RESEARCH COMMUNICATION

Diagnostic Performance of Gray-scale versus Combined Gray-scale with Colour Doppler Ultrasonography in the Diagnosis of Malignancy in Thyroid Nodules

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Abstract

Objective: To compare diagnostic performance of gray-scale ultrasound and combined gray-scale ultrasound with color Doppler ultrasound in predicting malignancy of thyroid nodules by using tissue diagnosis as the reference standard. Design: Diagnostic test with prospective data collection. Materials and Methods: Between November 2007 and October 2008, 31 patients (16 with solitary thyroid nodules and 15 with multiple thyroid nodules) were preoperatively evaluated with gray-scale ultrasound and color Doppler ultrasound. The nodules were classified as benign or malignant according to the established ultrasound criteria and were later compared with histologic findings obtained from surgical specimens. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of gray-scale US and combined gray-scale with color Doppler US were evaluated using histology as the reference. Results: The sensitivity, specificity, PPV and NPV of gray-scale ultrasonography were 80.0%, 84.6%, 50.0% and 95.7%, respectively. The sensitivity, specificity, PPV and NPV of preoperative combined gray-scale US with color Doppler ultrasonography were 40.0%, 96.2%, 66.7% and 89.3%, respectively. Conclusion: Combination of gray-scale US with color Doppler US findings improves specificity and PPV in the diagnosis of malignancy in thyroid nodules.

Key words: Ultrasonography - Doppler - gray-scale/colour - thyroid nodule

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Introduction

Thyroid nodules is very common problems in clinical practice. In general, almost 5% of adult population has a palpable thyroid nodule (Lyshchik et al., 2007). By ultrasonography (US), 10 - 67% of adults have thyroid nodules and nearly 50% of population has thyroid nodules found at autopsy (Frates et al., 2005). However, the prevalence is dramatically increased in the areas of iodine deficiency (Belfiore et al., 1995). Fortunately, the majority of thyroid nodules are benign nodules, less than 5% of them being malignant (Mazzaferri 1993).

Diagnosis of malignancy in patients with thyroid nodules is of paramount importance as it is one of the most curable malignancies. Ideally, diagnostic procedures should be not only of high accuracy but also less invasive. Fine needle aspiration (FNA) for cytology has been considered the most valuable method preoperatively in determining the nature of thyroid nodules. It can save substantial patients having benign condition from unnecessary operations. Furthermore, it can also direct some patients of a high malignant risk to proceed to the operation without delay from investigative procedures.

Although FNA, however, is considered a safe procedure with a high accuracy and low cost, two main disadvantages involve the nondiagnostic results and false negative findings. The nondiagnostic rate even in the centers with high experience may be as high as 15-20% (Gharib and Goellner, 1993). In nondiagnostic FNA patients, the rate of cancer in surgically resected nodules was found to be about 5-9% (Alexander et al., 2002). In addition, the false-negative results, reported in the range of 3-21%, can lead to delayed treatment and compromised prognosis (Wu et al., 2006 ; Yeh et al., 2004).

Presently, high-resolution real-time US not only detects the presence, site, number, and size of thyroid nodules but clearly shows their characteristics (Rago et al., 1998). Compared to FNA, US has the advantage of being non-invasive and giving immediate information. Furthermore, the availability of color Doppler US allows the evaluation of nodular blood flow which may help delineate nature of the nodule. Previous study suggested that intranodular flow or hypervascular central flow on color Doppler US may be associated with malignant nature (Stacul et al., 2007). However, the exact usefulness of this technique in predicting malignancy of thyroid nodules is still controversial (Mazzaferri 1993; Frates MC et al., 2003; Stacul et al., 2007; Papini et al., 2002)

Therefore, we aimed to prospectively evaluate the ability of gray-scale US alone or in combination with color-Doppler US performed preoperatively in predicting malignancy of thyroid nodules.

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Materials and Methods

The study protocol was approved of the Ethics Committee for Human Research, Khon Kaen University and written informed consent was obtained from all patients. Patients with thyroid nodule(s) who presented to the ENT Department at Srinagarind Hospital, Faculty of Medicine, Khon Kaen University were recruited. Upon clinical evaluation by ENT specialist and FNA cytology results, patients who were considered of having risk of thyroid malignancy and were scheduled for thyroid operation during November 2007 - October 2008 were asked to have preoperative gray-scale US and color Doppler US of the thyroid performed on the day before the operation.

One radiologist with ten years of head and neck sonography experience examined sonograms of thyroid glands in a standard manner. Sonography was performed using a 10-MHz (GE® LOGIQ 9) linear-array transducer. The radiologist was blinded to clinical information of the patients. Each thyroid nodule was assessed for its sonographic features on gray-scale technique and its vascularity on color Doppler technique. In patients with multiple thyroid nodules, only the largest nodule found by US was evaluated based on the fact that thyroid cancers in patients with multiple nodules are often found in the dominant or the largest nodule (Frates et al., 2003). These ultrasonographic findings of thyroid nodule were systematically recorded in the diagram for every patients.

For gray-scale US, the nodules were evaluated for its shape, echogenicity, internal content, the presence of spongiform appearance, margin, halo, the presence of calcification and morphology, and the relationship with surrounding tissue.

- Shape of the nodule was categorized as: “wider than tall” (antero-posterior diameter of nodule equal to or less than its transverse diameter on transverse or longitudinal plane) or “taller than wide” (antero-posterior diameter of nodule longer than its transverse diameter on a transverse or longitudinal plane.

- Echogenicity of the nodule was assessed by comparing echogenicity of the nodule with that of thyroid parenchyma and strap muscle, and was classified as “markedly hypoechoic” (nodule showing relatively more hypoechoic than adjacent strap muscle, (Figure 1a), “hypoechoic” (nodule showing relatively more hypoechoic than normal thyroid parenchyma), “isoechoic” (nodule showing isoechoic to normal thyroid parenchyma), or “hyperechoic” (nodule showing relatively more hyperechoic than adjacent normal thyroid parenchyma).

- Internal content of the nodule was categorized according to the ratio of cystic portion to the solid portion in the nodule and was classified as “predominantly solid” (< 50% cystic) or "predominantly cystic" (≥50% cystic). A spongiform appearance was defined as aggregation of multiple microcystic components in more than 50% of the volume of the nodule (Figure 1b).

- Margin of the nodule was categorized as “well-defined margin” or “indistinct margin".

- Discontinuity of peripheral halo sign of the nodule was evaluated.

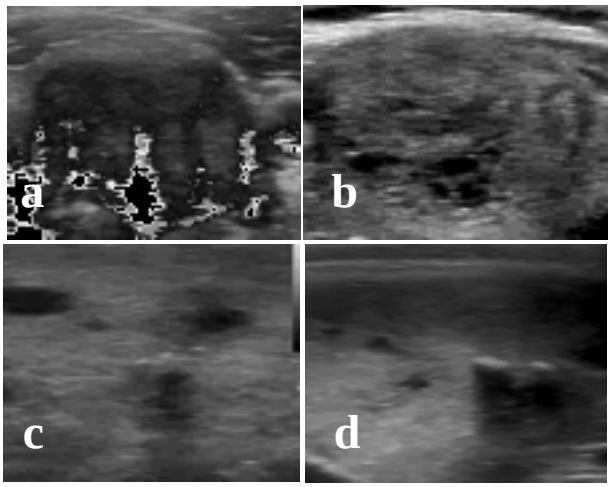

Figure 1. Examples of Findings for Thyroid Nodules by Gray Scale Ultrasonography. a) Marked hypoechogenicity; b) Spongiform appearance; c) Micro-calcification; d) Macrocalcification

- Calcification within the nodule was assessed regarding its size and was classified as “microcalcification” (tiny, punctuate echogenic foci of 1 mm or less either with or without posterior acoustic shadowing, Fig 1c) or “macrocalcification” (punctuate echogenic foci larger than 1 mm in size, Figure 1d).

- Relationship between the nodule and surrounding organ was assessed for evidence of invading adjacent structure, which appears as a subtle extension of tumor beyond the contours of thyroid gland or frank invasion of adjacent structure.

Based on ultrasonographic findings of gray-scale technique, each nodule was classified as being malignant or benign according to the established criteria. Nodules displaying marked hypoechogenicity (Moon et al., 2008), taller than wide (Hoang et al., 2007; Moon et al., 2008), indistinct margin (Papini et al., 2002; Koike et al., 2001; Ito et al., 2005; Hoang et al., 2007; Moon et al., 2008), microcalcification (Rago et al., 1998; Papini et al., 2002; Hoang et al., 2007; Stacul et al., 2007; Moon et al., 2008), discontinuity of peripheral halo (Stacul et al., 2007) or invading adjacent structure (Koike et al., 2001; Hoang et al., 2007; Stacul et al., 2007) were considered malignant. Nodules with spongiform appearance (Moon et al., 2008), well-defined margin (Stacul et al., 2007) or macrocalcification (Stacul et al., 2007) were classified as benign.

On color-Doppler US, according to the previous studies (Lyshchik et al., 2007; Rago et al., 1998; Papini et al., 2002; Hoang et al., 2007) three vascularity patterns were evaluated as follows.

- Pattern 1: Avascularity.

- Pattern 2: Peri-nodular flow, defined as the presence of vascularity around at least 25% of the circumference of a nodule (Figure 2a).

- Pattern 3: Marked intrinsic hypervascularity, defined as flow in central part of tumor greater than that in the surrounding thyroid parenchyma (Figure 2b).

Patterns 1 and 2 were considered benign disease (Hoang et al., 2007), whereas pattern 3 was regarded as

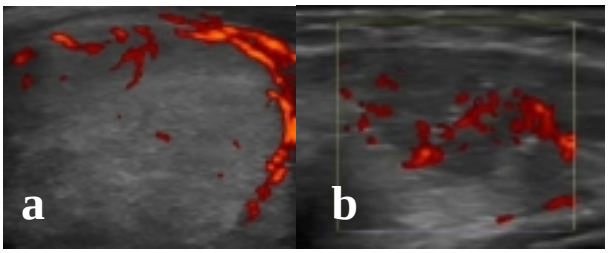

Figure 2. Vascular Flow of Thyroid Nodules by Color Doppler Ultrasonography. a) Peri-nodular flow (pattern 2); b) Marked intrinsic hyper-vascularity (pattern 3)

suspicious malignant (Rago et al., 1998 ; Papini et al., 2002 ; Hoang et al., 2007).

One pathologist examined all surgical specimens of included patients. To assure that the nodule examined histologically was the same nodule studied ultrasonographically, the diagram used during ultrasound recording was used to communicate with the pathologist with regard to the number, location and the size of nodule. Each nodule was classified as benign or malignant nodule based on histologic classification (Hedinger, 1977).

Statistical analysis

The diagnostic performance of gray-scale US and color Doppler US in characterizing thyroid nodules was assessed by calculating sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) using histology as the reference standard.

Results

All 31 patients with thyroid nodule(s) undergoing gray-scale US and color-Doppler US proceeded to the planned operation. Therefore, histologic result was obtained from the sonographically-examined thyroid nodules of all patients. Of 31 nodules, histologic examination revealed malignancy in 5 cases (16.1%) and benign conditions in 26 cases (83.9%). The thyroid nodules were solitary in 16 patients (1 man and 15 women; age range, 23-53 years; mean age, 38.9 years) and multiple in 15 patients (15 women; age range, 29-71 years; mean age, 44.8 years). Patient characteristics are demonstrated in Table 1.

Table 1. Patient Characteristics (n = 31)

Characteristic	Value
Age in year (mean ± SD)	41.8 ± 10.8
Sex (female : male)	30 : 1
Pathologic information	
Size of nodules (cm, mean and range)	3.5 (1-5.3)
Patient with nodule(s)	
Solitary nodules	16 (51.6%)
Multiple nodules	15 (48.4%)
Histologic diagnoses	
Malignant nodules	
Papillary carcinoma	4 (12.9%)
Follicular carcinoma	1 (3.2%)
Benign nodules	
Follicular adenoma	9 (29.0%)
Nodular goiter	8 (25.8%)
Multinodular goiter	5 (16.1%)
Hurthle cell adenoma	3 (9.7%)
Nodular hyperplasia	1 (3.2%)

Table 2. Proportion of Each Gray-Scale Ultrasonographic Finding in Histology-Proved Benign and Malignant Thyroid Nodules

Gray-scale findings	Malignant nodule n	Benign nodule n
Internal content		
Predominantly solid	5	18
Predominantly cystic	0	4
Spongiform appearance	0	4
Shape		
Wider than tall	5	25
Taller than wide	0	1
Margin		
Well-defined	2	23
Indistinct	3	3
Echogenicity		
Marked hypoechogenicity	1	0
Hypoechogenicity	2	11
Isoechogenicity	1	8
Hyperechogenicity	1	7
Calcification		
Absence	2	23
Microcalcification	3	0
Macrocalcification	0	3
Discontinuity of halo sign		
Presence	2	0
Absence	3	26
Invading adjacent structure		
Presence	1	0
Absence	4	26

Seven gray-scale sonographic findings and 3 color Doppler sonographic findings with respect to corresponding histologic results are shown in Table 2 and Table 3 respectively.

Of 31 thyroid nodules, each of which from each patient, examined by US, the gray scale criteria classified 23 nodules as benign and 8 nodules as malignant, whereas when gray scale and color Doppler criteria were combined, 28 nodules considered benign and 3 nodules were considered malignant (Table 4). Gray-scale US gave a correct diagnosis in 22 out of 26 (84.6%) benign lesions and in 4 out of 5 (80.0%) malignant lesions whereas combined gray-scale with color Doppler US gave a correct

Table 3. Proportion of Each Vascular Pattern on Color Doppler Ultrasound in Histology-Proved Benign and Malignant Thyroid Nodules

Vascular pattern	Malignant n = 5	Benign n = 26
Avascularity	0	0
Peri-nodular flow	3	20
Marked intrinsic hypervascularity	2	6

Table 4. Comparison Between Gray-Scale Ultrasound and Color Doppler Ultrasound Results with Reference to the Histologic Findings

Histology	Gray-scale alone			With color Doppler		
	Benign	Malignant	Total	Benign	Malignant	Total
Benign	22	4	26	25	1	26
Malignant	1	4	5	3	2	5
Total	23	8	31	28	3	31

Table 5. Comparison of Diagnostic Performance between Gray-scale Findings and Combined Gray-scale with Color-Doppler Findings in the Detection of Malignant Thyroid Nodules proven by Histology

Diagnostic performance	Gray-scale alone n	(%)	With color Doppler n	(%)
Sensitivity	4/5	80.0	2/5	40.0
Specificity	22/26	84.6	25/26	96.2
PPV	4/8	50.0	2/3	66.7
NPV	22/23	95.7	25/28	89.3

PPV, positive predictive value; NPV, negative predictive value

diagnosis in 25 of 26 (96.2%) benign lesions and 2 of 5 (40.0%) malignant lesions.

Diagnostic performance with regard to sensitivity, specificity, PPV and NPV between gray-scale US alone and combined gray-scale with color Doppler US in the detection of malignant thyroid nodule is shown in Table 5. It should be noted that although decreasing sensitivity in the detection of malignancy from 80% to 40%, addition of color Doppler findings to gray-scale findings increased the specificity from 84.6% to 96.2% and, to the greater extent, raised the PPV from only 50.0% up to 66.7%.

Diagnostic performance with regard to sensitivity, specificity, PPV and NPV between gray-scale US alone and combined gray-scale with color Doppler US in the detection of malignant thyroid nodule is shown in Table 5. It should be noted that although decreasing sensitivity in the detection of malignancy from 80% to 40%, addition of color Doppler findings to gray-scale findings increased the specificity from 84.6% to 96.2% and, to the greater extent, raised the PPV from only 50.0% up to 66.7%.

Discussion

The study showed that adding color Doppler ultrasonographic findings improved the specificity and PPV in the diagnosis of malignant thyroid nodules compared to the findings from gray-scale US alone.

Considering gray-scale findings of each thyroid nodule in our study, all 5 malignant nodules (100%) and almost 70% of benign nodules are predominantly solid. Therefore, in keeping with the previous report (Moon et al., 2008), a predominantly solid component finding alone is not a reliable sign in differentiating malignant from benign nodules. In addition, we found spongiform appearance only in 4 cases of benign nodules and none was found in patient with malignant nodules. This finding, therefore, supported the probability of being benign and our result was in according with that in previous study (Moon et al., 2008).

Although "taller than wide" shape was associated with suggest malignancy in thyroid nodule (Moon et al., 2008), this sign was found in only one case of our patients who was in the benign group. This should not be regarded as conflicting evidence from our study because it could occur by chance. Regarding the margin of the nodules, our study suggested that ill-defined nodular margin had a higher chance of being malignancy compared to those with well-defined border. This finding is consistent with a previous report (Moon et al., 2008).

We found that echogenicity types are varying in both benign and malignant nodules. Although marked hypoechogenicity was found in only one case in our study, it is found in malignant nodule. This finding is in accordance with that previously reported (Papini et al., 2002). Abnormal calcification was found in 6 patients in our study. Microcalcification was found in all 3 cases with later proved malignant nodules, while macrocalcification noted in another 3 cases was found only in benign thyroid nodules. Our results supported the findings in the literature (Frates et al., 2002; Papini et al., 2002; Moon et al., 2008) that microcalcification is for specific for malignant lesions and coarse or macrocalcification is more specific for benign nodules. In addition, we found 2 patients having discontinuity of halo sign and 1 with sonographic finding of thyroid nodule invading adjacent structure. None of these two signs were found in benign nodules.

Regarding color Doppler US findings, vascular patterns of thyroid nodules have been studied and classified to differentiate benign and malignant nodules. We found that patients who had nodules with peri-nodular flow had less chance of being cancer than those with marked intrinsic hypervascularity. Although, hypervascularity in the nodules is not a specific sign of malignancy, many studies have supported this finding (Rago et al., 1998; Papini et al., 2002; Varverakis et al., 2007).

Increased specificity in the detection of malignancy in thyroid nodules by combining color Doppler US to gray-scale US from our study is in keeping with those from the studies of Rago T et al(1998) and of Appetechhia M et al (2006). On the contrary, Stacul et al (2007) did not substantially improve diagnostic performance of malignant thyroid nodules. This disagreement may be in part due to dissimilarity of including criteria and the gold standard in the diagnosis of nodular nature. While our study used histology as the reference standard, the study by Stacul et al (2007) used cytology as the reference standard; therefore the results could be deviated from the false positive and false negative results.

It should be noted that one of our papillary thyroid carcinoma is follicular variant of papillary carcinoma. It was this patient that the gray-scale US falsely diagnosed the nodule as being benign. Kobayashi et al (2007) found that ultrasonographic features of follicular variant of papillary carcinoma were similar to those of benign follicular tumors (Kobayashi et al., 2007).

There are some limitations in this study. Firstly, the small number of patients was included. Secondly, our study participants all presented with clinically palpable thyroid nodule(s) of equal to or larger than 1 cm and we selectively enrolled only the patients who were scheduled for thyroid operation after clinical examination and FNA results obtained. Caution should be made when the results of this study will be generalized to the patients with nonpalpable or subcentimeter nodules.

The strength of our study included that we used histology obtained from surgical specimen as the reference

standard for US test. In addition, the thyroid nodules examined by US in our study were carefully matched with the nodules later examined histologically after the operation. This was made possible by using a pre-designed diagram clearly describing the size and location of the nodule. This is crucial particularly in the cases of having multiple nodules in order to make sure that the nodule studied later histologically is the same one that had been examined by US.

In summary, this study showed that color Doppler US gave an incremental value to gray-scale US in the diagnosis of malignancy in clinically palpable thyroid nodule. Due to a high specificity and PPV, findings of these combined two US techniques may help patients with thyroid nodule and their physicians in making decision regarding whether to proceed to thyroid operation.

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