Thyroid Nodule Size as a Predictor of Malignancy in Follicular and Hurthle Neoplasms

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Abstract

Introduction: The management of follicular (FN) and Hurthle cell neoplasms (HCN) is often difficult because of the uncertainty of malignancy risk. We aimed to assess characteristics of benign and malignant follicular and Hurthle neoplasms based on their shape and size. Materials and methods: Patients with Follicular adenoma (FA) or carcinoma (FC) and Hurthle Cell adenoma (HCA) or carcinoma (HCC) who had preoperative ultrasonography were included. Demographic data were retrieved. Size and shape of the nodules were measured. Logistic regression analyses and odds ratios were performed. Results: A total of 115 nodules with 57 carcinomas and 58 adenomas were included. Logistic regression analysis shows that the nodule height and the patient age are predictors of malignancy (p-values = 0.001 and 0.042). A cutoff value of nodule height ≥ 4 cm. produces an odds ratio of 4.5 (p-value = 0.006). An age ≥ 55 year-old demonstrates an odds ratio of 2.4-3.6 (p-value = 0.03). Taller-than-wide shape was not statistically significant (p-value = 0.613). Conclusion: FC and HCC are larger than FA and HCA in size, with a cutoff at 4 cm. Increasing age increases the odds of malignancy with a cutoff at 55 year-old. Taller-than-wide shape is not a predictor of malignancy.

Keywords: Follicular neoplasm- hurthle cell neoplasm- size- taller-than-wide
retrospectively reviewed pathology reports of patients who underwent thyroidectomy at our institution between January 2012 to December 2017 to identify patients with follicular or Hurthle cell adenomas or carcinomas in the final surgical pathology. Only subjects that have preoperative US with nodules can be identified surely in both transverse and longitudinal images, were included. Demographic data and thyroid stimulating hormone (TSH) level were recorded.

US evaluation

The nodules were measured in three axes by one neuroradiologist (AB). The first axis is the maximal dimension in the transverse image, the second is the maximal dimension perpendicular to the first dimension on the transverse image. These two axes are referred as width and depth, depending on the shape of the nodule. The last dimension (referred to as ‘height’) is the maximal dimension in the longitudinal image. (Tessler et al., 2017) (Figure 1)

A taller than wide shape appearance is determined based on the transverse image comparing the diameters parallel (tallness) and perpendicular (wideness) to the ultrasound beam (Tessler et al., 2017). From this description, we drew a bounding box around the nodule and calculated the ratio between the diameters in Y-axis and X-axis of the nodule in transverse image such that the X-axis was perpendicular to the US beam and the Y-axis was parallel (Figure 1). A Y/X axis ratio greater than 1 was classified as “beam-defined” taller than wide shape. We also calculated the ratio between depth and width from the three-axes measurement. These ratios would reflect the different angulation of the nodules which might simulate the various angulations on real time US. This parameter is referred to as the “diameter-defined” ratio in our study.

Statistical analysis

The SPSS v.22 software package was used for statistical analysis. Univariate binary logistic regression analysis was used for both categorical data (gender, TSH categories and shape) and continuous data (age, TSH value, width, perpendicular dimension and height). For each categorical data category, the predictor value and reference category were set. The independent variables which had P-value < 0.25 were included in the next step for multivariable analysis. For multivariable analysis, forward logistic regression (LR) and backward LR methods were performed. The independent variables, which were statistically significant (P-value < 0.05) in both methods, were then analysed by enter method LR to check the multicollinearity and interactions. The area under the curve (AUC) of receiver operator characteristic (ROC) curve was used for assessing the model performance. The beam-defined and diameter ratios for taller than wide shape are compared by paired t-test and correlation determination with Pearson’s correlation.

Results

We found 556 patients with FN and HN as the final surgical pathology in our database. Of those, 397 had preoperative US available for our review. In patients with multiple nodules, the specific location of the nodule was not stated in 162 patients, causing uncertainty of nodule localization in US and thus such cases were excluded. One hundred twenty of the patients did not have both transverse and longitudinal images. This left a total of 115 patients that could be analyzed, including 58 benign (39 FA and 19 HCA) and 57 malignant (35 FC and 22 HCC).

The gender, age, width, depth, height and taller-than-wide appearance is found to be statistically significant (P-values = 0.031, 0.014, 0.001, 0.001, <0.001, and 0.115, respectively) based on the univariable binary logistic regression analysis of each independent variable (Table 1). These variables were then analyzed by multivariable binary logistic regression analysis with forward LR and backward LR methods. In both methods, only height and age are considered statistically significant (P-values = 0.001 and 0.042, respectively) (Table 2). For visualization of P-value trend of other variables, logistic regression analysis with enter method was performed and shown in Table 2. The area under the curve (AUC) of this model is 0.72, representing a good model fit.

Nodule size was stratified by height and we found that increasing size increases the odds ratio (OR) of carcinoma. The categorized size reached statistical significance at size equal to or > 4 cm (P-value = 0.006, OR = 4.5) (Table 3 and Figure 2).

Table 1. Descriptive Data and Univariable Logistic Regression Analysis

|                     | Benign (n=58) | Malignant (n=57) | P-value | Exp (B) | 95% C.I.for EXP(B) |
|---------------------|--------------|------------------|---------|---------|--------------------|
| Gender (Female)     | Mean (SD) or Count (%) | Mean (SD) or Count (%) | 0.031† | 0.429 | 0.199 - 0.925 |
| Age                 | 55.2 (15)     | 62.6 (16)        | 0.014† | 1.032 | 1.006 - 1.058 |
| TSH Value (mIU/L)   | 2.28 (1.45)   | 2.48 (1.53)      | 0.585  | 1.094 | 0.792 - 1.513 |
| TSH level           |               |                  |         |        |                    |
| Low                 | 0/37 (0%)     | 1/32 (3.1%)      | 0.794  | 0      | 0                  |
| Normal              | 30/37 (81.1%) | 23/32 (71.9%)    |        |        |                    |
| High                | 7/37 (18.9%)  | 8/32 (25%)       |        |        |                    |
| Width (mm.)         | 22.7 (10.8)   | 32.9 (18.9)      | 0.001† | 1.048 | 1.018 - 1.079 |
| Depth (mm.)         | 19.2 (10.2)   | 28.9 (17.7)      | 0.001† | 1.059 | 1.023 - 1.096 |
| Height (mm.)        | 27.9 (12.2)   | 40.5 (20.2)      | <0.001†| 1.047 | 1.021 - 1.074 |
| Taller-than-wide    | 10 (17.2%)    | 17 (29.8%)       | 0.115† | 2.04  | 0.841 - 4.951 |

†, Statistically significant for univariable analysis.
**Discussion**

Our study showed that size and age are independent predictors of malignancy in follicular and Hurthle cell neoplasms. Stratiﬁed age groups showed increase OR for carcinoma with increase age. The optimal cutoff value is at 55 year-old (OR = 2.4-3.6, p-value = 0.03). (Table 4).

Pearson’s correlation demonstrated strong, positive correlation between beam-deﬁned and diametere-defined ratios (r = 0.768, p-value = 0.01) (Figure 3). The mean (SD) of beam-deﬁned and diameter-deﬁned ratios for nodule shape of all data were 0.85 (±0.21) and 0.88 (±0.26), respectively (p-value = 0.051). When excluded the equivocal ratios (ratios range from 0.9-1.1), the mean (SD) were 0.78 (±0.23) and 0.81 (±0.27), respectively (p-value = 0.118).

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**Table 2. Multivariable Logistic Regression Analysis**

| predictor     | B         | S.E.  | Wald     | df | Sig.   | Exp(B)  | 95% C.I. for EXP(B) |
|---------------|-----------|-------|----------|----|--------|---------|---------------------|
| Age*          | 0.027     | 0.013 | 4.148    | 1  | 0.042  | 1.028   | 1.001               |
| Gender**      | -0.297    | 0.471 | 0.398    | 1  | 0.528  | 0.743   | 0.295               |
| Taller-than-wide** | 0.324   | 0.642 | 0.256    | 1  | 0.613  | 1.383   | 0.393               |
| Height*       | 0.045     | 0.013 | 11.433   | 1  | 0.001  | 1.046   | 1.019               |
| Width**       | -0.001    | 0.041 | 0        | 1  | 0.989  | 0.999   | 0.923               |
| Depth**       | 0         | 0.039 | 0        | 1  | 0.998  | 1       | 0.925               |

*, Variables analyzed by forward logistic regression (LR) and backward LR methods, **, Variables analyzed by enter method, a Statistically significant for multivariable analysis.

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**Table 3. Odds Ratio of Tumor Size According to Height**

| Tumor size     | OR | 95% C.I. | P-value |
|----------------|----|----------|---------|
| 1-1.9 cm.      | 1  | 0.042    | 0.042   |
| 2-2.9 cm.      | 2.013 | 0.195   | 0.698   | 5.806   |
| 3-3.9 cm.      | 1.687 | 0.446   | 0.439   | 6.489   |
| ≥ 4 cm.        | 4.5 | 0.006†   | 1.549   | 13.07   |

OR, Odds ratio; †, Statistical significant difference at size equal to or more than 4 cm.

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**Table 4. Odds Ratio of Age**

| Age (year) | OR | 95% C.I. | P-value |
|------------|----|----------|---------|
| ≤ 55       | 1  | 0.032    |         |
| 56-75      | 2.431 | 0.033†   | 1.072   | 5.512   |
| ≥ 76       | 3.647 | 0.027†   | 1.161   | 11.457  |

OR, Odds ratio; †, Statistical significant difference at age more than 55 year-old.

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Figure 1. Transverse (A, B and C) and longitudinal (D) US images of an isoechoic solid thyroid nodule demonstrating the measurement method (A, B and D; depth, width and height diameters). Bounding box is drawn around the nodule (C) and the ratio between Y and X axes represents the shape of nodule. The shape of this nodule is taller-than-wide. The final pathology is a follicular adenoma.
tumors. FC and HC are significantly larger than adenomas with the optimal cutoff at size ≥ 4 cm (OR = 4.5, p-value = 0.006). Several studies mentioned that FC and HCC tend to be larger in size as compared to other types of malignancy but they did not compare them to their benign counterparts (Méndez et al., 2008; Gulcelik et al., 2008; Choi et al., 2009; Ibrahim et al., 2015; Jin et al., 2018). Increasing tumor volume was also reported to increase the risk of malignancy in FN (Sillery et al., 2010). Previous studies on FN cytology reported that size was not a predictor of malignancy, however these studies compared final pathology of malignancy with final benign pathology without subclassification of a specific tumor subtype; e.i. Follicular and papillary carcinomas were considered all together as malignancy (Méndez et al., 2008; Gulcelik et al., 2008; Choi et al., 2009; Parikh et al., 2013; Ibrahim et al., 2015). When it comes to the size, measurement method is crucial. Our study is one of the few studies describing the method of measurement, which we did according to a standard system (Tessler et al., 2017).

Even though increasing age unsurprisingly increases risk of malignancy, we showed the odds ratio of each age group, which could be of additional value for triaging patients based on this basic parameter. We found an optimal cutoff age at 55 year-old (OR = 2.4-3.6, p-value = 0.03).

To the best of our knowledge, our study is the first showing that taller-than-wide shape is not an independent predictor for malignancy in FN and HCN. Taller-than-wide shape has been well accepted to be an important malignant US feature in thyroid cancer. However, most studies on thyroid cancer are weighted toward findings of papillary carcinoma which has different nature both clinically and histologically (Raparia et al., 2009; Yoon et al., 2010; Castro et al., 2011; Ren et al., 2015; Espinosa De Ycaza et al., 2016; Tessler et al., 2017; Yang and Fried, 2018). A previous study using CT comparing shape of FN and nodular hyperplasia found that taller-than-wide shape is significantly more common in FN, irrespective of adenoma or carcinoma (Lee et al., 2016). Several studies have reported that follicular variant of PTC has significantly less taller-than-wide appearance as compared to conventional PTC (Kim et al., 2009; Anuradha et
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