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Sonographic features of medullary thyroid carcinomas — a systematic review and meta-analysis

Cechy sonograficzne raków rdzeniastych tarczycy — przegląd systematyczny i metaanaliza

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Abstract

Introduction: Thyroid nodular goitre is one of the most common endocrine disorders. Differentiating between benign and malignant lesions is an emerging challenge in endocrinological practice. Ultrasonography (US) remains the most commonly applied method in the preliminary assessment of lesions and is the basis for the decision as to fine needle aspiration biopsy (FNAB) and further diagnostics. Many studies have evaluated the diagnostic value of US malignancy features. However, they focused mainly on papillary thyroid cancer (PTC). It remains unclear whether other types of thyroid carcinoma (TC) are also characterised by the same US features. The aim of this study was to assess the usefulness of US features considered as markers in the diagnosis of medullary thyroid cancer (MTC).

Material and methods: The PubMed/MEDLINE and Cochrane Library databases were searched to identify studies on US features of MTCs. The random-effects model was used to calculate pooled sensitivity and specificity and odds ratios (OR) — if a comparison with PTCs was available.

Results: Hypoechogenicity was present in 83.4% of MTCs, and 32.7% were markedly hypoechogenic. None of the 157 MTCs was hyperechogenic. Sensitivity of halo absence was 88.9%, but irregular margins were present in 38.0%. 35.5% of MTCs had microcalcifications, and 27.0% had macrocalcifications. 14.4% presented 'taller than wide feature' (higher anteroposterior than transverse diameter). Apart from macrocalcifications, all these features occurred insignificantly less often in MTCs than in PTCs.

Conclusions: US features commonly considered as markers of malignancy can be useful also in the diagnostics of MTCs. However, MTCs tend to possess suspicious US features slightly less often than PTCs. Some features, such as hyperechogenicity, can be considered to be strong markers of benign status. Although the US appearance of the thyroid lesion is an important diagnostic factor, it is worth remembering that it does not allow for a definitive differentiation between benign and malignant nodules. In the case of MTCs, as well as other TCs, US examination remains a valuable diagnostic tool, but should always be interpreted carefully in the context of other examinations. **(Endokrynol Pol 2014; 65 (4): 314–318)**

Key words: *thyroid; nodular goitre; medullary thyroid cancer; thyroid cancer; thyroid nodules; ultrasonography; meta-analysis*

Streszczenie

Wstęp: Guzki tarczycy należą do najczęstszych zaburzeń spotykanych w endokrynologii. Różnicowanie zmian łagodnych i złośliwych stanowi wyzwanie w praktyce endokrynologicznej. Badanie ultrasonograficzne (USG) pozostaje najczęściej stosowaną metodą wstępnej oceny zmian, a także podstawą dla decyzji o biopsji cienkoigłowej i dalszej diagnostyce. W licznych pracach oceniano wartość diagnostyczną cech sonograficznych uważanych za markery złośliwości. Były one jednak skupione głównie na rakach brodawkowatych tarczycy (RBT). Przedmiotem kontrowersji pozostaje, czy inne typy raków tarczycy charakteryzują się tymi samymi cechami sonograficznymi. Celem pracy było określenie użyteczności cech sonograficznych uznawanych za markery złośliwości w diagnostyce raków rdzeniastych tarczycy (RRT).

Materialy i metody: Przeszukano bazy danych Pubmed/MEDLINE oraz Cochrane Library w celu odnalezienia prac zawierających dane o cechach sonograficznych raków rdzeniastych. Model efektów zmiennych został użyty do obliczenia czułości, swoistości oraz ilorazów szans — gdy dostępne były również dane dotyczące raków brodawkowatych.

Wyniki: Hipoechogenność była obecna w 83,4% przypadków raków rdzeniastych, 32,7% RRT wykazywało głęboką hipoechogenność. Żaden ze 157 RRT nie był hiperechogenny. Czułość braku "halo" wynosiła 88,9%, jednak nierówne granice były obecne jedynie w 32,7% przypadków. 35,5% RRT posiadało mikrozwapnienia, 27,0% — makrozwapnienia. 14,4% RRT posiadało cechę "*taller than wide*" (przewaga wymiaru przednio — tylnego nad poprzecznym). Za wyjątkiem makrozwapnień, wszystkie wymienione cechy występowały nieistotnie statystycznie rzadziej w RRT niż RBT.

Wnioski: Cechy sonograficzne uważane za markery złośliwości są przydatne również w diagnostyce raków rdzeniastych tarczycy. Jednakże w przypadku RRT występują one nieco rzadziej niż w przypadku RBT. Niektóre cechy, jak hiperechogenność, można uznać za przemawiające silnie za nieobecnością RRT. Jakkolwiek obraz sonograficzny zmian ogniskowych w tarczycy stanowi wartościowy element diagnostyczny należy pamiętać, że nie pozwala on na definitywne rozstrzygnięcie charakteru zmiany. W przypadku raków rdzeniastych, podobnie jak innych typów raka tarczycy, USG pozostaje wartościowym narzędziem, jego wynik powinien być jednak interpretowany ostrożnie, z uwzględnieniem wyników innych badań. **(Endokrynol Pol 2014; 65 (4): 314–318)**

Słowa kluczowe: *tarczyca; wole guzkowe; rak rdzeniasty tarczycy; guzki tarczycy; rak tarczycy; ultrasonografia; metaanaliza*

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Introduction

Thyroid nodular goitre is one of the most common endocrine disorders [1,2]. Differentiating between benign and malignant lesions is an emerging challenge in endocrine practice. Ultrasonography (US) remains the most commonly applied method in the preliminary assessment of lesions and forms the basis for the decision as to fine needle aspiration biopsy (FNAB) and further diagnostics.

Numerous studies have evaluated the diagnostic value of sonographic malignancy features. However, they have focused mainly on papillary thyroid cancer (PTC) as the most frequent thyroid malignancy [3–5]. The controversial issue is whether other types of thyroid carcinoma (TC), such as medullary thyroid cancer (MTC), are also characterised by the same US features.

MTC accounts for 3.5–10% of all TCs [6]. It derives from the parafollicular C-cells, which produce the hormone calcitonin. About 75% of MTCs are sporadic and 25% are hereditary cases [7]. This tumour is usually difficult to diagnose, and consequently 35% of patients at the time of diagnosis have MTC extending beyond the thyroid [8]. Routine measurement of calcitonin level is not commonly used in diagnosing patients with thyroid nodules because of the high cost [9]. Thus there arises a question about the US appearance of MTCs which is crucial in the initial steps of diagnostics.

The aim of this study was to assess the usefulness of ultrasound features considered to be markers of malignancy in the diagnosis of medullary thyroid cancer.

Material and methods

Literature search and data extraction

We searched the PubMed/MEDLINE and Cochrane Library databases in order to identify all relevant research articles. The search terms 'medullary thyroid cancer' or 'medullary thyroid carcinoma' and ultrasound or ultrasonography or elastography or 'power Doppler' or 'color Doppler' were used. The following filters were applied — English language and publication between January 2000 and May 2013. The literature search was performed independently by two authors (K.W. and M.R-Ł.). All papers, including data on US, ES and Doppler examination features of histhopatologically confirmed MTCs, were included.

Statistical analysis

Pooled sensitivities and specificities of particular markers of malignancy were calculated using a random-effect model according to the methodology described by Borenstein et al. [10]. Results of studies comparing frequencies of particular features in MTCs and PTCs were combined using Statistica v. 10 from StatSoft. A *P* value under 0.05 was considered statistically significant. Meta-analysis was performed if at least three studies provided data on a particular marker of malignancy.

Results

Six studies containing data on sonographic features of 169 MTCs were included into the meta-analysis (Table I). All these studies had a retrospective character. Three of them encompassed also comparisons with PTCs, and two with benign thyroid nodules. The steps of selection are shown on the flowchart (Fig. 1). Results of included studies on the US appearance of MTCs are summarised in Table II.

Hypoechogenicity

Five studies containing data on 157 MTCs provided data on the occurrence of hypoechogenicity. The pooled frequency was 83.4% (95% CI 46.5–100.0%). There was no evidence for significant heterogeneity (Q = 0.11, p = 1.0). Three studies included comparisons between MTCs and PTCs. Pooled OR was 0.97 (95% CI 0.64 – 1.46). There was no evidence for significant heterogeneity (Q = 0.03, p = 0.98). None of the 157 MTCs was hyperechogenic.

Table I. *General characteristics of studies on the US features of medullary thyroid cancers*
Tabela I. *Ogólna charakterystyka prac o cechach sonograficznych raków rdzeniastych tarczycy*

Author	Year	Number of MTCs	Number of patients	Sex	Age [mean, ± standard deviation]	Comments
Trimboli et al. [5]	2012	12	12	7 women, 5 men	62.8 ± 15.1	Comparison with PTCs
Choi et al. [11]	2011	36	30	21 women, 9 men	48.7 ± 14.4	
Cai et al. [14]	2010	35	27	14 women, 13 men	45.7 ± 12.8	
Kim et al. [4]	2009	21	18	15 women, 3 men	50.4	Comparison with PTCs
Lee et al. [3]	2009	42	42	29 women, 13 men	48	Comparison with PTCs
Saller et al. [15]	2002	19	19	9 women, 10 men	46 ± 17	Comparison with benign nodules

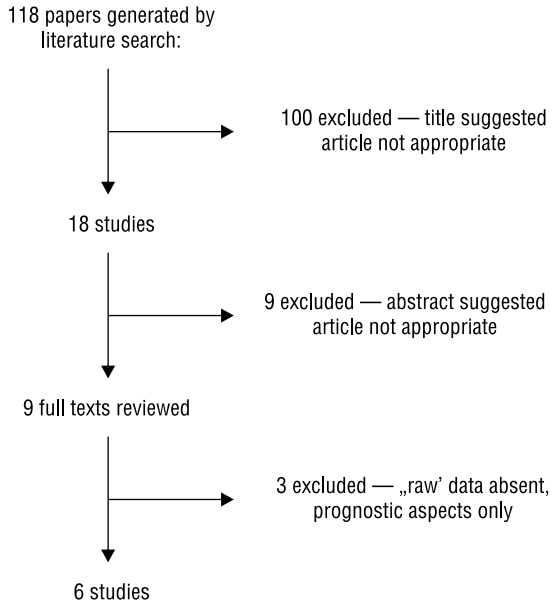

Figure 1. *Flowchart demonstrating the steps of the literature search*

Rycina 1. *Diagram pokazujący etapy selekcji prac*

Marked hypoechogenicity

Four studies containing data on 134 MTCs provided data on the occurrence of marked hypoechogenicity. The pooled frequency was 32.7% (95% CI 21.8–49.1%). There was no evidence for significant heterogeneity (Q = 3.01, p = 0.39). Two studies included comparisons between MTCs and PTCs [3, 4]. Both showed that marked hypoechogenicity was insignificantly less frequent in MTCs.

Microcalcifications

Six studies containing data on 169 MTCs provided data on the occurrence of microcalcifications. The pooled frequency was 35.5% (95% CI 25.8–49.0%). There was no evidence for significant heterogeneity (Q = 0.00, p = 1.0). Three studies included comparisons between MTCs and PTCs. Pooled OR was 0.64 (95% CI 0.38–1.10). There was no evidence for significant heterogeneity (Q = 4.27, p = 0.12).

Macrocalcifications

Six studies containing data on 169 MTCs provided data on the occurrence of macrocalcifications. The pooled frequency was 27.0% (95% CI 18.3–39.8%). There was no evidence for significant heterogeneity (Q = 3.74, p = 0.59). Three studies included comparisons between MTCs and PTCs. Pooled OR was 1.77 (95% CI 0.83–3.79). There was no evidence for significant heterogeneity (Q = 1.44, p = 0.49).

Absent or irregular halo

Three studies containing data on 66 MTCs provided data on the occurrence of halo irregularity or absence. The pooled frequency was 89.9% (95% CI 31.9–100.0%). There was no evidence for significant heterogeneity (Q = 0.00, p = 1.00). One study included a comparison between MTCs and PTCs [5]. It showed that halo absence was insignificantly less frequent in MTCs (p = 0.06).

Solid composition

Six studies containing data on 169 MTCs provided data on the occurrence of solid composition. The pooled frequency was 79.2% (95% CI 51.8–100.0%). There was no evidence for significant heterogeneity (Q = 0.25, p = 1.00). Three studies included comparisons between MTCs and PTCs. Pooled OR was 0.79 (95% CI 0.52–1.18). There was no evidence for significant heterogeneity (Q = 0.43, p = 0.80). There were no pure cystic MTCs, and only one predominantly cystic MTC, reported in the included studies.

Table II. ***Results of included studies on the US appearance of medullary thyroid cancers***

Tabela II. ***Wyniki prac o cechach sonograficznych raków rdzeniastych tarczycy***

	Trimboli et al. [5]	Choi et al. [11]	Cai et al. [14]	Kim et al. [4]	Lee et al. [3]	Saller et al. [15]
Hypoechogenicity	6 of 8 solid;	35/36	34/35	20/21	36/42	19/19
Marked hypoechogenicity	–	9/36	15/35	11/21	9/42	–
Microcalcifications	2/12	17/36*	10/35	6/21	18/42	7/19
Macrocalcifications	2/12	7/36*	13/35	5/21	8/42	11/19
Absent or irregular halo	9/12	26/36	34/35	–	–	18/19
Irregular margins	0/12	17/36**		–	19/42	–
'Taller than wide'	–	6/36	1/35	4/21	6/42	–
Solid composition	8/12	33/36	29/35	19/21	31/42	18/19

* three MTCs contained both micro and macrocalcifications; ** margins defined as speculated or ill defined were included

Irregular margins

Four studies containing data on 114 MTCs provided data on the occurrence of irregular margins. The pooled frequency was 38.0% (95% CI 21.4–67.4%). There was no evidence for significant heterogeneity (Q = 3.82, p = 0.28). Three studies included comparisons between MTCs and PTCs. Pooled OR was 0.33 (95% CI 0.09–1.26). There was evidence for significant heterogeneity (Q = 6.49, p = 0.04).

'Taller than wide' feature

Four studies containing data on 134 MTCs provided data on the occurrence of 'taller than wide' feature. The pooled frequency was 14.4% (95% CI 8.6–24.2%). There was no evidence for significant heterogeneity (Q = 2.90, p = 0.41). Two studies included comparisons between MTCs and PTCs. Both showed that the 'taller than wide' feature was less frequent in MTCs: the result of one of them was on the border of statistical significance (Kim et al., p = 0.055), and the second achieved significance (Lee et al., p = 0.001) [3, 4].

Discussion

Hypoechogenicity, halo absence, and solid composition are the most common sonographic features of MTCs. Also calcifications are frequent findings in MTCs. Microcalcifications occurred in 35.5%, and macrocalcifications in a further 27.0%. Irregular margins were moderately common (38.0%) in MTCs; however, there was significant heterogeneity due to the great dispersion of results of particular studies — from 0% [5] to nearly 50% [11]. Partly this could be the effect of the small number of studies assessing this feature. Furthermore, this attribute has been described by some authors as being characterised by low intra- and interobserver agreement [12, 13]. The 'taller than wide' feature turned out to be rarely present in MTCs.

The amount of available data on the US features of MTCs is low. Six included studies contained descriptions of 169 MTCs. As the panels of assessed features were partly different in particular studies, the amount of information about some of the markers is even lower. There was not enough data on Colour Doppler (CD) and Power Doppler (PD) examinations to meta-analyse. However, a few studies contained some information on this topic. Trimboli et al. [5] reported that three of 12 MTCs presented intranodular flow in CD. According to Cai et al. [14], seven of 29 examined cancers had strong intranodular flow, and 15 had moderate flow. Saller et al. [15] assessed the usefulness of PD: intranodular flow was present in six of 14 examined MTCs, and intranodular flow with concomitant perinodular signal in a further five tumours. We did not find any study containing information about the appearance of MTCs in soelastography, which is believed to be an important improvement on conventional US. This has been described as a valuable tool in differentiating between benign and malignant thyroid nodules [16, 17], diagnostic of other thyroid diseases, such as Graves' disease, chronic or subacute thyroiditis [18–20].

Three studies compared the occurrence of these markers of malignancy in MTCs and PTCs, including data on 79 MTCs and 208 PTCs. Macrocalcifications were slightly more frequent in MTCs, hypoechogenicity occurred in fact equally often in both groups (OR = 0.97), and all other meta-analysed features were somewhat less common in MTCs. However, none of these differences achieved statistical significance. This is probably partly due to the small number of studies and investigated cancers. Commonly used US markers, apart from macrocalcifications and hypoechogenicity, seem to be less sensitive in the diagnostics of MTCs, but further studies are needed to reach a definite conclusion. Most studies did not compare the US appearance of sporadic and hereditary MTCs. The study performed by Saller et al. did not reveal significant differences, although it encompassed only ten patients with sporadic MTC, seven with MEN 2A, and two with MEN 2B [15].

According to our results, typical MTC appears as a solid, hypoechogenic (often markedly) lesion without a halo and quite commonly containing micro- or macrocalcifications. However, the first three features are known to be very unspecific [21, 22], and the other two are less sensitive. In our opinion, the presence of a lesion with the appearance described above should arouse a suspicion of MTC and should be considered as an argument for further diagnostic steps, such as calcitonin measurement. On the other hand, most MTCs do not present all of the above features, and some of them can have a relatively benign US appearance. Particularly in cases of family history of MTC, the absence of the abovementioned US malignancy features is insufficient to exclude this type of malignancy. However, some attributes can be considered as markers of benign status. Especially hyperechogenicity and pure or predominantly cystic character seem to be extremely uncommon in MTCs. Isoechogenicity, halo presence, and minor cystic components also decrease the risk that a particular tumour is MTC, as these features are present in about 10% to 20% of MTCs.

In conclusion, US features commonly considered as markers of malignancy can be useful also in diagnosing MTCs. However, MTCs tends to possess suspicious US features slightly less often than PTCs. Some features, such as hyperechogenicity, strongly decrease the risk of MTC. Although the US appearance of the thyroid lesion

is an important diagnostic factor, it is worth remembering that it does not allow for a definitive differentiation between benign and malignant nodules. In a case of MTC, as well as other TCs, US examination remains a valuable diagnostic tool, but it should always be interpreted carefully in the context of other examinations.

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