ULTRASOUND FACTORS ASSOCIATED WITH CENTRAL AND LATERAL LYMPH NODE METASTASES IN THYROID CARCINOMA

LES FACTEURS ÉCHOGRAPHIQUES ASSOCIÉS AUX MÉTASTASES GANGLIONNAIRES CENTRALES ET LATÉRALES DANS LES CARCINOMES DE LA THYROÏDE

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ABSTRACT

The purpose of this study is to identify ultrasound predictive factors for both central and lateral lymph node metastases of thyroid carcinoma.

We performed a retrospective study collecting 120 data charts of patients managed for thyroid cancer in our department over five years (2016-2020). We included all data of patients who underwent total thyroidectomy with central lymph no+de dissection with or without lateral lymph node dissection. We analyzed ultrasound features of all nodules then we performed a statistical study to identify ultrasound predictive factors of lymph node metastasis.

The incidence of central and lateral lymph node metastasis of thyroid carcinoma was 45.8% and 35 %, respectively. Round-shaped nodules, strongly hypoechoic character, presence of microcalcifications, lymph nodes, and EU-TIRADS III and V scores were the ultrasound features significantly associated with lymph node metastases in the univariate analysis. In multivariate analysis, the presence of lymph nodes on ultrasound was the only predictor of metastasis in the central and lateral groups. However, calcifications, round-shaped nodule, and EU-TIRADS III score were exclusively predictive factors for central metastases.

We concluded that the presence of lymph nodes on ultrasound is the only predictive factor of lymph node metastases of thyroid carcinoma. Paradoxically, thyroid nodules with a low risk of malignancy (EU-TIRADS III) are predictive factors for central metastases.

Keywords: differentiated thyroid carcinoma; ultrasonography; lymph node metastasis; neck dissection; thyroidectomy

RÉSUMÉ

L'objectif de cette étude est d'identifier les facteurs échographiques prédictifs de métastases ganglionnaires du secteur central et latéral dans les carcinomes de la thyroïde. Pour cela, nous avons mené une étude rétrospective ayant colligé 120 dossiers médicaux de patients pris en charge pour un carcinome de la glande thyroïde dans notre service durant une période de cinq ans (2016-2020). Nous avons inclus toutes les données de patients qui ont eu une thyroïdectomie totale avec un évidement ganglionnaire du secteur central associé ou non à un évidement du secteur latéral. Nous avons analysé les caractéristiques échographiques de tous les nodules puis établi une étude statistique afin d'identifier les facteurs échographiques prédictifs de métastase ganglionnaire aussi bien dans le secteur central que dans le secteur latéral.

L'incidence de métastase ganglionnaire au niveau du secteur central et latéral était respectivement de 45,8% and 35 %. Après l'analyse univariée, les facteurs échographiques suivant étaient statistiquement associés aux métastases ganglionnaires: la forme ronde des nodules, leur caractère fortement hypoéchogène, la présence de microcalcifications, la présence d'adénopathie cervicale et les stades EU-TIRADS III et V. l'analyse multivariée a montré que la présence d'adénopathie cervicale à l'échographie était le seul facteur prédictif de métastase ganglionnaire aussi dans le secteur central que latéral. Cependant, la présence de calcifications, la forme ronde du nodule et le stade EU-TIRADS III étaient exclusivement prédictifs de métastases ganglionnaires centrales.

Nous concluons que la présence échographique d'adénopathies cervicales est le seul facteur prédictif de métastase ganglionnaire dans les carcinomes de la thyroïde. Paradoxalement, les nodules thyroïdiens avec un risque faible de malignité (EU-TIRADS III) sont prédictifs de métastases ganglionnaires au niveau du secteur central.

Mots-clés: carcinome différencié de la thyroïde; échographie; métastase ganglionnaire, évidement cervical; thyroïdectomie

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INTRODUCTION

The incidence of thyroid cancers is increasing significantly [1]. The important role of lymph node metastasis as a predictor of local metastasis and recurrence has been widely reported [2]. The treatment of patients with clinical signs of lymph node metastasis requires total thyroidectomy and neck dissection. Prophylactic neck dissection in patients with no clinical lymph node (cN0) is still controversial [3]. Preoperative imaging plays an important role in the diagnosis and staging of thyroid cancer. We anticipated that the ultrasound results would be related to the natural properties of thyroid cancer and attempted to find an association between preoperative ultrasound (US) findings and cervical lymph node metastases. In our present study, we aim to identify the US predictive factors of lymph node metastases.

MATERIALS AND METHODS

Study design and patients

We reviewed retrospectively 120 data charts of patients who underwent total thyroidectomy with neck dissection for thyroid carcinoma. All of them were managed in the ENT and Head and Neck Surgery department of Fattouma Bourguiba University Hospital of Monastir in Tunisia from January 2016 to December 2020. A preoperative US examination was performed in all patients to assess thyroid nodules (TNs) and lymph node status.

TNs were then classified according to EU- TIRADS (European thyroid imaging-reporting and data system) risk stratification criteria without prior knowledge of the cytological results. This classification system stratifies nodules in classes I to V (I: normal, II: benign, III: low risk, IV: intermediate risk, V: high risk).

Thyroid tumors and lymph node metastases were categorized according to the 8th edition of TNM/AJCC classification.

Statistical analysis

Statistical analysis was performed with IBM SPSS 22 software. The relationship between lymph node metastases and US features was determined using univariate analysis. The Student's t-test was used to analyze quantitative variables and the chi-square test for qualitative variables. The multivariate analysis was performed on variables with $p<0.05$ in the univariate analysis, then predictive factors of lymph node metastases were determined using the binary logistic regression model and the data was expressed in OR. A $p < 0.05$ was considered statistically significant.

RESULTS

Epidemiology

This study included 120 patients with a median age of 46 years (range 12-84 years), both sexes were affected with a female predominance. The sex ratio was 6.5. The total number of evaluated nodules was 181.

Thyroid Ultrasound results

Ultrasonographic characteristics of thyroid nodules are summarized in Table 1 and illustrated in figure 1. Multinodularity was noted in 50.8% (n=61). The nodules were sized from 3 to 80 mm with a mean size of 17 mm. Nodule shape was defined as ovoid in 91.7% and round in 8.3%. Most nodules were solid (69.1%), whereas 29.8% were mixt solid and cystic, and 1.1% were exclusively cystic. Most of the nodules were markedly hypoechoic (52.5%). The nodules showed a regular margin in 61.9% of cases, while an irregular margin was noted in 30.9%. Microcalcifications were noted in 33.7% of cases. The Doppler study distinguished four results related to the vascularization type (Table I). The presence of lateral lymph nodes on ultrasound was observed in 50 patients (41.7%).

TABLE I. US features of thyroid nodules

US findings	Number of TNs (n=181)
Nodule limit	
Regular	112 (61.9%)
Irregular	56(30.9%)
Indistinct	13(7.2%)
Composition	
Solid	125(69.1%)
Cystic	2(1.1%)
Mixt	54(29.8%)
Shape	
Round	15(8.3%)
Ovoid	166(91%)
Echogenicity	
Markedly Hypoechoic	95(52.5%)
Moderately hypoechoic	47(26%)
Isoechoic	24(13.2%)
Hyperechoic	13(7.2%)
Spongiform	2(1.1%)
Calcifications	
Microcalcifications	61(33.7%)
Macrocalcifications	26(14.1%)
Vascularization*	
Type I	20(11.2%)
Type II	9(4.8%)
Type III	83(46%)
Type IV	23(12.7%)

*Type I: Absence of intra-nodular or peri-nodular vascularization, type II: peri-nodular vascularization, type III: intra-nodular vascularization, type IV: mixed vascularization

According to the EU-TIRADS stratification system, nodules were classified in EU-TIRADS II in 1.1% (n=2), EU-TIRADS III in 11% (n=20), EU-TIRADS IV in 24.9% (n=45) an EU-TIRADS V in 63% (n=114) (Figure 1).

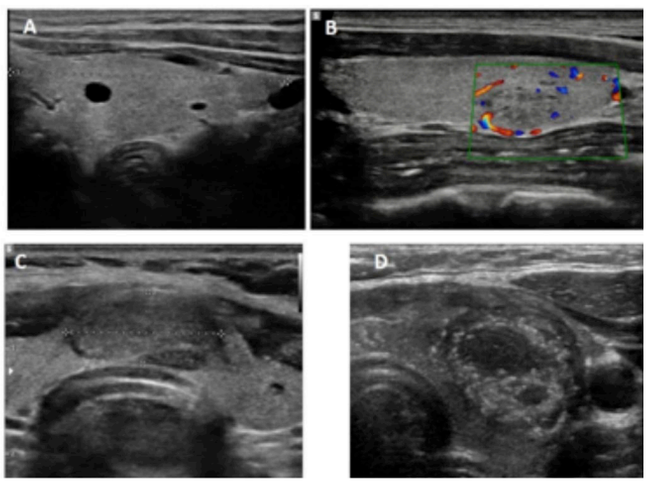

Figure 1: Ultrasound features of thyroid nodules

A. Anechoic thyroid nodules with regular margin classified **EU-TIRADS II**
B. Iso-echoic, ovoid-shaped thyroid nodule sized 15 mm classified **EU-TIRADS III**
C. A moderate hypoechogenic thyroid nodule sized 24 mmm with regular margins classified **EU-TIRADS IV**
D. Markedly hypoechogenic thyroid nodule with micro-calcifications classified **EU-TTIRADS V**

Surgical treatment

Total thyroidectomy with lymph node neck dissection was performed in all patients. The dissection involved the central compartment in 49% of cases. It was bilateral in 40% of cases. Lateral neck dissection was performed in 35% of patients and was bilateral in 16%.

Anatomopathological results

Papillary carcinoma was the predominant histological type observed in 90.6 %. The other histologic types were vesicular carcinomas (4.2%), medullary carcinomas (2.6%), poorly-differentiated carcinoma (1.3%), and anaplastic carcinoma (1.3%). Multifocality was noted in 50.8%. The tumor was staged pT1 in 58.3%, pT2 in 29.2%, pT3 in 11.7%, and pT4 in 0.8% of cases. Lymph nodes were classified as pN0 in 19.2%, pN1a in 45.8%, and pN1b in 35% of cases**.**

Ultrasound factors associated with lymph node metastasis

Histological lymph node metastases of the central and lateral groups were both significantly associated with the following nodules US features: a round shape nodule, markedly hypoechoic character, micro-calcifications, the presence of lymph nodes and scores EU-TIRADS III, and V (Tables II and III). The irregular margin was only associated with central group metastases (Table II), whereas macro-calcifications were associated with lateral metastases (Table III).

Tumor size, multi-focality, composition, and vascularization seem not influence lymph node metastases occurrence (Tables II and III).

On multivariate analysis, US predictive factors of central lymph node metastases were: calcification, TNs round shaped, the presence of lymph nodes, and EU-TIRADS III score (Table IV). However, the presence of lymph nodes was the only US predictive factor in lateral group metastases (Table V).

TABLE III. Univariate analysis of US factors associated to central lymph node metastasis (N1a)

Clinical characteristics		Total	OR	95%CI	P value
Ultrasound features					
Tumor size (mm)	≤5	7(3.9%)	0.757	0.262-2.183	0.606
	5-10	32(17.7%)	1.074	0.576-2.003	0.822
	10-20	25(13.8%)	0.845	0.440-1.622	0.613
	>20	33(18.2%)	1.257	0.671-2.357	0.475
EU-TIRADS score	II	0	NA	NA	NA
	III	2(1.1%)	0.079	0.018-0.353	0.00
	IV	26(14.4%)	1.207	0.615-2.368	0.584
	V	69(38.1%)	2.272	1.227-4.206	0.008
Markedly hypoechoic		60(33.1%)	2.381	1.310-4.329	0.004
Irregular shape		36(19.9%)	1.950	1.018-3.734	0.042
Microcalcification		41(22.7%)	2.423	1.272-4.613	0.006
Macrocalcification		18(9.9%)	2.221	0.912-5.411	0.074
Round shape		13(7.2%)	1.500	1.422-29.704	0.006
Solid		71(39.2%)	1.630	0.864-3.076	0.130
Intra-nodular vascularity		14(7.7%)	1.442	0.590-3.524	0.42
Multifocality		28(23.3%)	1.006	0.490-2.062	0.988
Lymph node		35(29.2%)	5.833	2.630-12.940	0.000

NA: not applicable

TABLE III. Univariate analysis of US factors associated with lateral lymph node metastasis (N1b)

Clinical characteristics		Total	OR	95%CI	P value
Ultrasound features					
Tumor size (mm)	≤5	5(2.8%)	0.956	0.312-2.931	0.937
	5-10	20(11%)	0.977	0.507-1.882	0.944
	10-20	16(8.8%)	0.870	0.434-1.741	0.693
	>20	21(11.6%)	1.135	0.590-2.182	0.704
EU-TIRADS	II	0	NA	NA	NA
	III	2(1.1%)	0.187	0.042-0.834	0.015
	IV	14(7.7%)	0.793	0.386-1.629	0.527
	V	46(25.4%)	2.156	1.098-4.234	0.024

Markedly hypoechoic	42(23.2%)	2.615	1.374-4.977	0.003
Microcalcification	27(14.9%)	1.929	1.016-3.659	0.043
Macrocalcification	14(7.7%)	2.601	1.120-6.042	0.023
Irregular shape	23(12.7%)	1.537	0.800-2.935	0.196
Round shape	9(5%)	3.198	1.082-9.449	0.028
Solid	47(26%)	1.647	0.823-3.295	0.156
Intra-nodular vascularity	5(2.8%)	0.492	0.174-1.396	0.176
Multifocality	24(20%)	1.477	0.694-3.146	0.310
Lymph node	36(30%)	27.429	9.696-77.593	0.000

NA: not applicable

TABLE IV. Multivariate analysis of US predictive factors for central lymph node metastasis (N1a)

Ultrasound features		OR	95%CI	P value
EU-TIRADS score	III	0.080	0.15-0.24	0.003
	V	0.385	0.109-1.355	0.137
Severely hypoechoic		2.156	0.763-6.087	0.147
Microcalcification		3.051	1.264-7.365	0.013
Macrocalcification		3.567	1.259-10.103	0.017
Irregular shape		1.028	0.461-2.295	0.946
Round		9.722	1.795-52.650	0.008
Lymph node		5.833	2.630-12.940	0.000

TABLE V. Multivariate analysis of US predictive factors for lateral lymph node metastasis (N1b)

Ultrasound features		OR	95%CI	P value
EU-TIRADS score	III	0.847	0.129-5.582	0.863
	V	0.658	0.148-2.917	0.582
Severely hypoechoic		2.227	0.648-7.659	0.204
Microcalcification		1.459	0.565-3.674	0.435
Macrocalcification		2.308	0.795-6.698	0.124
Round		1.753	0.500-6.144	0.380
Lymph node		27.429	0.305-1.407	**0.000**

DISCUSSION

Thyroid cancer is the most common cancer of endocrine glands. It accounts for 1% of all cancers worldwide, and its incidence is increasing [4].

Cervical lymph node metastases are present at diagnosis in 20-50% of patients with papillary carcinoma and a smaller proportion of patients with other histologic types [5]. Lymph node involvement appears to have a relatively small influence on survival; however, it increases the risk of loco-regional recurrence and distant metastases [6].

Studies have shown that thyroid cancer salvage is difficult and increases surgical complications [3,7]. So initial accurate assessment of lymph node status is important to plan the appropriate lymph node surgery.

In the last decade, cervical ultrasound has become highly affordable, which has led to an increase in the diagnosis of thyroid cancers [8]. Ultrasound features of thyroid cancer are strongly associated with clinico-pathological features and prognosis [9]. It has become essential to define reliable and reproducible ultrasound selection criteria [10]. In the literature, most ultrasound findings are for papillary thyroid cancers, explained by their frequency, while data are limited and inconsistent for other types, including medullary carcinomas [8].

The EU-TIRADS classification is used to assess the risk of malignancy of nodules and describe in details the ultrasound semiology [11,12].

Nodules with ultrasound features at high risk of malignancy require active ultrasound surveillance [10,11].

The correlation between sonographic presentation and lymph node metastasis is poorly reported in the literature. Therefore, for cervical lymph node Management, it is necessary to investigate the risk factors for cervical lymph node metastasis in these patients.

Risk factors for central cervical lymph node metastasis

In our study, we found that the ultrasound size of the tumor nodule was not correlated with central lymph node metastasis, whereas other studies have reported the opposite.

Several studies reported that cervical lymph node metastasis was positively related to the size of the primary tumor with different thresholds, but this is not consistent with our results.

The tumor size was reported to be a risk factor for central lymph node metastasis by several studies. Ahn et al [5] considered as a risk factor a tumor size ≥ 1 cm, while Yan et al [13] reported a tumor size ≥ 2.5 mm, and > 5mm for Huang el al [14].

In our current study, we evaluated the suspicious preoperative US features that predict lymph node metastasis in thyroid cancer and found that round shaped, irregular contours, highly hypoechoic character, presence of microcalcifications and macrocalcifications, cervical lymph node on ultrasound, and EU-TIRADS III and V scores were significant predictors of central lymph node metastasis. However, this was not the case for US features such as intra-nodular vascularity, solidity, and EU-TIRADS categories II and IV.

Our results are in accordance with those of the Liu *et al* study [7], only for micro-calcifications and central vascularization, and Yun *et al* [15] for micro-calcifications and irregular contour.

Gomez et al [16], have shown in their study that tumor calcifications were predictive of lymph node metastasis in papillary carcinoma. In fact, micro-calcifications

reflect massive cell proliferation and are the main predictor of malignancy [11,16]. Significant results found by Zhaou *et al* [9], concerning the presence of clinical lymph nodes on ultrasound (cN1), suggest that this preoperative imaging feature is predictive of the presr ence of pN1a. Whereas, the absence of clinical lymph node involvement (cN0), is classified in the low-risk group and routine prophylactic central node dissection is not recommended [14].

Yun *et al* [15], reported in their study on medullary carcinoma that TIRADS class 5 was significantly associated with lymph node metastasis (p = 0.033). There is no work investigating EU-TIRADS score as a risk factor for other histological types, including papillary carcinoma.

Risk factors for lateral cervical lymph node metastasis

Many studies investigated the ultrasound factors assoe ciated lateral lymph node metastases, but the results of these studies are controversial.

Similarly, for lateral metastasis, size was not a risk factor in our study. But in the literature, tumor size >1 cm was significantly associated with lateral cervical metastasis in medullary carcinoma [7,17,18].

Regarding lateral metastasis, we found that highly hypoechoic character, round shaped, presence of microcalcifications and macrocalcifications, and US cervical lymph node were significant predictive factors for metastasis.

Kwak *et al* found that microcalcifications were predictive of lateral metastasis in papillary microcarcinoma (p 0.001) [19].

Some studies have shown that malignant ultrasound features such as irregular contours are associated with lateral lymph node metastases [20,21].

A number of studies have found that patients with clinical lymph nodes are predictive of lateral metastases [1, 21]. According to the literature, the US is the best exam for lymph node metastases detection with a sensitivity of 84% and a specificity of 95% [5,22,23]. Thus it guides the decision for lateral lymph node dissection.

A study done by Park *et al* showed that a higher number of suspicious ultrasound features classified by the TIRADS is in association with N1b [24].

Although N1a is reported to predict N1b [7], it was the same in our study However, Lin et al did not consider central metastasis as a risk factor for cervical lateral metastasis [21].

We found that EU-TIRADS scores III and V were predictive of lateral metastases but we did not find any studies investigating this classification in predicting lateral metastases.

CONCLUSION

In summary, we considered that the following US features were statistically significant predictors of lymph node metastasis in patients with thyroid cancer: a round shaped nodule, the presence of calcifications, the strongly hypoechoic character, the presence of cervical lymph nodes, and EU-TIRADS III and V scores. The ability to predict lymph node involvement in thyroid cancer patients may help determine the appropriate preoperative workup, patient counseling, and mainly for central or/and lateral neck dissection performing.

Ethical statement

All data were anonymized, and the requirement for individual consent for this retrospective analysis was waived. The data of the patients were retrieved directly from medical charts.

Conflicts of interest: Authors declare no conflicts of interest.

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