A retrospective review of the role of B-mode and color Doppler ultrasonography in the investigation of primary hyperparathyroidism: Features that differentiate benign from malignant lesions

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Abstract

Purpose: To identify the variant features encountered in parathyroid abnormalities and document those suggesting malignant change.

Materials and methods: Data were collected from a cohort of patients who underwent investigation for primary hyperparathyroidism over a 10-year period. Ultrasonographic features: shape, presence of calcification, cystic changes, heterogeneous echogenicity, vascularity, capsular thickening, local invasion, and vascularity were reviewed retrospectively and were used to correlate with final histological findings.

Results: One hundred forty-seven patients with histology and concurrent ultrasonographic scans were reviewed, and divided into benign parathyroid lesions (nodular hyperplasia ($n=44$), adenoma ($n=93$)) and parathyroid carcinoma ($n=10$). Parathyroid carcinomas were significantly larger than benign parathyroid lesions ($P=0.030$). Benign parathyroid lesions showed variant sonographic features: irregular shape (16.8%), heterogeneous echogenicity (24.1%), calcification (1.5%), capsular thickening (1.5%), and cystic change (19.7%). A significantly higher proportion of parathyroid carcinomas demonstrated heterogeneous echogenicity ($P=0.022$), capsular thickening ($P=0.023$), and infiltrative margin ($P<0.0001$) than benign parathyroid lesions. Of the 137 benign parathyroid lesions, 38 (27.7%), 76 (55.5%), 23 (16.8%) were avascular, vascular, and hypervascular, respectively. Of the 10 parathyroid carcinomas, 4 (40%), 3 (30%), and 3 (30%) of lesions were avascular, vascular, and hypervascular, respectively. The vascularity of the lesions did not differ significantly between the parathyroid carcinoma and benign parathyroid lesions ($P=0.281$).

Conclusion: Ultrasonographic features such as irregular shape, heterogeneous echogenicity, cystic change, and vascularity are nondiscriminatory features between benign or malignant lesions. Large lesion size together with the presence of calcification, capsular thickening, or infiltrative margin strongly raises the suspicion of a malignant parathyroid lesion, and management should be altered.

Keywords

Color Doppler, parathyroid adenoma, parathyroid carcinoma, primary hyperparathyroidism, sonography, ultrasound

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Introduction

Primary hyperparathyroidism is a relatively uncommon clinical presentation accounting for approximately 0.4% of the population in Western countries.¹ Parathyroid adenoma and hyperplasia contribute to approximately 85% and 15–20% of presentation with hyperparathyroidism, respectively.^{2,3} Parathyroid carcinoma is a rare disease, accounting for less than 1% of the primary hyperparathyroidism⁴ with an annual incidence of less than 1 per million.⁵ The diagnosis of parathyroid carcinoma remains challenging for several reasons. Firstly, parathyroid carcinoma has a broad spectrum of clinical presentation overlapping with benign diseases. Secondly, biochemical markers such as serum calcium and parathyroid hormone (PTH) level are not discriminatory.⁶ Although patients with parathyroid carcinoma tend to have higher levels of serum calcium and PTH, patients with benign pathology may also present with elevated levels of calcium and PTH.⁷ Thirdly, pre-operative diagnosis with ultrasonography (US) is often challenging due to lack of specific features to differentiate benign from malignant lesions. The role of pre-operative US has been traditionally limited to localization but not characterizing the parathyroid lesion.

Diagnosis of parathyroid carcinoma requires the presence of vascular or capsular invasion following pathological examination of the surgical specimen.⁸ Unlike thyroid lesions, both benign and malignant parathyroid lesions require surgery. However, treatment for benign parathyroid lesions differ from parathyroid carcinoma in that minimally invasive surgery often suffices in adenomas and hyperplasia whilst radical neck surgery is required to treat carcinoma.^{9–11} Critically, the prognosis of parathyroid carcinoma depends on the removal of the whole lesion as well as nodal clearance at the first surgical procedure. Therefore, it would be advantageous to raise suspicion of a malignant parathyroid lesion prior to surgery, allowing appropriate surgical planning and, importantly, advising the patient of the consequences of more radical surgery. A number of case reports and small case series have investigated US features that aid identification of parathyroid carcinoma which includes irregular shape, heterogeneity, presence of intra-lesional calcification, cystic change, capsular thickening, infiltration, and unique color Doppler US features. Descriptive US features of malignant parathyroid lesions in the literature are inconsistent, making interpretation in the clinical setting problematic.¹²

A prior study with a cohort of 67 patients investigated ultrasound features of parathyroid carcinoma by comparing them with parathyroid adenoma and gland hyperplasia in lesions > 15 mm found features such as infiltration, calcification, capsular thickening, and

lesions inhomogeneity are useful discriminatory features.¹² The aim of this study is to identify all the variant US imaging patterns that are encountered in both benign and malignant parathyroid abnormalities regardless of their sizes, document those that are associated with malignant change, and identify the features that consistently distinguish malignant from benign parathyroid abnormalities in a much larger patient cohort.

Materials and methods

The study was performed following local ethical committee approval to report this cohort of patients. The US examination was part of routine clinical care. Verbal consent was obtained from all patients.

Study population

Patients undergoing investigation for primary hyperparathyroidism and subsequently found to have a solitary parathyroid lesion identified on US were retrospectively identified from a local hospital database from 2003 and 2013 at our institution. Patient demographic data (gender and age) and relevant serum calcium and serum PTH levels prior to the surgery were recorded from the patient electronic database.

Ultrasonographic imaging and study review

All the examinations were conducted by two experienced radiologists with over 10 years of experience in parathyroid imaging (PSS and NM) using standard department protocol with patient scanned in a supine position. The grey scale and color Doppler images were acquired using broadband high frequency linear transducers, either with an Acuson Sequoia 512 (Siemens, Mountain View, CA) with a 15L8w transducer or a Siemens S2000 (Siemens, Mountain View, CA) with a 9L4 transducer. All images were recorded and stored on a Picture Archiving and Communication System (PACS) (GE, Barrington, IL) for subsequent review. Retrospective reviews of the imaging characteristics were carried out by three radiology residents with 2–6 years of formal radiology training, not involved in data acquisition, blinded to the histopathology report. The three reviewers reviewed cases together and reached a consensus for each case. Histology reports were reviewed only after a consensus for grey and color Doppler characteristics was reached.

The following features were assessed from a pre-agreed proforma of US features. Lesion location (right or left, upper, or lower) and size were taken from radiology reports and if not available, directly

from the images with the largest single dimension recorded. Grey scale US features including irregular shape (non-oval shape), cystic change, heterogeneity of the lesions (in terms of echogenicity of the solid part of the lesion) intra-lesional calcification (identified as hyperechoic foci with posterior acoustic shadow), capsular thickening (loss of thin echogenic rim), and infiltration (loss of well-defined lesional boarder) were reviewed. The color Doppler characteristics were analyzed using the stored images. The vascularity of the parathyroid lesions were recorded as avascular, vascular, or hypervascular after comparing with the vascularity from the adjacent thyroid parenchyma. Classifying the vascularity into three groups namely avascular, vascular, and hypervascular relative to the adjacent thyroid vascularity allowed for easier interpretation without in-depth pattern analysis, which would be subjective in a retrospective study.

Histological analysis

All surgical specimens were prepared according to standard practice. All parathyroid adenomas, hyperplasia, and parathyroid carcinomas were confirmed on histopathologic examination post-surgical removal by histopathologist as per the standard protocol.

Statistics

The analysis was performed using SPSS version 22 (IBM Corp, Armonk, NY). The variables were first

tested for normality using the Kolmogorov–Smirnova test and median or mean values were calculated accordingly. The median value of the serum calcium, parathyroid hormone level, age of the patient, and size of the lesion were compared between the benign and malignant histology group using Wilcoxon Mann–Whitney test. Comparison of the categorical US features between the benign and malignant groups was performed using the Fisher's exact test or Chi-square test. A statistical significance was recorded if a *P* value was <0.05. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of each sonographic feature were calculated.

Results

In total, there were 147 patients with imaging, biochemical, and histology results, which included 137 benign parathyroid lesions and 10 parathyroid carcinomas. There were 111 female patients and 36 male patients. The demographics and biochemical data of the study cohort are summarized in Table 1. The median age for patients with benign lesions and parathyroid carcinoma were 56 years old (range 10–84 years old) and 57.5 years old (range 32–80 years old), respectively. The median lesion size for benign lesions was 14 mm (range 1–48 mm) and 21 mm (range 8–53 mm) for the parathyroid carcinoma. The median serum calcium level (mMol/L) was 2.74 mMol/L (range 2.00–4.00 mMol/L) for benign lesions and 2.77 mMol/L (range 2.00–4.00 mMol/L) for parathyroid carcinoma.

Table 1. Comparison between demographics and biochemical data of the study cohort

		Median ^a	Range	<i>P</i> value
Serum Calcium (mMol/L)	Parathyroid adenoma/hyperplasia	2.74	2.00–4.00	0.735
	Parathyroid carcinoma	2.77	2.00–4.00	
Parathyroid Hormone (ng/L)	Parathyroid adenoma/hyperplasia	177	10–2000	0.125
	Parathyroid carcinoma	265	13–1599	
Size (mm)	Parathyroid adenoma/hyperplasia	14	1–48	0.03*
	Parathyroid carcinoma	21	8–53	
Age (years)	Parathyroid adenoma/hyperplasia	56	10–84	0.601
	Parathyroid carcinoma	57.5	32–80	
Gender ^a F/M	Parathyroid adenoma/hyperplasia	105/32		0.260
	Parathyroid carcinoma	6/4		

*Significant *P* value.

^aRepresent median values except gender where it represents the number of female versus male.

The median PTH level (ng/L) for benign lesions was 177 ng/L (range 10–2000 ng/L) and 265 ng/L (range 130–1599 ng/L) for parathyroid carcinoma. Age, gender, serum calcium level, PTH level were not significantly different between the benign lesions and parathyroid carcinoma. However, lesion size was significantly larger in parathyroid carcinoma compared to the benign lesions ($P=0.030$).

There were 137 benign parathyroid lesions including 93 parathyroid adenoma and 44 parathyroid hyperplasia. There was no statistically significant differences between the parathyroid adenoma and parathyroid hyperplasia in terms of irregular shape ($P=0.850$), size ($P=0.206$), heterogenous echogenicity ($P=0.549$), cystic change ($P=0.880$), intra-lesional calcification ($P=0.541$), capsular thickening ($P=1.000$), and vascularity pattern ($P=0.666$). The serum PTH and calcium were not significantly different between the adenoma and parathyroid hyperplasia with P values of 0.320 and 0.360, respectively.

Calcification was present in 1.5% ($n=2$) of benign parathyroid lesions, while 10% ($n=1$) of parathyroid carcinoma demonstrated intra-lesional calcification. Cystic changes were present in 19.7% ($n=27$) of benign parathyroid lesions and 30% ($n=3$) of parathyroid carcinoma. Heterogenous echogenicity was present in 24.1% ($n=33$) and 60% ($n=6$) of the benign parathyroid lesions and carcinoma respectively. 1.5% ($n=2$) of benign parathyroid lesions showed features of capsular thickening compared to 20% ($n=2$) of the malignant parathyroid lesions. Definitive evidence of local infiltration on US was seen in 50% ($n=5$) parathyroid carcinoma, but it was not present in either nodular hyperplasia or adenoma. Parathyroid lesions were found to be non-oval/round shape in 16.8% ($n=23$) benign parathyroid lesions compared to 40% ($n=4$) of the parathyroid carcinoma. With the grey scale US features, a significantly higher proportion of parathyroid carcinoma demonstrated features of capsular thickening ($P=0.023$), infiltrative margin ($P<0.0001$), and heterogenous echogenicity ($P=0.022$). However, irregular shape ($P=0.087$), site of the lesion ($P=0.709$), presence of intra-lesional calcification ($P=0.192$), and intra-lesional cystic change ($P=0.333$) were not significantly different between the parathyroid carcinoma and benign parathyroid lesion (Table 2). In benign parathyroid lesions, parathyroid hyperplasia/adenomas were avascular, vascular, and hypervascular in 27.7% ($n=38$), 55.5% ($n=76$), and 16.8% ($n=23$) of the cohort, respectively. The parathyroid carcinomas were avascular, vascular, and hypervascular in 40% ($n=4$), 30% ($n=3$), and 30% ($n=3$) of case, respectively. The vascularity of the lesion did not differ significantly between the parathyroid carcinoma and benign parathyroid lesions ($P=0.281$).

Table 2. Distribution of location and US features among parathyroid adenoma/hyperplasia and carcinomas

	Parathyroid adenoma/hyperplasia ($n=137$)	Parathyroid carcinoma ($n=10$)	P value
Site			0.709
LU	13 [9.5%]	0 [0%]	
LL	61 [44.5%]	4 [40%]	
RU	10 [7.3%]	1 [10%]	
RL	53 [38.7%]	5 [50%]	
Shape			0.087
Oval/round	114 [83.2%]	6 [60%]	
Irregular	23 [16.8%]	4 [40%]	
Echogenicity			0.022*
Homogenous	104 [75.9%]	4 [40%]	
Heterogenous	33 [24.1%]	6 [60%]	
Calcification	2 [1.5%]	1 [10%]	0.192
Capsular thickening	2 [1.5%]	2 [20%]	0.023*
Infiltrative margin	0 [0%]	5 [50%]	<0.0001*
Cystic change	27 [19.7%]	3 [30%]	0.333

LU: left upper; LL: left lower; RU: right upper; RL: right lower.

*Significant P value.

Sensitivity and specificity

The sensitivity, specificity, positive predictive, and negative predictive values of the grey scale features including cystic change, heterogeneity, nonoval/round shape, calcification, capsular thickening, and infiltration are listed in Table 3.

Discussion

We have shown that parathyroid adenoma and parathyroid hyperplasia are indistinguishable sonographically, which is in agreement with a previous study.¹³ Our study confirms the established features of benign parathyroid lesions: oval/round shaped, hypoechoic, and homogenous reflectivity with a median size less than 15 mm¹⁴ (Figure 1). However, we have demonstrated variant US features of both parathyroid adenomas and hyperplasia: larger size, nonoval/round

shape, and lesions demonstrating heterogenous echogenicity (in lipoadenomas)¹⁵ and cystic degeneration,^{16–19} which were not infrequently observed in benign parathyroid pathology with our data demonstrating heterogenous echogenicity (24.1%) being the most frequently observed followed by cystic change

Table 3. Sensitivity and specificity of US features in detecting parathyroid carcinoma

	Sensitivity %	Specificity %	PPV	NPV
Cystic change	30.0	80.3	10.0	94.0
Heterogeneity	60.0	75.9	15.4	96.3
Shape	40.0	83.2	14.8	95.0
Calcification	10.0	98.5	33.3	93.8
Capsular thickening	20.0	98.5	50.0	94.4
Infiltration	50.0	100.0	100.0	96.5

PPV: positive predictive value; NPV: negative predictive value.

(19.7%) nonoval/round shape (16.8%) (Figure 2). All these variant features were also present in our parathyroid carcinoma cohort. This is supported by previously published case reports and case series as summarized by Sidhu et al.¹² In addition, these variant features were more frequently observed in parathyroid carcinoma with observed frequencies from 30% (cystic change) to 60% (heterogenous echogenicity). Our data show a statistically significant higher proportion of parathyroid carcinomas demonstrate heterogenous echogenicity than the benign group ($P=0.022$). Hara et al.²⁰ have shown 16/16 of their parathyroid carcinoma displayed heterogenous echogenicity. However, intralesional cystic change, heterogenous echogenicity, and irregular shape were neither specific nor sensitive enough to allow a confident diagnosis of parathyroid carcinoma.

Other variant features including intra-lesional calcification, capsular thickening, and infiltrative margin were present in 10%, 20%, and 50% of the parathyroid carcinoma cohort respectively (Figure 3) compared to 1.5%, 1.5%, and 0% of the benign group which was statistically significant for capsular thickening ($P=0.023$) and presence of infiltrative margin ($P<0.0001$). They demonstrated a specificity of

Figure 1. Typical parathyroid adenoma (arrows) with small size, oval shape, hypoechoic reflectivity, and well-defined border.

Figure 2. Variant features of parathyroid adenoma including lobulated margin (between cursors, arrow) (a), intra-lesional cystic change (arrows) (b), and hyper/iso-echoic reflectivity (arrows) (c).

Figure 3. A parathyroid carcinoma demonstrates (a) capsular thickening (long white arrow), intra-lesional calcification (short white arrows) and (b) infiltrative boarder (black arrow).

98.5–100%, which was higher than the frequency of the benign lesions in our data cohort i.e. 93.2% indicating they were unlikely to be associated with benign lesion. However, they showed low sensitivities which indicate that these US features will not detect all parathyroid carcinoma.

The variant features demonstrated in our cohort has also been reported in a cohort of 7 parathyroid carcinomas and 32 adenomas, Nam et al.²¹ noted that the parathyroid carcinomas had heterogeneous echotexture, were of irregular shape, contained intra-nodular calcification, and exhibited local invasion with these features demonstrating a statistically higher proportion within the parathyroid carcinoma group. Our study is in agreement with this, but we did not demonstrate a statically significant higher proportion of parathyroid carcinomas with intra-lesional calcification. In the context of primary hyperparathyroidism, we have confirmed that intra-lesional calcification is a rare event, which were observed only in 2/137 benign lesions.^{12,21} Intra-lesional calcification is suggested to be associated with malignancy due to increased frequency observed in 4/8 and 3/7 patients in previous studies; we have observed only 1/10 parathyroid carcinoma with intra-lesional calcification, and may be likely due to sampling variation of a small cohort size.

Any investigation of the US features to differentiate parathyroid carcinoma from their benign counter parts remains challenging due to the rare incidence of parathyroid carcinoma. Relatively high specificity and negative predictive values of US features can be deceptive due to low incidence of the malignant lesion in the population. Therefore, diagnostically significant specificity would need to be interpreted in conjunction with the incidence of benign lesions.

Although size is not a specific feature, the National Cancer Data Base 2000 review demonstrated

that in a group of 286 confirmed parathyroid cancers the average size was 3.3 cm.²² Sidhu et al.¹² have previously proposed that parathyroid masses larger than 15 mm on US are predictive of parathyroid carcinoma. Our study agrees with the previous studies, which showed malignant parathyroid lesions were statistically larger than their benign counter parts^{12,21} and large tumor size should raise the suspicion of malignancy.

Reports have suggested that the presence of a feeding artery, polar vascularity, and peripheral vascular arch are useful color Doppler US features to aid localization of parathyroid adenoma from a lymph node^{23,24} and the presence of intra-lesional vessels, radial in nature with no clearly demonstrated supplying vessel raises concern for malignancy.¹² However, any retrospective review of parathyroid vascularity is difficult for several reasons. Firstly, often only a limited number of color Doppler US images are recorded and rarely recorded as a cine-loop. Secondly, the accuracy of the color Doppler US assessment often depends on the optimal settings; not always achieved by all operators. We chose to classify the vascularity into three groups namely avascular, vascular, and hypervascular relative to the adjacent thyroid vascularity, which allowed for easier interpretation without in-depth pattern analysis that would be subjective in a retrospective study (Figure 4). From our results, both benign and malignant parathyroid lesions can demonstrate different vascular characteristics ranging from avascular to hypervascular compared to the adjacent thyroid tissue, with no significant difference identified to classify the lesion ($P=0.281$).

Previous studies and case reports have reported remarkable increase in serum ionized calcium and PTH levels in patients with parathyroid carcinoma as compared to that of adenoma.^{7,25} Sidhu et al.¹² have also found significant differences in serum calcium and PTH level between benign and malignant parathyroid

Figure 4. Color Doppler assessment demonstrates an avascular (a), vascular (b), and hypervascular (c) parathyroid adenoma.

lesions over 15 mm. However, our result in this larger cohort showed the serum calcium and PTH levels did not demonstrate significant differences between benign and malignant pathologies. A recent study by Nam et al.²¹ has also demonstrated similar findings.

Many more female patients were assessed in our cohort, consistent with established preponderance of females with parathyroid abnormalities who are three times more likely than males to present with primary hyperparathyroidism.²⁶

There are limitations within our study. This is a retrospective study with two operators. Reviews were from images saved on the PACS system and reports scrutinised for any features of importance. There were a small number of malignant lesions compared with a larger number of benign lesions, reflecting the rarity of malignancy parathyroid lesion, and size mismatch would affect the analysis. Nevertheless, the number of parathyroid carcinomas in the current series represents one of the largest reported in the literature.

In conclusion, none of the sonographic features including irregular shape, cystic change, heterogenous echogenicity, intra-lesional calcification, capsular thickening and infiltrative margin are sensitive enough to identify malignant lesions but are found to be specific for malignancy. Benign lesions will demonstrate increased vascularity, cystic change and may be large. However, in daily clinical practice if a large parathyroid lesion together with the presence of calcification, capsular thickening or infiltrative margin is identified, this strongly raises the suspicion of a malignant parathyroid lesion, and a radical neck surgery should be considered.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Guarantors

CF and PSS.

Contributorship

All authors were involved in the study design, data acquisition, manuscript drafting, approval of final version of submitted manuscript. Data analysis: CF, EK, SB. Manuscript editing: CF, MAH, NJM, KMS, PSS.

Ethics approval

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