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REVIEW ARTICLE

# Ultrasound Imaging of Cervical Anatomic Variants

Michael Cordes[1,2,*], Stephan Coerper[3], Torsten Kuwert[2] and Christian Schmidkonz[2]

[1]Radiologisch-Nuklearmedizinisches Zentrum, Nürnberg, Germany; [2]Nuklearmedizinische Klinik, Universitätsklinikum Erlangen, Germany; [3]Klinik für Chirurgie, Martha-Maria-Krankenhaus, Nürnberg, Germany

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**Abstract:** Embryologic developmental variants of the thyroid and parathyroid glands may cause cervical anomalies that are detectable in ultrasound examinations of the neck. For some of these developmental variants, molecular genetic factors have been identified. Ultrasound, as the first-line imaging procedure, has proven useful in detecting clinically relevant anatomic variants. The aim of this article was to systematically summarize the ultrasound characteristics of developmental variants of the thyroid and parathyroid glands as well as ectopic thymus and neck cysts. Quantitative measures were developed based on our findings and the respective literature. Developmental anomalies frequently manifest as cysts that can be detected by cervical ultrasound examinations. Median neck cysts are the most common congenital cervical cystic lesions, with a reported prevalence of 7% in the general population. Besides cystic malformations, developmental anomalies may appear as ectopic or dystopic tissue. Ectopic thyroid tissue is observed in the midline of the neck in most patients and has a prevalence of 1/100,000 to 1/300,000. Lingual thyroid accounts for 90% of cases of ectopic thyroid tissue. Zuckerkandl tubercles (ZTs) have been detected in 55% of all thyroid lobes. Prominent ZTs are frequently observed in thyroid lobes affected by autoimmune thyroiditis compared with normal lobes or nodular lobes (P = 0.006). The correct interpretation of the ultrasound characteristics of these variants is essential to establish the clinical diagnosis. In the preoperative assessment, the identification of these cervical anomalies *via* ultrasound examination is indispensable.

**Keywords:** Cervical anomalies, cervical cysts, thyroid anomalies, parathyroid gland anomalies, cervical ultrasound, zuckerkandl tubercles (ZTs).

## 1. INTRODUCTION

### 1.1. Anatomical Aspects of Normal Thyroid and Parathyroid Glands

According to recent investigations, the thyroid gland varies markedly in size and structure [1]. Several factors, such as sex, iodine deficiency, and ethnicity, have some influence on the size of the normal gland. From autopsy studies, the mean volume of the gland has been calculated to be approximately 12 mL in adults, with some variation [2]. However, *in vivo* examinations of the thyroid gland by ultrasound volumetry can yield higher normal values. Extensive international surveys showed normal thyroid volumes between 3 to 20 mL with mean values of approximately 8 to 15 mL for young adults [3-5]. A correlation of thyroid volume with body surface in adults and with age in children was described [4].

The presence of a pyramidal lobe has been found to be variable. It has been described in about 50% of autopsy cases with a mean length of 2.3 cm [2]. The apex of the pyramidal lobe is frequently attached to the hyoid bone. The presence of a pyramidal lobe seems to correlate with a levator glandulae thyroideae [6]. The pyramidal lobe may originate from the isthmus or the junction of the isthmus with the right or left lobe.

In more than 90% of people, the isthmus overlies the trachea at the level from the inferior rim of the cricoid to the fifth tracheal ring. However, in some autopsy investigations, the isthmus is absent in up to 30% of the individuals [7].

In most people, four parathyroid glands are present. About 2% to 3% of individuals develop supernumerary glands, and only a minority of people develop a total of five to six glands [8]. Most of the cranial parathyroid glands are located at the cricothyroid junction posteriorly. In this position, the glands lie in close proximity to the recurrent laryngeal nerve and the adjacent vascular branches. In some cases, the cranial parathyroid glands are found in the retropharyngeal or retroesophageal space.

With respect to their position, the caudal glands show a higher degree of variation [8]. The parathyroid glands may also be found in other positions, such as in the lower neck within the thymic tongue, inside the thymus, below the sternal notch, or within the mediastinum.

For a single parathyroid gland, a minimum diameter of 1 mm and a maximum diameter of 12 mm have been found. The shape of the glands shows a wide spectrum. In terms of appearance, connotations such as spherical, oval, rod-like, teardrop-like, and leaf-like have been used [8].

*Address correspondence to this author at the Radiologisch-Nuklearmedizinisches Zentrum, Nürnberg, Germany; Tel: +49 911 58 60 148; E-mail: michael.cordes@rpnl.de

## 1.2. Embryology of the Thyroid and Parathyroid Glands

The embryonic thyroid gland develops from two anlages. The larger medial part arises from the tuberculum impar at the pharyngeal floor. The embryologic development has been described in detail elsewhere [9, 10]. The organogenesis begins on day 20 of gestation and extends over some weeks. Endogenous thyroid hormone synthesis usually becomes apparent on or after the 11th week of gestation.

Several genes have been found to regulate thyroid development (Table **1**). Mutations or inactivations of these and other genes may result in developmental disorders of the thyroid gland. For instance, deficiency in Fgf10 and Fgfr2b has been reported to cause athyreosis in mice [11, 12].

**Table 1. Selected genes involved in embryonic thyroid gland development.**

| Gene | Abbreviation |
|---|---|
| thyroidal peroxidase | TPO |
| three four transferase 1 | Tft1 |
| paired box 2, 5, 8 | Pax2, 5, 8 |
| forkhead box E4 | FoxE4 |
| fibroblast growth factor 2, 8, 10 | Fgf 2, 8, 10 |
| fibroblast growth factor receptor 2b | Fgfr2b |

During embryonic development, malformations of the thyroid gland have been identified. The most severe malformations represent athyreosis. Minor malformations become evident as hypoplasia or ectopic glands, such as a sublingual thyroid organ.

With respect to the parafollicular cells (C cells), recent investigations have identified the anterior endoderm as the only source of differentiated C cells [13, 14].

The primordial parathyroid glands originate from the third and fourth pharyngeal pouch bilaterally. It has been acknowledged that the development of the parathyroid glands is closely linked to the development of the thymus since the third and fourth pharyngeal pouches also represent the origin of the thymus.

In analogy to the evolution of the thyroid gland, active genes play a crucial role in achieving the undisturbed organogenesis of the parathyroid glands (Table **2**). For instance, mutation of the Pth gene may cause primary hypoparathyroidism [15].

**Table 2. Selected genes involved in embryonic parathyroid gland development.**

| Gene | Abbreviation |
|---|---|
| parathormone | PTH |
| glutamyl aminotransferase subunit A | GATA3 |
| glial cells missing homolog 2 | Gcm2 |
| sex determining region y box 3 | Sox3 |

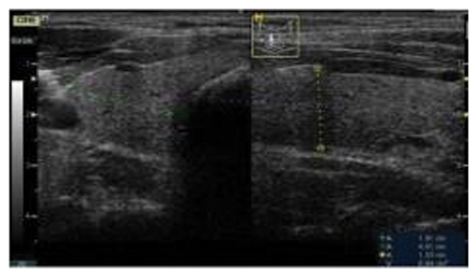
## 1.3. Ultrasound Findings in Developmental Anomalies of the Thyroid and Parathyroid Glands

### *1.3.1. Thyroid Agenesis and Hypoplasia*

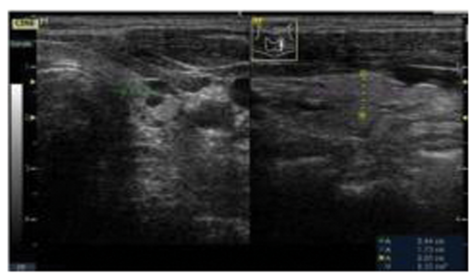
Thyroid agenesis and hypoplasia occur as congenital disorders. In this context, the whole gland or a single lobe may be affected [16]. In patients with thyroid hemiagenesis, the remaining lobe may be affected by a variety of disorders. In a recent study, hemiagenesis had an estimated prevalence of 0.08% and was more frequently observed in females [17]. In that study, the remaining lobe was almost always affected by nodular or autoimmune disorders.

Besides the congenital occurrence, the absence of the thyroid gland or of one lobe may be seen after surgical treatment. Atrophy of the thyroid gland that may mimic hypoplasia or agenesis can be seen as radiogenic atrophy after treatment with radioactive iodine or in the course of chronic inflammation [18].

In our experience, hypoplasia of one thyroid lobe occurs more frequently than aplasia. In ultrasound examinations, the structure of the hypoplastic lobe is not different from the ultrasound appearance of a normal-sized lobe (Fig. **1**).



**(a)**



**(b)**

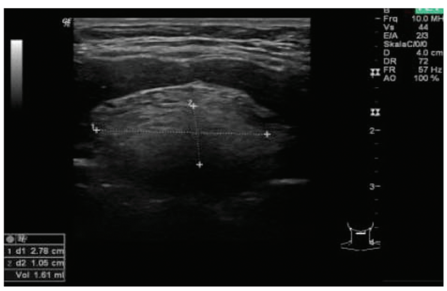
**Fig. (1).** Hypoplastic thyroid lobe in a male patient aged 47 years. **a)**: Normal-sized right lobe (volume approximately 6.8 mL). **b)**: Hypoplastic left lobe (volume approx. 0.3 mL). Both lobes are shown in transverse and longitudinal directions. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Surgical remarks: The results of preoperative ultrasound examinations are essential for the planning of an appropriate intraoperative strategy. Nowadays, the surgical procedure strongly depends on an accurate preoperative ultrasound. In order to preserve healthy thyroid tissue, the preoperative ultrasound findings are useful in determining whether thyroidectomy, hemithyroidectomy or subtotal or nearly total thyroidectomy may optimally be performed [19].

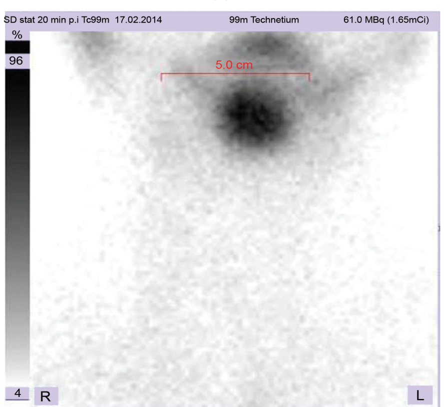
The presence of a pyramidal lobe is often missed on scintigraphy but can be demonstrated by ultrasound. The knowledge of a pyramidal lobe is important, particularly in thyroid surgery for Graves' disease that involves the removal of this additional lobe [20].

### *1.3.2. Ectopic Thyroid Tissue*

Due to the developmental descent, ectopic thyroid tissue may be found along the axis from the base of the tongue to the pretracheal region. Most cases of ectopic thyroid tissue are reported to be observed in the midline of the neck [21], and it has a prevalence of 1/100,000 to 1/300,000. Lingual thyroid accounts for 90% of cases of ectopic thyroid tissue [22]. Women are more affected than men. In 75% of the cases, an orthotopic thyroid gland is absent. Most of the patients with hypothyroidism need levothyroxine replacement therapy. Some patients suffer from oropharyngeal obstruction. Ultrasound examinations show the absence of orthotopic thyroid tissue in most cases [23]. Depending on the size of the lingual thyroid, a mass-like lesion can be depicted posteriorly to the hyoid bone by ultrasound in some patients (Fig. **2**).




(a)




(b)

**Fig. (2).** Lingual thyroid in a 15 year old female patient. **a)** The ultrasound examination in transverse direction demonstrates a sublingual mass with an echogenicity equal to thyroid tissue. **b)** The thyroid scintigraphy using 99mTechnetium-pertechnetate reveals a tracer uptake in the sublingual region and thus confirms the lingual thyroid.

### *1.3.3. Zuckerkandl Tubercle*

The Zuckerkandl tubercle (ZT) is an anatomical feature that is also called the posterior process of the thyroid gland. The tubercle arises from the lateral anlages, which become the posterior and lateral parts of the thyroid gland (see Embryology of the Thyroid and Parathyroid Glands). Anatomically, a constant relationship between the recurrent nerve and the ZT has been identified [9]. The ZT is a feature of all thyroid glands. However, the size and shape of the tubercle show considerable variations. Therefore, a grading system with respect to the size of the tubercle has been suggested [24]. In this system, grade 0 represents an unrecognizable tubercle, grade 1 represents only a thickening of the lateral edge of the thyroid lobe, grade 2 represents a tubercle smaller than 1 cm, and grade 3 represents a tubercle larger than 1 cm.

In the diagnostic workup of thyroid disorders, ultrasound examinations may be considered the first-line imaging procedure. Unfortunately, there are no specific scientific reports on ultrasound findings of the ZT. Therefore, we evaluated our data on this anatomical feature.

This evaluation comprised 100 consecutive cervical ultrasound examinations in individuals between 15 and 81 years (males, 17; females, 83). The ultrasound examinations revealed normal thyroid glands (n = 31), autoimmune thyroiditis (n = 29), or nodular goiters (n = 40). All ultrasound examinations were performed with high-resolution longitudinal probes at 12 MHz. Standard longitudinal and transverse sections were performed and stored digitally in a picture and archiving communicating system (PACS). The images were read by a single physician with extensive experience in thyroid ultrasound examinations.

The presence of ZTs in the 200 thyroid lobes of the 100 individuals was graded according to Pelizzo *et al.* [24]. In total, we found that 55% of all thyroid lobes had a ZT. ZTs were more frequently detected in the right lobe than in the left lobe (59% versus 41%).

Interestingly, in our evaluation, grade 3 ZTs were more frequently observed in thyroid lobes affected by autoimmune thyroiditis compared with normal lobes or nodular lobes (P = 0.006, H-test). The distribution of the ZT grades with respect to lobular morphology is shown in Fig. (**3**).

Lee *et al.* [25] identified ZTs in 70% of patients who underwent computed tomography examinations of the neck. The tubercle frequency was higher in right lobes (89%) than in left lobes (73%).

The number of surgically identified tubercles varies greatly. Page *et al.* [26] reported that ZTs were found in 7% of 79 patients undergoing thyroid surgery. The authors emphasized that only grade 3 ZTs were subjected to surgical identification. Specifically, large nodular goiters that involve the posterior aspect of the thyroid gland may lead to a prominent tubercle. However, in other series, ZTs have been surgically found in up to 55% of cases [27].

Surgical remarks: The ZT is preoperatively diagnosed in very few patients. From a surgical perspective, knowledge of a ZT might be important because the tubercle overlaps the course of the recurrent laryngeal nerve, and the nerve is often adherent to the thyroidal tissue. The intraoperative

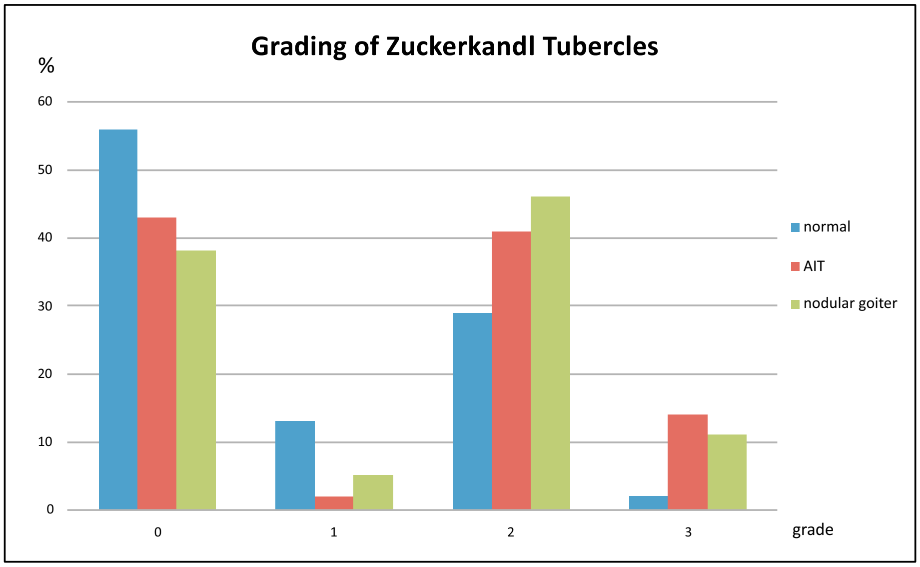



**Fig. (3).** Grading of Zuckerkandl Tubercles. Grade 0 represents an unrecognizable tubercle, grade 1 represents only a thickening of the lateral edge of the thyroid lobe, grade 2 represents tubercle smaller than 1 cm, and grade 3 represents larger than 1 cm in normal thyroid glands (blue columns), autoimmunethyroiditis (AIT) (red columns) and nodular goiters (green columns). (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

strategy must take this situation into account because the careless tearing of the thyroid gland might cause nerve damage. This involves a cautious preparation of the tubercle and neurolysis of the recurrent laryngeal nerve prior to the standard mobilization of the gland.

### 1.4. Ultrasound Findings in Developmental Anomalies of Ectopic Thymus and Neck Cysts

#### *1.4.1. Ectopic Thymus*

Thymus tissue or thymic remnants may be found within the anterior triangle of the neck, the deeper fascial layers, and the thyroid lobes (see Embryology of the Thyroid and Parathyroid Glands) [28]. Two patients with intrathyroidal thymus tissue were first described in 1937 [29]. In two recent ultrasound studies, pediatric patients were examined with respect to intrathyroidal thymic tissue. Bang *et al.* [30] found lesions consistent with ectopic thymus tissue in 16 of 690 patients (2.3%). In 15 of these patients, the ectopic tissue was located within the thyroid lobes. In the study by Kabaalioglu *et al.* [31], 3.9% of the pediatric patients had lesions that were consistent with intrathyroidal ectopic thymus tissue. However, one limitation of these studies is that the ultrasound findings were not confirmed by histology.

Intrathyroidal thymic tissue has been reported to be characterized as fusiform in longitudinal ultrasound orientations and as nodular in transverse orientations. The borders have been found to be well-defined but slightly irregular. The lesions may appear hypoechoic with punctate internal echoes. The sizes of the lesions vary from a few millimeters to approximately 2 cm in pediatric patients (Fig. **4**) [30].

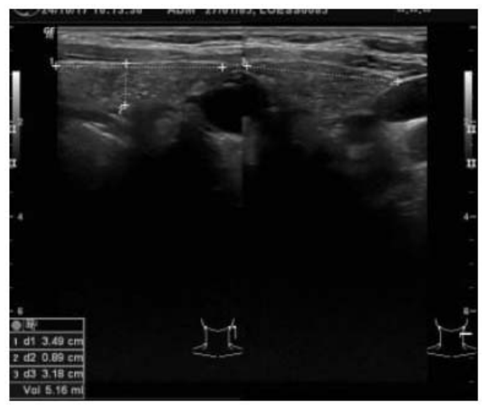



**Fig. (4).** Ectopic thymus tissue adjacent to the left thyroid lobe in a 33 year old female patient. The ultrasound image in transverse and longitudinal directions shows slightly isoechogenic tissue with punctuate hyperdense lesions (histologically confirmed). (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Histologically, it is of some interest that oxyphilic aggregates are found in thymic tissue. These aggregates comprise degenerated reticular cells and are termed Hassall's bodies. They can demonstrate punctate calcifications. In cases of intrathyroidal thymic tissue, these calcifications may mimic psammoma bodies and may be mistaken for papillary thyroid carcinomas [32].

#### *1.4.2. Neck Cysts*

Neck cysts have a low prevalence in patients with neck tumors who undergo surgery. Bula *et al.* found neck cysts in only 0.2% of more than 17,000 operated patients [33]. About two-thirds represented median cysts of the neck, and one-third were lateral cysts.

### *1.4.3. Median Neck Cysts*

Cystic remnants of the thyroglossal duct appear as median cysts of the neck [28]. Median neck cysts are the most common congenital cervical cystic lesions. A prevalence of 7% has been reported in the general population [34]. These median neck cysts can vary in size, with diameters ranging from millimeters to centimeters.

Approximately 60% of these cysts are located between the thyroid gland and the hyoid bone, and 40% of these lesions may be detected cranially from the hyoid bone [35]. Histologically, the cysts demonstrate a capsule of epithelial cells and are filled with serous fluid. Debris and blood components may accumulate within the cysts. Complications such as inflammation or malignant transformation have been recognized in rare cases [36].

The ultrasound appearance shows a lesion with thin walls and an anechoic central component (Fig. **5**). Occasionally, internal debris can be depicted as echogenic complexes [23]. Internal debris can sometimes be visualized as punctate hyperechogenic spots. Thickening of the capsule and septations may indicate acute or remote infections of the cyst [37].

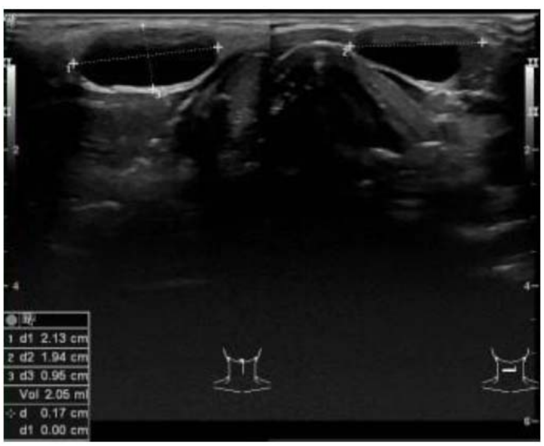



**Fig. (5).** Median neck cyst in a 32 year old female patient. The median neck cyst is depicted in the longitudinal and transverse direction. The cyst has a volume of 2mL and lies in the ventral and lateral position of the trachea. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

**Table 3. Bailey´s classification of 2nd branchial cleft cysts.**

| Type | Characterization |
|---|---|
| I | Superficial location. Between anterior margin of the sternocleidomastoid muscle and platysm. |
| II | Lateral to the carotid artery and medial to the sternocleidomastoid muscle, posterior of the submandibular gland. |
| III | Medially between carotid bifurcation and lateral wall of the pharynx. |
| IV | Within pharyngeal mucosal space. |

### *1.4.4. Lateral Neck Cysts*

Lateral cysts of the neck arise from the pharyngeal clefts. They are congenital in origin. However, these cysts usually appear clinically between the second and fourth decades [38]. Approximately 90% of lateral neck cysts are derived from the second branchial cleft. A classification of the second branchial cleft cysts was suggested in early work (Table **3**) [39]. It has been argued that this classification should be superseded by an individual description of the size and location of the lesion [40].

In ultrasound examinations, lateral neck cysts appear as spheric or ellipsoid anechoic or hypoechoic lesions. Ahuja *et al.* [41] have reported that 12% of neck cysts can be hyperechoic in ultrasound studies and that 24% show septa and internal debris. In their series, the cysts had maximum diameters of 17 to 53 mm. In cysts with inflammatory reactions, wall thickening may be detected. Depending on the size of the cysts, displacement of the sternocleidomastoid muscle or the carotid artery may be present.

The differential diagnosis of lateral neck cysts comprises a broad spectrum of neck disorders. The differential diagnosis may be subdivided into inflammatory and non-inflammatory lesions. Inflammatory lesions can be encountered as lymphadenitis (viral, bacterial, or tuberculous) or thrombophlebitis. Non-inflammatory lesions of the lateral neck include congenital disorders (cystic hygromas or external laryngoceles) and both benign (lipomas and dermoids) and malignant tumors (lymphomas, lymph node metastases, and sarcomas) [40].

## 2. CURRENT LIMITATIONS AND FUTURE DIRECTIONS

Ectopic tissues of the thyroid gland, the parathyroid glands, and the thymus may be located in retrotracheal, retroesophageal, or retrosternal positions. Ectopic tissues in these anatomic regions are frequently not detectable by the use of ultrasound imaging modalities. Therefore, the detection of ectopic tissues in these anatomical localisations represents a current limitation of ultrasound imaging.

The association of cervical anatomical variants with hormonal or metabolic dysfunctions should be the subject for further research. Molecular genetic studies might be useful to elucidate potential relationships of anatomical variants as an indicator for endocrine imbalances.

## CONCLUSION

Embryologic developmental variants of the thyroid and parathyroid glands may cause cervical anomalies that are detectable in ultrasound examinations of the neck. For some of these developmental variants, molecular genetic factors have been identified. Ultrasound, as the first-line imaging procedure, has proven useful in detecting clinically relevant anatomic variants. The correct interpretation of the ultrasound characteristics of these variants is essential to establish the clinical diagnosis. In the preoperative assessment, the identification of these cervical anomalies by ultrasound examinations is considered indispensable.

## CONSENT FOR PUBLICATION

Not applicable.

## FUNDING

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## CONFLICT OF INTEREST

Dr. Kuwert receives honoraria from Siemens Healthineers for occasional lectures. The Clinic of Nuclear Medicine in Erlangen has research cooperation with that company in the field of SPECT/CT.

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