

Differential Diagnostic Ultrasound Criteria of Papillary and Follicular Carcinomas: A Multivariate Analysis

Differentialdiagnostische Ultraschallkriterien papillärer und follikulärer Schilddrüsenkarzinome: Eine multivariate Analyse

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Key words

- thyroid carcinoma
- papillary thyroid carcinoma
- follicular thyroid carcinoma
- ultrasound

Abstract



Purpose: The purpose of the study was to test the hypothesis that papillary thyroid carcinomas (PTCs) and follicular thyroid carcinomas (FTCs) appear with different ultrasound characteristics.

Material and Methods: 90 patients (70 females, 20 males) were included in the study in whom after thyroidectomy the diagnoses of PTCs or FTCs were established. 33 patients (25 females, 8 males) with the diagnosis of follicular adenoma were included in the study as controls (KONs). All patients had ultrasound examinations of the thyroid preoperatively. These ultrasound examinations were evaluated retrospectively with respect to the ultrasound characteristics: "size", "shape", "contour", "structure", "echogenicity" and "calcifications".

Results: In PTCs, FTCs and KONs "size" was significantly different (PTCs: MW = 12.5 mm, SD = 8.1 mm – FTCs: MW = 35.4 mm, SD = 19.6 mm – KONs: MW = 22.7 mm, SD = 14.5 mm; $p < 0.001$ for PTCs vs. FTCs, $p < 0.001$ for PTCs vs. KONs, $p = 0.013$ for FTCs vs. KONs). Differences were also found with respect to "contour" and "echogenicity" among PTCs, FTCs and KONs ($p \leq 0.035$). The parameters "size", "contour", "echogenicity" and "calcifications" correlated for PTCs, FTCs and KONs with a correlation coefficient $r = 0.57$ ($p < 0.05$, multivariate regression analysis).

Conclusions: PTCs and FTCs appear with different sonographic characteristics. Although there is some overlapping of the sonographic appearances of PTCs and FTCs, the knowledge of these differences should have some impact of the risk adapted further work up.

Key Points:

- ▶ In preoperative ultrasound examinations FTCs appear significantly larger than PTCs.

- ▶ The sonographically detected structure of FTCs can be classified as inhomogeneous predominantly, whilst PTCs are equally homogeneous or inhomogeneous.
- ▶ The knowledge of the different sonographic appearance of PTCs and FTCs is of importance within the context of risk-adapted further work-up.

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Zusammenfassung



Ziel: In der vorliegenden Arbeit sollte die Hypothese überprüft werden, dass sich papilläre Schilddrüsenkarzinome (PTCs) von follikulären Schilddrüsenkarzinomen (FTCs) bezüglich ihrer Ultraschallcharakteristika unterscheiden.

Material und Methoden: Untersucht wurden 90 Patienten (70 weiblich, 20 männlich), bei denen nach Thyreoidektomie histologisch die Diagnosen von PTCs oder FTCs gestellt wurde. Als Kontrollen (KONs) dienten 33 Patienten (25 weiblich, 8 männlich) mit einem follikulärem Adenom. Hochauflösende Ultraschalluntersuchungen erfolgten präoperativ mit Erfassung der Ultraschallcharakteristika: „Größe“, „Form“, „Kontur“, „Binnenstruktur“, „Echogenität“ und „Kalzifikationen“.

Ergebnisse: PTCs, FTCs und KONs unterschieden sich hinsichtlich „Größe“ (PTCs: MW = 12,5 mm, SD = 8,1 mm – FTCs: MW = 35,4 mm, SD = 19,6 mm – KONs: MW = 22,7 mm, SD = 14,5 mm; $p < 0,001$ für PTCs vs. FTCs, $p < 0,001$ für PTCs vs. KONs, $p = 0,013$ für FTCs vs. KONs). Auch im Hinblick auf „Kontur“ und „Echogenität“ konnten Unterschiede zwischen PTCs, FTCs und KONs gefunden werden

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($p \leq 0,035$). „Größe“, „Kontur“, „Echogenität“ und „Kalk“ ergaben für PTCs, FTCs und KONS einen Korrelationskoeffizienten $r = 0,57$ ($p < 0,05$, multiple Regressionsanalyse).

Schlussfolgerungen: Hinsichtlich ihres sonografischen Erscheinungsbildes gibt es Unterschiede zwischen PTCs und FTCs. Wenngleich große Überlappungen vorkommen können, erscheint die Kenntnis der Unterschiede im sonografischen Erscheinungsbild für eine risikoadaptierte Abklärungsdiagnostik von Bedeutung.

Introduction

For some years an increasing incidence of differentiated thyroid cancer has been noted in Germany [1]. This increased incidence is mainly due to a rise in observed papillary thyroid cancer (PTC). For differentiated follicular carcinomas of the thyroid (FTC), the incidence has remained constant. An investigation in the USA taking into account the time period between 1973 and 2002 showed that in particular small PTCs influenced the increase in incidence [2]. Of the increase observed in this time frame, 49% was due to PTCs smaller than 1 cm in size, and 87% involved papillary tumors smaller than 2 cm.

Ultrasonography is playing an increasingly important role in the detection of nodules in the thyroid [3, 4]. Using currently available technology, the tiniest lesions down to a size of approx. 1 mm can be detected [5]. Characteristics discovered during sonography that indicate a potential malignant thyroid tumor include calcifications, irregular contours, hypoechogenicity, a so-called “taller than wide” (TTW) sign and increased blood flow disclosed in power Doppler imaging [6].

However, on the whole these criteria do not have a high test accuracy, resulting in many malignant thyroid tumors being classified as benign [7].

Differentiated papillary thyroid carcinomas can be reliably detected using fine needle biopsy due to their cytological characteristics [8]. In contrast, for reasons of principle, differentiation between FTC and follicular adenomas cannot be provided by cytology [9]. Such cases are classified as “follicular neoplasia” requiring histological clarification after a thyroid operation.

To date numerous published ultrasound investigations have described the findings of differentiated thyroid carcinomas and related test accuracy. The purpose of this article, however, is an investigation of the hypothesis that papillary thyroid cancers differ from follicular thyroid cancers with respect to their characteristics as revealed by ultrasound.

Patients and Methods

Patients

The study included 90 examined patients (70 female, 20 male), ranging in age from 16 to 87 and a standard deviation of ± 14.8 years.

The cohort was made up of patients suspected of thyroid disease examined at RNZ outpatient thyroid clinic between 07/01/2009 and 06/30/2012, who subsequently underwent thyroidectomy in various hospitals due to thyroid nodules

which consequently could be determined to be papillary or follicular thyroid cancer.

The control group (CON) contained 33 examined patients (25 female, 8 male), ranging in age from 25 to 73 and a standard deviation of ± 12 years, all of whom underwent thyroidectomy during the same time period, and for whom a follicular adenoma (micro- or macrofollicular) could be histologically ascertained.

In the event of cytologically atypical results, a thyroid operation was always indicated. Cytologically atypical results included ambiguous follicular changes, follicular neoplasia or findings that could be attributed to a PTC. Further, in the event an FNAB was not performed or was not usable, a thyroid operation was also indicated if there were factors that indicated the necessity of histological evaluation [10].

Preoperative examinations included a physical examination, an ultrasound examination of the neck region as well as determination of in vitro thyroid gland parameters. Patients with thyroid nodules > 10 mm diameter additionally underwent a thyroid scintigram with $[^{99m}\text{Tc}]_0_4$ to exclude focal thyroid gland autonomy.

Upon receipt of the histological results, the ultrasound examinations stored in the PACS were reevaluated retrospectively according to the sonographic criteria. Excluded from the assessment were patients for whom an unambiguous assignment of differentiated thyroid carcinoma to a corresponding sonographic correlate was not possible ($n = 4$). Also excluded were carcinomas ≤ 1 mm, since due to their small size, sonographic criteria could not be reliably evaluated ($n = 4$). In all cases, these were papillary thyroid cancers.

Ultrasound Examinations

Ultrasound examinations of the neck region were performed using a SonoAce 8000 SE unit with a 7.5 MHz linear probe. These examinations were performed by physicians specialized in radiology and/or nuclear medicine. Representative images in two planes were stored in a PACS unit. Tumor size was measured on three planes using an implemented cursor; this provided the diameter in the lateral (dx), anterior-posterior (dy) and craniocaudal (dz) axes. The largest maximum diameter was used for statistical processing.

Upon receipt of the histological results, a physician specializing in radiology and nuclear medicine performed a retrospective image analysis on a PACS console. Tumors were assessed according to six sonographic criteria and the following characteristics:

- ▶ Size
 - ▶ Maximum diameter on one plane (dx, dy or dz)
- ▶ Shape
 - ▶ Round: Diameter $dx = dy = dz$ ($\pm 10\%$)
 - ▶ Oval: one axis surpasses the other axes by $> 10\%$ (Exception: Taller-Than-Wide, see below)
 - ▶ Irregular: undulating or complex shape
 - ▶ Taller-Than-Wide (TTW): anterior-posterior diameter $>$ lateral diameter, craniocaudal diameter not considered.
- ▶ Contour
 - ▶ Smooth
 - ▶ Spiculated or indistinctly delineated

- ▶ Structure
 - ▶ Homogeneous
 - ▶ Inhomogeneous
- ▶ Echogenicity
 - ▶ Hypoechogetic: nodule density between anechoic and less than the echogenicity of the perinodal tissue
 - ▶ Hyperechogetic: nodule density greater than that of the perinodal tissue
 - ▶ Cystic components: anechoic components within the nodule
- ▶ Calcification
 - ▶ Present
 - ▶ Not present

Statistical Evaluation

Statistical evaluation was performed using WinStat[®], version 2009. Statistical significance was presumed at values of $p < 0.05$.

Results

Distribution by Age and Sex

The average age was mean = 48.7 years with a standard deviation of ± 14.4 years for patients with papillary thyroid cancer and mean = 55.7 years with standard deviation of ± 14.3 years for patients with follicular thyroid cancer. The average age in the control group was mean = 48.5 years with a standard deviation of ± 12.3 years. The age difference among patients in the PTC, FTC and CON groups was not statistically significant ($p = 0.09$, ANOVA).

The patients were divided into age classes (Age class 1: 10 – 19 years, 2: 20 – 29 years, etc.). The percentage distribution of age classes did not vary significantly among PTC, FTC and CON (0.98, ANOVA) (Fig. 1).

In the PTC group, 21 % of the patients were male, and 79 % female; in the FTC group, 25 % were male and 75 % female; the CON group was composed of 24 % male patients and 76 % female. Statistically this distribution between PTC patients and CON patients or between FTC patients and CON

patients yielded no differences ($p = 0.48$ and $p = 0.81$, respectively, chi test).

Multifocality

- PTC: In the case of 53 patients there was a unifocal carcinoma, and 13 patients had a multifocal carcinoma.
- FTC: 23 patients had a unifocal carcinoma, and 1 patient had a multifocal carcinoma.
- CON: 28 patients had a unifocal adenoma, and 5 patients had a multifocal adenoma.

The greater proportion of multifocal tumors among PTC patients compared to the FTC group was statistically significant ($p < 0.001$, chi test). Regarding multifocality there was no difference between the PTC and CON groups ($p = 0.16$, chi test). However, difference between the FTC and CON groups was significant ($p < 0.001$, chi test).

Ultrasound Characteristics (including all PTC, FTC and CON patients)

Size:

For the PTC group, determination of maximum diameter was mean = 12.5 mm with a standard deviation of 8.1 mm; for the FTC group, mean = 35.4 mm and a standard deviation of 19.6 mm. For the CON group, mean = 22.7 mm with a standard deviation of 14.5 mm (Fig. 2).

Statistically, the following significances were found (t test): $p < 0.001$ for PTC vs. FTC, $p < 0.001$ for PTC vs. CON, $p = 0.013$ for FTC vs. CON.

The manifestations of the ultrasound characteristics “shape”, “contour”, “structure” “echogenicity” and “calcification” for PTC, FTC and CON patients are shown in Table 1.

Fig. 3 show a PTC and an FTC; the respective ultrasound characteristics are described.

Using an incremental multiple regression analysis, correlation to the dependent variable (PTC, FTC, CON) was calculated for the independent variables “size”, “shape”, “contour”, “structure”, “echogenicity” and “calcification”. It was demonstrated that the variables “size”, “echogenicity” and “calcification” correlated most strongly with the dependent variables with a correlation coefficient of $r = 0.57$. Ignoring

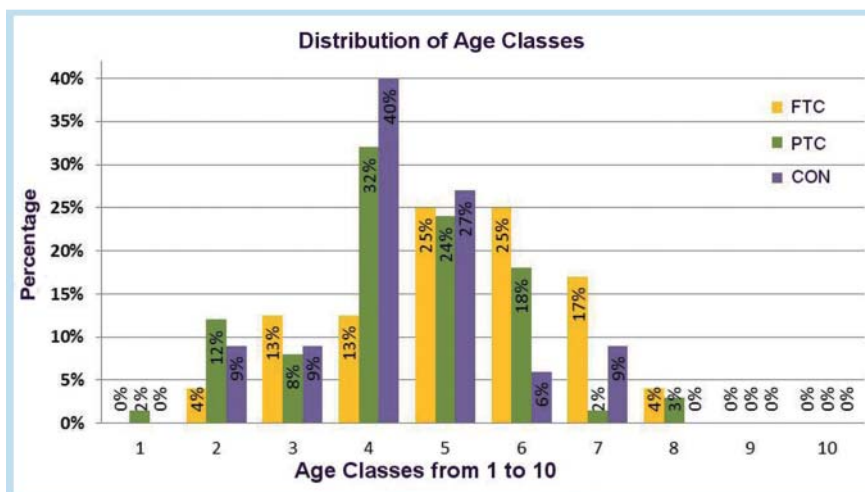


Fig. 1 Age distribution (1: 10 – 19 years; 2: 20 – 29 years etc.), green bar: patients (PTCs), yellow bar: patients (FTCs), purple bar: control (CONs) (data in percent).



Fig. 2 a Distribution of the ultrasound characteristic "size", b Distribution of the ultrasound characteristic "shape". c Distribution of the ultrasound characteristic "contour", d Distribution of the ultrasound characteristic

"structure", e Distribution of the ultrasound characteristic "echogenicity". f Distribution of the ultrasound characteristic "calcification".

the "size" variable, there was a correlation coefficient of $r=0.50$ for the variables "contour", "echogenicity" and "calcification". (Table 2).

Ultrasound Characteristics (excluding papillary microcarcinomas ≤ 10 mm)

Ultrasound characteristics for the patient group ($n=28$) with papillary thyroid cancer without papillary microcarcinomas (PTCo) were identified separately compared to the FTC and CON groups.

Size:

For the PTCo group, determination of maximum diameter was mean = 19.3 mm with a standard deviation of 8.5 mm. Statistically, the following significances were found with respect to PTC and CON (t test):

$p < 0.001$ for PTCo vs. FTC,
 $p = 0.23$ for PTCo vs. CON.

The manifestations of the ultrasound characteristics of the PTCo group compared to the FTC and CON groups are shown in Table 3.

Discussion



Epidemiological investigations indicate an increasing incidence of thyroid cancer. In Germany, the incidence of newly diagnosed cases has increased continuously, particularly for women under 60 years of age, but also for younger men [1]. The increasing rate of new diagnoses appears to be largely influenced by the rise in cases of PTC. One American survey

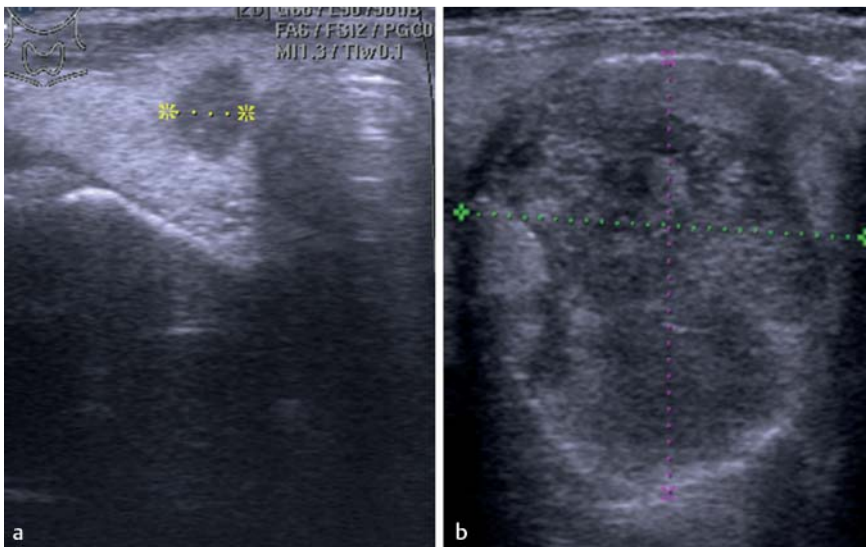


Fig. 3 a Ultrasound results for thyroid carcinoma, PTC with a size of 10 mm (maximum diameter). Shape: ttw, contour: irregular, structure: homogeneous, echogenicity: hypoechoogenic, calcification: no. b Ultrasound results for thyroid carcinoma, FTC with a size of 59 mm (maximum diameter). Shape: oval, contour: irregular, structure: inhomogeneous, echogenicity: hypoechoogenic, calcification: no.

Table 1 Manifestation frequency of ultrasound characteristics of PTC, FTC und CON (in percent) as well as significance values p.

	PTC	FTC	CON	PTC vs FTC P	PTC vs CON P	FTC vs CON P
shape				<0.001	<0.001	=0.001
- round	39	24	34			
- oval	36	64	53			
- irregular	14	8	13			
- TTW	11	4	0			
contour				<0.001	<0.001	<0.001
- smooth	47	24	74			
- irregular	53	76	26			
internal structure				<0.001	=0.84	<0.001
- homogeneous	43	12	42			
- inhomogeneous	57	88	58			
echogenicity				=0.035	<0.001	<0.001
- hypoechoogenic	82	72	24			
- hyperechoogenic	13	24	76			
- empty/cystic	5	4	0			
calcifications				=0.37	<0.001	<0.001
- present	32	28	8			
- not present	68	72	92			

documented an incidence rate increase of PTC diagnoses from 2.7 per 100,000 in 1973 to 7.7 per 100,000 in 2002 [2]. There are no uniform epidemiological data with respect to the incidence of FTC. A current study showed an increase in the USA of 30% between 1980 and 2009 for occurrences of FTC [11]. In all age groups, FTC appeared more frequently among women. On the whole, men were less frequently affected. However, in the male population the increase in incidence was primarily in advanced age.

In our study, the average age of patients with FTC was greater compared to patients with PTC, the age classes were shifted upward and the proportion of women was lower; however none of these parameters reached a level of statistical significance. Higher age and lower percentage of women among patients with FTC compared to patients with PTC could be likewise be demonstrated. In a study originating

Table 2 Values of the incremental regression analysis of r and p taking into account size, contour, echogenicity and calcifications (column a) as well as the exclusion of size (column b).

	a		b	
	r	p	r	p
size	0.57	<0.001	-	-
contour	0.57	=0.013	0.50	0.043
echogenicity	0.57	<0.001	0.50	<0.001
calcifications	0.57	=0.002	0.50	=0.002

Table 3 Manifestation frequency of ultrasound characteristics of PTCo, FTC und CON (in percent) as well as significance values p.

	PTCo	FTC	CON	PTCo vs FTC P	PTCo vs CON P	FTC vs CON P
shape				<0.001	<0.001	=0.002
- round	21	24	34			
- oval	28	64	53			
- irregular	34	8	13			
- TTW	17	4	0			
contour				=0.086	<0.001	<0.001
- smooth	28	24	74			
- irregular	72	76	26			
internal structure				<0.001	<0.001	<0.001
- homogeneous	24	12	42			
- inhomogeneous	76	88	58			
echogenicity				=0.003	<0.001	<0.001
- hypoechoogenic	72	72	24			
- hyperechoogenic	17	24	76			
- empty/cystic	10	4	0			
calcifications				<0.001	<0.001	<0.001
- present	52	28	8			
- not present	48	72	92			

in Würzburg, Germany, both parameters achieved a level of significance [12].

Among our patients, the size of the FTC tumors was larger on average than the PTC tumors. This finding has been confirmed by other investigations. Data from the National Can-

cer Institute's Surveillance Epidemiology and End Results (SEER) program indicate a significantly higher proportion of larger tumors among FTC patients compared to PTC patients [13]. In their study, Verburg et al. could likewise demonstrate that at the time of diagnosis, patients with PTC exhibited larger tumors compared to patients with FTC. (FTC: average approx. 32 mm; PTC: approx. 19 mm) [12]. However, this study showed a greater percentage of multifocal carcinomas among FTC patients. We were not able to confirm these findings using our data. Among patients we examined, multifocality was indisputably statistically significant in the case of PTC.

A comparison of the size of PTCs, FTCs and CONs in our study demonstrates that PTC tumors are on average smaller than among the FTC and CON groups. There was likewise a statistical difference between the FTC and CON groups, even though the largest follicular adenoma was almost the size of the largest follicular carcinoma.

Papillary microcarcinomas were frequently found in operated thyroids. The publication by Davies et al. [2] notes that papillary carcinomas below 2 cm in size, including papillary microcarcinomas, essentially explain the increase in the incidence of differentiated thyroid cancers.

In our investigation, the portion of patients with papillary microcarcinomas (i.e. tumors ≥ 10 mm) was 57%. This explains the smaller number of smaller PTC tumors on average compared to FTC tumors.

Excluding papillary microcarcinomas in the statistical size calculation, it can be demonstrated that FTC tumors are significantly larger than PTC tumors at the time of surgery. However, there would no longer be a difference between PTC tumors and follicular adenomas that functioned as controls in our study.

A number of factors are taken into consideration for the geographical and biographical differences in the different stages. In addition to genetic factors [14], nutritional reasons, among others, play a role [15]. In this context, there is an association of FTC with a lack of dietary iodine [15].

In a recently published study of 4955 patients and 7348 assessed thyroid nodules, it was shown that there is not a linear association of increasing nodule size and malignancy risk [16]. In addition, the authors found that with increased nodule size, the percentage of PTC decreased compared to FTC. In this study, the percentage of PTC with a nodule size up to 19 mm was 92%; only 74% had a nodule greater than 4 cm. In contrast to our study, other sonographic criteria were not included for the differentiated thyroid cancers.

Moleculargenetic analyses indicate that specific genetic changes are associated with both subtypes of differentiated thyroid cancer. In cases of PTC, BRAF as well as modified RET/PTC and trc oncogenes could be verified, whereas in cases of FTC, PAX8/PPAR γ rearrangements and RAS mutations could be found [14].

Whether FTC develops directly from follicular thyroid cells or from follicular adenomas is still a matter of scientific controversy [14, 17]. In addition to the described mutations, epigenetic factors leading to gene activation or deactivation may play a role in the development of differentiated thyroid cancer and are co-determinants of the phenotypical ap-

pearance of PTC and FTC tumors [18]. These phenotypical manifestations are reflected in the ultrasound characteristics of the thyroid carcinomas.

Popowicz et al. recently emphasized that hypoechogenicity, a TTW sign and verification of microcalcification represent independent risk factors for the presence of thyroid cancer [19]. Although this study distinguished between the sonographic manifestation of small and large nodules (cutoff 15 mm), it did not distinguish between PTC and FTC however. Our study showed that PTC and FTC exhibited hypoechogenicity in approx. 70–80% of cases, but a TTW sign in only 4–11% of cases and microcalcification in approx. 30% of cases. With respect to manifestation differences between PTC and FTC, structure, in addition to size, was the best indicator: only 12% of FTC cases exhibited a homogeneous internal structure, but 88% showed a partially pronounced inhomogeneous internal structure. Among the PTC cases, this was 43% and 57% respectively.

However, regarding structure, it must be kept in mind that this does not represent a reliable criterion to distinguish between the PTC and CON groups, if papillary microcarcinomas must be taken into account. If we exclude papillary microcarcinomas from consideration, then structure – seen statistically – remains a differentiation criterion within the three investigated groups.

It is interesting to note that in the entire group of PTC and FTC cases, there was no distinction with respect to the presence of calcification. However, if papillary microcarcinomas are excluded, PTC more frequently exhibits calcification than FTC. In contrast, calcification was less frequently detected in follicular adenomas.

This study contains several limitations. This concerns first of all the retrospective evaluation and the selection of patients involved. Only those patients for whom we had a histological finding could be assessed. Although we carefully correlated histologically defined carcinomas to corresponding nodules in the ultrasound examinations, a false correlation cannot be excluded in every instance.

Because the histological findings were made in different facilities, there was no standardization. Consequently there was, for example, no data regarding histological grading for the FTC cases.

Since in our study, assessment was performed retrospectively, and power Doppler or color-coded Doppler ultrasound results were not available for all malignant or benign nodules, we did not consider nodule perfusion as a criterion. Consequently, our study could not classify nodules detected during the ultrasound examination following a TIRADS breakdown, since perfusion behavior is a component of this classification method [20].

Since the study in which the TIRADS classification was initially suggested, no differentiation was made between perfusion behavior of PTC and FTC, it would be useful to examine this criterion in a future study.

Although the values of the sonographic characteristics of the PTCs and FTCs greatly overlap, the investigator should keep the differences in mind in order to control an adequate management process. A risk-adapted FNAP should be an integral part of the diagnostic evaluation of steadily increasing differentiated thyroid carcinomas [21, 22].

Clinical Relevance

- ▶ Papillary and follicular thyroid cancers exhibit differing ultrasound characteristics, although there is occasionally significant overlap.
- ▶ At the time of surgery, follicular tumors are significantly larger in ultrasound examination compared to papillary thyroid tumors.
- ▶ The reasons for these different size manifestations have not yet been clearly defined and can, for example, be due to a malignant transformation of a follicular adenoma or difficult histological detection of malignancy in small FTC tumors.
- ▶ In ultrasound examinations, papillary and follicular thyroid cancers are distinguished by criteria pertaining to shape, contour, structure and echogenicity. These distinctions are significant for a risk-adapted diagnostic assessment.
- ▶ A “taller-than-wide” sign is an indication of malignancy. However, this sign is found among relatively few differentiated thyroid cancers.

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