimoto's thyroiditis: an association less understood. Indian J Surg Oncol 2014;5:199–204. https://doi.org/10.1007/s13193-014-0325-4.

[25] Fiore E, Rago T, Scutari M, Ugolini C, Proietti A, Di Coscio G, et al. Papillary thyroid cancer, although strongly associated with lymphocytic infiltration on histology, is only weakly predicted by serum thyroid auto-antibodies in patients with nodular thyroid diseases. J Endocrinol Invest 2009;32:344–51.

[26] Fiore E, Rago T, Latrofa F, Provenzale MA, Piaggi P, Delitala A, et al. Hashimoto's thyroiditis is associated with papillary thyroid carcinoma: role of TSH and of treatment with L-thyroxine. Endocr Relat Cancer 2011;18:429–37. https://doi.org/10.1530/ERC-11-0028.

[27] Watkinson JC, British Thyroid Association. The British Thyroid Association guidelines for the management of thyroid cancer in adults. Nucl Med Commun 2004;25:897–900.

[28] Gharib H, Papini E, Paschke R, Duick DS, Valcavi R, Hegedüs L, Vitti P. AACE/AME/ETA Task Force on Thyroid Nodules. American Association of Clinical Endocrinologists, Associazione Medici Endocrinologi, and European Thyroid Association medical guidelines for clinical practice for the diagnosis and management of thyroid nodules. J Endocrinol Invest 2010;33(Suppl. 5):1–50. https://doi.org/10.4158/EP.16.3.468.

[29] Nardi F, Basolo F, Crescenzi A, Fadda G, Frasoldati A, Orlandi F, et al. Italian consensus for the classification and reporting of thyroid cytology. J Endocrinol Invest 2014;37:593–9. https://doi.org/10.1007/s40618-014-0062-0.

[30] Cibas ES, Ali SZ. The bethesda system for reporting thyroid cytopathology. Am J Clin Pathol 2009;132:658–65. https://doi.org/10.1309/AJCPPHLWMI3JV4LA.

[31] Baloch ZW, LiVolsi VA, Asa SL, Rosai J, Merino MJ, Randolph G, et al. Diagnostic terminology and morphologic criteria for cytologic diagnosis of thyroid lesions: a synopsis of the national cancer institute thyroid fine-needle aspiration state of the science conference. Diagn Cytopathol 2008;36:425–37. https://doi.org/10.1002/dc.20830.

[32] Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 2015 American thyroid association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American thyroid association guidelines task force on thyroid nodules and differentiated thyroid cancer. Thyroid 2016;26:1–133. https://doi.org/10.1089/thy.2015.0020.