Systematic inclusion of clinical and laboratory data improves diagnostic accuracy of fine-needle aspiration biopsy in solitary thyroid nodules

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In this study, we identified clinical and laboratory markers of malignant thyroid nodules and determined whether systematic inclusion of these data could improve diagnostic accuracy of fine-needle aspiration biopsy in solitary thyroid nodules. The patients were 24 men and 105 women who underwent surgical removal of solitary thyroid nodules and had adequate fine-needle aspiration biopsy performed prior to surgery. Including fine-needle aspiration biopsy’s diagnosis of suspected malignancy in the same category as malignancy, the sensitivity and specificity of fine-needle aspiration biopsy were 71.4% and 85.1%, respectively, with an accuracy of 82.2%. Using stepwise linear regression analysis, clinical data, i.e. increasing age, irregular nodule surface, hard consistency of nodule, and high serum thyroglobulin concentration, were associated with an increased risk of malignancy when the cytological result was excluded. When cytology was also considered, male sex, irregular nodule surface and high serum thyroglobulin concentration were found to be associated with an increased risk of malignancy. The diagnostic value of clinical data alone, even in combination with cytology or laboratory data, was inferior to that of fine-needle aspiration biopsy alone. The specificity and accuracy of fine-needle aspiration biopsy could be increased to 98.0% and 90.7%, respectively, whereas its sensitivity was decreased to 64.3% when these variables were considered in combination. Therefore, of fine-needle aspiration biopsy, clinical and laboratory data, fine-needle aspiration biopsy alone has the highest diagnostic value, which can be increased only when both clinical characteristics and serum thyroglobulin concentration are systematically included.

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Recently, fine-needle aspiration biopsy has become of substantial diagnostic help in patients with a solitary thyroid nodule (1, 2). Depending on the experience of the cytopathologist interpreting the cytology and method of calculation, sensitivity, specificity and accuracy in diagnosing malignant thyroid nodules have been reported to be in the range of 70 to over 90% (3–8). However, a more recent report of re-analysis of the accuracy of fine-needle aspiration biopsy has indicated that the prediction of neoplasia by fine-needle aspiration biopsy is less reliable than is widely accepted (9). In this context, it has been recommended that clinical features considered together with fine-needle aspiration biopsy results should increase diagnostic accuracy (10). However, this notion has not been methodologically evaluated.

The present study was undertaken to identify clinical and laboratory markers of malignant thyroid nodules. It was further determined whether the diagnostic value of fine-needle aspiration biopsy could be optimized by the systematic inclusion of relevant clinical and laboratory data using multivariate analysis which can simultaneously analyse multiple risk factors for malignancy.

Patients and methods

The study population comprised 129 patients with solitary thyroid nodules who were referred to the thyroid clinic at Ramathibodi Hospital, Bangkok, Thailand. A structured interview and physical examination of each patient were conducted. After obtaining informed consent, fine-needle aspiration biopsy of the thyroid nodule was performed using a 25-gauge needle with local anaesthesia by an attending endocrinologist or fellows in endocrinology. The aspirated material was smeared on to glass slides using a smearing technique similar to that used in standard peripheral blood smears, and immediately fixed with methanol and stained with Papanicolaou’s stain. All cytological samples were examined by the same cytopathologist. Blood was drawn and assayed for thyroglobulin using the double antibody radioimmunoassay method (Diagnostic Products Corporation, USA), antithyroglobulin and antimicrosomal antibodies using the hemagglutination method (Thymune-T and Thymune-M, respectively, Wellcome Company, UK). The nodule was then surgically removed.
The diagnostic value, i.e. sensitivity, specificity and accuracy of fine-needle aspiration biopsy in diagnosing malignant nodules was calculated by cross tabulation. The diagnostic values of other variables, identified from logistic linear regression analysis, in combination were calculated using the corresponding regression equations and cutoff points from receiver operating characteristic (ROC) curves (16) which provided the highest sensitivity and specificity. These values were then compared to that of cytology alone, using a test for comparison of proportion (17). The method used in estimating the coefficients in the logistic models in the present study is a maximum likelihood approach which makes no particular assumption concerning the distribution of variables. This less restrictive assumption makes the potential inaccuracy caused by large differences in category size or unequal variances less likely (18). Moreover, the goodness-of-fit of each logistic regression model has been tested using the Hosmer-Lemeshow's H statistic (19) with the results that each model fits the observed data well. Data are presented as mean ± SEM; p value less than 0.05 was considered to be statistically significant.

Results

Of the 129 patients studied, 24 were males and 105 were females. Mean age was 40.7 ± 1.2 years, ranging from 19 to 75 years. The majority of the patients resided in Bangkok and in the vicinity, which is an iodine sufficient area. No patients had a previous history of external radiotherapy to the head or neck. Fine-needle aspiration biopsy revealed malignancy in 18 (13.9%) of the nodules, suspect malignancy in 17 (13.2%) and benign in 94 (72.9%). Malignancy was histologically proved in 14 (77.8%) of the malignant category, in 6 (35.3%) of the suspect category and in 8 (8.5%) of the benign category.

As shown in Table 1, age, surface characteristics and consistency of the nodule were significantly different in...
patients with malignant and benign nodules. These and other variables from the literature were then used in stepwise logistic linear regression. As shown in Table 2, when cytology was excluded, increasing age, irregular surface, hard consistency of the nodule and serum thyroglobulin concentration were associated with an increased risk of malignancy. However, when cytology was considered, too, it was shown that cytology, serum thyroglobulin concentration, irregular surface and male sex were associated with an increased risk of malignancy, as shown in Table 3.

Table 4 shows the significant risk factors for malignancy, their corresponding logistic regression models and the cutoff probability derived from ROC curves.

As shown in Fig. 1, when considered alone in diagnosing malignant nodules, the sensitivity, specificity and accuracy of cytology from fine-needle aspiration biopsy were 71.4%, 85.1% and 82.2%, respectively. Clinical data alone had lower specificity and accuracy than cytology, whereas their sensitivities were not significantly different. When clinical data or serum thyroglobulin concentration were considered in addition to cytology, the diagnostic values were not increased significantly. Similarly, the diagnostic value of clinical data was not significantly increased when serum thyroglobulin alone was included. However, when serum thyroglobulin concentration and clinical data were considered together with cytology, specificity and accuracy were increased significantly to 98.0% and 90.7% respectively, while sensitivity was decreased to 64.3%.

Of the 17 nodules found to be suspected of malignancy by fine-needle aspiration biopsy, 6 were malignant and 11 were benign according to the pathological results. Applying the last regression model in Table 4 to this set of data, the number of nodules correctly diagnosed, corresponding sensitivity and specificity derived were demonstrated in Table 5. It can be seen that the inclusion of sex, surface characteristics of nodule and serum thyroglobulin concentration increased the accuracy to 94.1%, compared to 35.2% when all suspect nodules were considered potentially malignant and sent to surgery.

Discussion

The relatively high prevalence of malignancy (22%) in this study may be due to preselection of patients by general practitioners or internists before they were referred to the thyroid clinic. Certain clinical variables like exposure to ionizing radiation or familial papillary thyroid carcinoma have been established risk factors of malignancy in solitary thyroid nodules (20, 21). However, there have been conflicting reports regarding the risk associated with factors like sex, advancing age (22), compression symptoms (23, 24), rapid growth (23, 25) or lymphadenopathy (23). Most studies have used only a univariate

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**Table 4. Risk factors, their corresponding logistic linear regression equations, and cutoff probability which provided the highest sensitivity and specificity.**

<table>
<thead>
<tr>
<th>Category</th>
<th>Z</th>
<th>Probability*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td>$1.046Sf + 0.037Cs + 0.046A - 5.44$</td>
<td>0.2</td>
</tr>
<tr>
<td>Cytology</td>
<td>$4.44 + 2.80Cy - 1.575Sx + 1.08Sf$</td>
<td>0.4</td>
</tr>
<tr>
<td>Clinical</td>
<td>$2.86 - 2.85Cy + 0.0025T$</td>
<td>0.3</td>
</tr>
<tr>
<td>Cytology + clinical</td>
<td>$1.24Sf + 0.36Cs + 0.037A + 0.0044T - 6.03$</td>
<td>0.2</td>
</tr>
<tr>
<td>Cytology + clinical + T</td>
<td>$4.56 - 2.97Cy - 1.86Sx + 1.23Sf + 0.0034T$</td>
<td>0.4</td>
</tr>
</tbody>
</table>

* Cutoff probability which gave the highest sensitivity and specificity by ROC curve.

Probability of malignancy = $1/(1 + e^{-Z})$

$A =$ age of patient (years), $Cs =$ consistency of nodule (soft = 1, cystic = 2, firm = 3, rubbery = 4, hard = 5, stony hard = 6). $Cy =$ cystologic result (suspect or malignant = 1, benign = 2). $Sf =$ surface characteristic of nodule (smooth = 1, irregular = 2, lobulated = 3). $Sx =$ sex of patient (male = 1, female = 2). $T =$ serum thyroglobulin concentration ($\mu$g/l).

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**Table 5. Prediction of malignancy in nodules suspected of malignancy using sex, surface characteristics of the nodules and serum thyroglobulin concentration according to the last regression model in Table 4.**

<table>
<thead>
<tr>
<th>Prediction by regression model</th>
<th>Histological result</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Malignant</td>
</tr>
<tr>
<td>Malignant</td>
<td>5</td>
</tr>
<tr>
<td>Benign</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>6</td>
</tr>
</tbody>
</table>

Sensitivity = true positive/number malignant = 5/6 = 83.3%.

Specificity = true negative/number benign = 11/11 = 100%.

Accuracy = (true positive + true negative)/total number = (5 + 11)/17 = 94.1%.
statistical method, which may not identify valid risk factors whose other confounders are not adequately controlled. In this study we attempted to systematically include these clinical and other laboratory data to the fine-needle aspiration biopsy result by multivariate analysis to determine whether or not it could improve diagnostic accuracy.

When fine-needle aspiration biopsy was excluded, age and physical characteristics of the nodule, i.e. consistency and surface characteristics, were shown to be associated with an increased risk of malignancy. Using these data in combination, a moderately high degree of diagnostic value could be attained but still inferior to that of fine-needle aspiration biopsy alone. This infers that clinical data, even when considered in combination, are not as reliable in differentiating malignant from benign nodules as fine-needle aspiration biopsies. In addition, the diagnostic accuracy of clinical variables alone was not improved when serum thyroglobulin concentration, which may or may not be elevated in the presence of malignancy (26), was included for consideration. This is in contradiction to a recommendation by a recent report suggesting surgery regardless of fine-needle aspiration biopsy result when malignancy suspected based on clinical grounds alone is high (27).

We have further demonstrated methodologically that both clinical data and serum thyroglobulin concentration, only in combination, can add to the diagnostic value of fine-needle aspiration biopsy. Because of its high specificity, this combination may be helpful in confirming the diagnosis of malignancy when the cytology result is considered to be only suspected malignancy. Accordingly, we have shown that a high degree of diagnostic accuracy could be attained for such nodules when clinical characteristics and serum thyroglobulin concentration were also considered. However, risk factors for malignancy and parameters of the predicting model may vary among places if the accuracy of fine-needle aspiration biopsy and pertinent characteristics of the population significantly differ (28). With this limitation in mind, and using the mentioned strategy appropriately, the number of patients undergoing unnecessary operations may be further reduced and true positivity in suspect nodules increased substantially.

By multivariate analysis, we conclude that among fine-needle aspiration biopsy, clinical and laboratory data, fine-needle aspiration biopsy alone has the highest diagnostic value and can be increased only when both clinical characteristics and serum thyroglobulin concentration are included. In the setting of this study, sex, surface characteristics of the nodule and serum thyroglobulin concentration may be systematically combined with cytology to increase diagnostic accuracy in nodules suspected of malignancy. However, as a screening test, measuring serum thyroglobulin and considering clinical data in addition to performing fine-needle aspiration biopsy may not be cost-effective, since they do not increase the sensitivity of fine-needle aspiration biopsy.

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References


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