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Multivariate Analysis in Solitary Cold Thyroid Nodules for the Diagnosis of Malignancy

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Abstract—*A stepwise logistic regression (SLR) was performed on 162 patients with a solitary and cold thyroid nodule in order to discriminate between malignant and benign lesions. Sixteen variables were recorded for each patient. The predictions of the logistic regression model were compared to the histological diagnoses in order to evaluate the accuracy of the classification. The value of the logistic function (LF) was calculated for each patient. Using the ROC curve approach, an optimum threshold value (OTV) corresponding to a 100% sensitivity was defined. The classification obtained with the OTV was validated using a cross-validation procedure (CVP).*

The significant variables selected by the SLR are (from the most significant to the least significant): cytologic result, sex, irregular margin on the Tc scintigraphy and homogeneity on the ultrasound examination. The OTV corresponds to a specificity of 73% for a sensitivity of 100%. The specificity and the sensitivity obtained with the CVP are 73% and 96% respectively.

In conclusion, the classification of the patients according to the value of the LF is a highly accurate diagnostic procedure.

INTRODUCTION

THE BASIC problem in the management of solitary thyroid nodules is discrimination between the malignant nodules which must be removed and the benign nodules. Several diagnostic variables have been proposed to perform this discrimination [1–6]. The value of these variables has been evaluated in many papers [7–17]. However, only univariate procedures have been used and no author took into account the correlation between the variables.

This paper reports the results of a multivariate analysis performed on 162 patients who underwent surgery between 1/1/83 and 7/1/84 for the removal of a solitary cold thyroid nodule. The significant variables for the diagnosis of malignancy were selected using the logistic model which permits the calculation of a probability of benignity for each patient [18,19]. In order to choose a threshold value for this probability, the ROC curve approach was used. The resulting classification was validated using a cross-validation technique.

PATIENTS AND METHODS

Patients

Data concerning 217 patients investigated in our Nuclear Medicine Department for a thyroid nodule which was solitary according to the clinical examination and which was cold on the 99m Tc scan have been used. Patients with a purely cystic nodule were excluded. A nodule was considered to be purely cystic if it was anechoic and presented a regular margin on the ultrasound scan and if complete regression was obtained after fine needle aspiration (FNA). All 217 patients underwent surgery. The decision for surgery was assessed either just after the first examination or after a 3 month delay during which thyroid hormone suppression was performed. The 217 patients represent 65% of all the 334 patients (Table 1) with a solitary, cold and solid or mixed nodule who were examined in our department during the same period of time. Seventy-eight patients did not undergo surgery because of a refusal or a contra-indication. For 39 patients, surgery was not performed on account of partial or complete regression after suppression assuming that any of the following criteria was present: history of cervical irradiation, age less than 20, cervical lymph node, ultrasonic diameter greater than 30 mm, suspect or malignant cytologic result. Up to now, these 39 patients have been reexamined on at least one occasion in our department and no malignant lesion was found.

All the data concerning the patients included in this study were collected by only three physicians.

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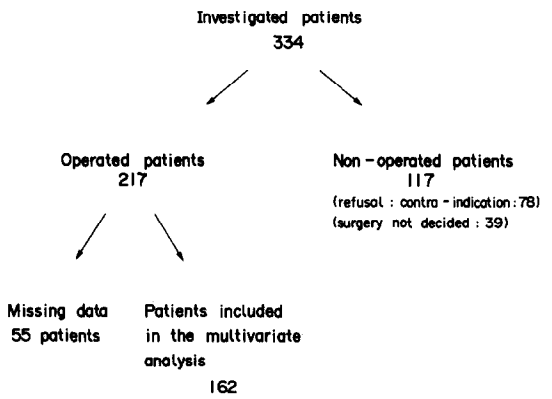

Table 1. *Distribution of the patients with a cold, solitary and not purely cystic thyroid nodule investigated in our department between* 1/1/83 *and* 7/1/84

Variables concerning history of irradiation and compression sign (the compression sign means that the nodule is responsible for dysphagia and/or dyspnea and/or hoarseness) have not been used since none of the patients had a history of exposure to irradiation and only one patient had a compression sign. The 'toughness' sign means that the nodule is firm or hard by palpation. The 99m Tc images have been obtained using an ACTI-CAMERA CGR equipped with a pinhole collimator, with 300–600,000 counts per frame. The real-time ultrasound equipment (Toshiba) used consists of a 3.5 MHz linear probe. FNA [20] was performed using a 22–26 gauge needle and with a syringe. The May–Grünwald–Giemsa stain was used exclusively. The cytologists had to answer using a four level rating technique: benign, doubtful, suspicious, malignant.

Table 2 gives the type and the coding of the 16 variables included in this study. They concerned history, clinical examination, scintigraphic examination, ultrasound examination and FNA. The scintigraphic or ultrasound data were missing for 10 patients and the FNA specimens were inadequate for proper cytologic interpretation in 48 of the 217 patients.

The final histological result was assessed on the operative specimen. The malignant tumors were classified using the descriptive classification proposed by the European Organization for Research and Treatment of Cancer (EORTC) thyroid cancer group [21, 22]. A malignant lesion was found in 29 of the 217 nodules.

Statistical methods

The diagnostic value of each variable was first evaluated by comparing its distribution in the benign group with its distribution in the malignant group. The comparison test was the χ^2 test for the binary or categorical variables and the t test for the continuous variables.

In order to limit the number of variables in the multivariate analysis only the variables with a P value less than 0.20 have been included. Because of the missing data concerning scintigraphic, ultrasound and FNA variables (Table 1), the multivariate analysis is performed on only 162 patients (24 malignant nodules, 138 benign nodules). Using a χ^2 test we found that the frequency of malignant nodules in the 162 patients included in the analysis does not differ significantly ($P = 0.25$) from the frequency of malignant nodules in the 55 excluded patients.

The chosen multivariate analysis method is the logistic regression analysis [18, 19] which is preferable to discriminant analysis when some variables are discrete and some variables are continuous [23]. We performed a stepwise logistic regression (SLR) using the BMDP LR program. The selection of the significant variables is made using the asymptotic covariance matrix estimate. The chosen limit of P value is 0.10 to enter a variable and 0.15 to remove it. For each significant variable the regression coefficient and its standard error are estimated.

Using the values of the regression coefficients, each patient is characterized by the value of the logistic function (LF) which is the probability of benignity (see Appendix).

Once a threshold value (TV) is chosen, a nodule is classified as malignant if the probability of benignity is less than this threshold value. Using a chosen TV and applying this classification method to all the patients it is possible to determine the sensitivity and the specificity of the method (see Appendix). The BMDP LR program provides the value of the sensitivity and the specificity for 60 TV uniformly distributed between 0 and 1. This allows us to plot a ROC curve (see Appendix) which gives the sensitivity vs. 1 − the specificity [24, 25]. The TV which corresponds to the highest specificity for a sensitivity of 100% has been defined as the optimum threshold value (OTV) for the management of the patients. The choice of this value is motivated by the high cost of a false negative.

In order to assess the role of 'cytologic result' two SLRs were performed: one including 'cytologic result' in the analysis and one without 'cytologic result'. The 'cytologic result' was originally given using a 4 level rating technique. Since 'cytologic result' was included in the SLR as a binary variable, its optimum operating point for the classification of the nodules was determined. Thus, SLR including 'cytologic result' was performed three times, each time using one of the three operating points. The sensitivity and the specificity of 'cytologic result' were calculated for each of the three operating points.

A cross-validation procedure [26], derived from the Jackknife technique [27] was used in order to

Table 2. Type and coding of the 16 variables recorded for each patient

Variable	Type	Coding
History variables		
Age	Continuous	
Sex	Binary	(female = −1; male = 1)
Nodule duration	Binary	(>1 year = −1; <1 year = 1)
Clinical variables		
Goiter	Binary	(yes = −1; no = 1)
Toughness	Binary	(no = −1; yes = 1)
Pain	Binary	(no = −1; yes = 1)
Cervical nodes	Binary	(no = −1; yes = 1)
Scintigraphic variables		
Irregular margin	Binary	(no = −1; yes = 1)
Number of nodules	Binary	(more than one = −1; one = 1)
Localization	Binary	(lateral = −1; isthmic = 1)
Ultrasound variables		
Diameter	Continuous	
Solid	Binary	(no = −1; yes = 1)
Homogeneous	Binary	(no = −1; yes = 1)
Hypoechoic	Binary	(no = −1; yes = 1)
Fine needle aspiration variables		
Aspect	Binary	(liquid = −1; solid = 1)
Cytologic result	Categorical	(0 = benign, 1 = doubtful, 2 = suspicious, 3 = malignant)

Table 3. Results of the univariate analysis. The two first columns give the mean or the proportion in the benign group and in the malignant group. The third column gives the significance level of the comparison test. The last column indicates the variables which have been included in the multivariate analysis

Variable	Mean or proportion		Significance level	Inclusion in the SLR
	Benign	Malignant		
History variables				
Age	40 year	44 year	$P < 0.01$	Yes
Sex (male)	10%	28%	$P < 0.01$	Yes
Nodule duration (<1 year)	68%	72%	$P > 0.20$	No
Clinical variables				
Goiter (no)	74%	82%	$P > 0.20$	No
Toughness (yes)	46%	68%	$P < 0.10$	Yes
Pain (yes)	4%	11%	$P > 0.20$	No
Cervical nodes (yes)	1%	16%	$P < 0.05$	Yes
Scintigraphic variables				
Irregular margin (yes)	51%	83%	$P < 0.01$	Yes
Number of nodules (one)	93%	95%	$P > 0.20$	No
Localization (isthmic)	12%	11%	$P > 0.20$	No
Ultrasound variables				
Diameter	33mm	35mm	$P < 0.15$	Yes
Solid (yes)	66%	93%	$P < 0.01$	Yes
Homogeneous (yes)	39%	68%	$P < 0.01$	Yes
Hypoechoic (yes)	26%	61%	$P < 0.001$	Yes
Fine needle aspiration variables				
Aspect (solid)	70%	96%	$P < 0.01$	Yes
Cytologic result			$P < 0.0001$	Yes
(benign)	75%	20%		
(doubtful)	8%	0%		
(suspicious)	15%	24%		
(malignant)	2%	56%		

Table 4. Results of the multivariate analysis including cytologic result. Regression coefficient with standard error and significance level of the variables retained in the SLR. The variables are listed from the most significant to the least significant

Variable	Coefficient	Standard error	Significance level
Cytologic result	−2.472	0.489	$P < 0.0001$
Sex	−1.252	0.397	$P < 0.004$
Irregular margin	−0.870	0.384	$P < 0.01$
Homogeneous	−0.497	0.335	$P < 0.08$
Constant (B_0)	−0.301		

Table 5. Results of the multivariate analysis not including cytologic result. Regression coefficient with standard error and significance level of the variables retained in the SLR. The variables are listed from the most significant to the least significant

Variable	Coefficient	Standard error	Significance level
Sex	−1.067	0.329	$P < 0.06$
Irregular margin	−0.796	0.300	$P < 0.002$
Age	−0.045	0.018	$P < 0.01$
Solid	−0.900	0.411	$P < 0.03$
Constant (B_0)	+3.890		

determine how the LF would classify the patients who have not been used in the estimation of the regression coefficients. It consists of 162 SLRs performed successively with the same methodology as described above and including 'cytologic result'. Each time one patient is excluded. The value of the LF is then calculated for the excluded patient and used for his classification. Then, this classification is compared with the final histological diagnosis.

RESULTS

Table 3 gives the means or the proportions and the significance level of the univariate comparison tests. Table 3 also indicates the variables which were included in the subsequent multivariate analysis. Among the history and clinical variables, 'age', 'sex', 'toughness' and 'cervical lymph nodes' have been included. The only scintigraphic variable included is 'irregular margin'. All the ultrasound variables were included: 'diameter', 'solid', 'homogeneous' and 'hypoechoic'. The two FNA variables were included and 'cytologic result' is the most significant among the 16 variables.

Table 4 gives the significance level, the value and the standard error of the regression coefficients for the significant variables retained by the SLR performed on the 11 variables selected in Table 3, including 'cytologic result'. The best classification of the nodules was obtained with the following binary coding of 'cytologic result': benign, suspicious, doubtful = −1; malignant = +1. In this table, the variables are listed from the most significant to the least significant.

In the same way, Table 5 gives the results of the SLR performed on the variables selected in Table 3, except 'cytologic result'. As with 'cytologic result', 'sex' and 'irregular margin' are retained in the first steps. 'Age' and 'solid' are now retained in the model whereas 'homogeneous' is not retained.

The two ROC curves corresponding to the two SLRs are presented in Fig. 1. As shown on this figure the diagnostic value of the LF established without 'cytologic result' is lower than that of the LF established with 'cytologic result'. The difference essentially appears in the right part of the two curves, indicating that it is possible to achieve a higher specificity for a given sensitivity with the LR including 'cytologic result'. The three operating points of 'cytologic result' stand between the two ROC curves.

The OTV for the LF including 'cytologic result' is 0.942 and corresponds to a specificity of 73% (the sensitivity is 100% by definition of the OTV). When 'cytologic result' is not included in the LF the OTV is of no practical interest since the specificity must fall to 6% to obtain a sensitivity of 100%.

Table 6 gives the results of the cross-validation procedure. One hundred and one of the 138 benign nodules have been correctly classified. This corresponds to a specificity of 73%. Only one malignant

Table 6. Results of the cross-validation procedure. Distribution of the patients according to the reference diagnosis and the classification resulting of the SLR

		Histological diagnosis	
		Benign	Malignant
SLR	Benign	101	1
Classification	Malignant	37	23
	Total	138	24

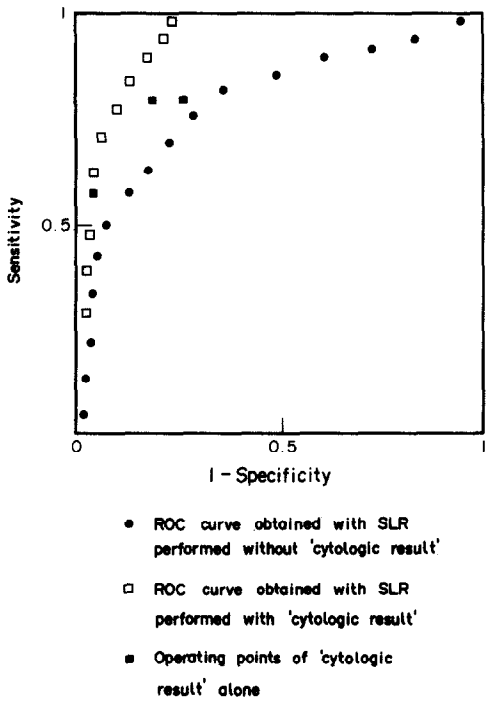

Fig. 1. ROC curves corresponding to the two SLRs. The three operating points of 'cytologic result' are also plotted alone.

nodule has been misclassified.This corresponds to a sensitivity of 96%. This cross-validation study shows the high accuracy of this diagnostic procedure.

DISCUSSION

The management of patients with a cold thyroid nodule is based on data from history, clinical examination, scintigraphic examination [4, 6], ultrasound examination [5] and fine needle aspiration [2, 15]. The integration of the information contained in these data is difficult because the information is often redundant, so that multivariate methods are needed to evaluate the joint effects of the correlated variables.

This integration can be performed by multivariate analysis which, as far as we know, has not yet been used in this field. Variables are generally considered separately [7–17] or in a combination of two or three [1, 16, 28] sometimes using decision analysis [29, 30] which does not actually take into account the correlation beween the variables.

A recent paper [31] uses multivariate analysis for cytologic data without taking into account other information as we do in this paper.

In this study, logistic regression [18, 19] is used because the normality hypothesis required by discriminant analysis [23] is no longer valid when discrete variables are used.

Multivariate analysis requires a large number of patients when many variables are used. So, we have been very cautious to use a sufficient number of patients with regard to the number of variables included in the SLR.

One criticism often made about multivariate analysis is that the results are evaluated on the population on which the regression is performed. The cross-validation procedure [26] used in this study avoids this bias.

The population used in this study is only a part of the population of patients with a cold thyroid nodule who underwent surgery. This is a potential source of bias. One hundred and seventeen patients amongst the 334 with a thyroid cold nodule were not operated on. Seventy-eight of these patients did not undergo surgery either because of their refusal to do so or a contra-indication. The remaining 39 patients were not operated on because they presented no criterion for malignancy. The subsequent follow-up of these patients (minimum of 30 months) demonstrated no malignant lesion. Then, the exclusion of those 39 patients leads to an underestimation of the specificity of the proposed method.

The most significant variable is 'cytologic result' as it is shown by both univariate and multivariate analysis. The result is in accordance with that of many papers [9, 14, 15, 16, 29, 32] although Lo Gerfo *et al.* [13] think that coarse needle biopsy is better than FNA. The high diagnostic value of 'cytologic result' is confirmed by the difference between the ROC curve obtained with the logistic function including 'cytologic result' and the ROC curve obtained with the logistic function not including 'cytologic result'. In particular, the specificity corresponding to the OTV is very low when 'cytologic result' is not included in the logistic function but it is high when 'cytologic result' is included. This result emphasizes the role of FNA, in particular the

need for adequate specimen and the necessity to reaspirate when the first sampling is not satisfactory.

Nevertheless, this study does not suggest that the good results obtained by 'cytologic result' make the other data useless. Figure 1 shows that the three points corresponding to 'cytologic result' are below the ROC curve obtained with the logistic function including 'cytologic result'. This means that other variables provide useful information beyond that provided by 'cytologic result'. This was already noticed by Harsoulis *et al.* [10]. The lack of sensitivity of 'cytologic result' was demonstrated by Akerman *et al.* [7] who found a sensitivity of 57% on 203 malignant tumors. But 'cytologic result' may probably be improved by using additional technique such as cytometric DNA measurements [33].

'Sex' is a highly significant variable since it is the second choice when 'cytologic result' is included in the SLR and it is the first choice when 'cytologic result' is not included in the SLR. The greater probability of malignancy in males has rarely been emphasized as it should. Thomas *et al.* [16] and Messaris *et al.* [3] have shown a higher frequency of malignancy nodules in males but Tourniaire *et al.* [17] have found no diagnostic value for 'sex' and Mustachi *et al.* [34] reported that the likelihood of malignancy was higher for females in their series.

'Irregular margin' has been retained as significant in the two SLRs. Although the diagnostic value of this variable has already been assessed by Yeung *et al.* [6], it is seldom used. Other 99m Tc scan variables such as vascular invasion [35] seem useful for the diagnosis of malignancy but it was impossible to use them in this work which uses only static scintigraphic images. We did not use any other scintigraphic examination such as thallium scan [4], the value of which is still controversial [11].

The significant ultrasound variables selected were 'homogeneous' in the SLR including 'cytologic result' and 'solid' in the SLR not including 'cytologic result'. These two variables are strongly correlated since all the homogeneous nodules are solid. The greatest likelihood of malignancy in solid thyroid nodules has already been assessed by Aschcraft and Van Herle [8] who reviewed 16 published series of patients. In this study, we did not take into account the halo sign [36] the diagnostic value of which has not yet been established [5].

In the same way, the diagnostic value of 'age' remains controversial in the literature [3, 12, 16, 17]. Yet, in this study 'age' was highly significant according to the univariate test. It was selected in the SLR not including 'cytologic result'. The non selection of 'age' in the SLR including 'cytologic result' may be explained by a high correlation between 'age' and 'cytologic result'.

It must be emphasized that none of our patients had a history of cervical irradiation [37] and that only one patient had a cervical compression. None of the other clinical variables has been selected in the SLR. This result agrees with those already published since the clinical variables are often considered unreliable for differentiating malignant from benign lesions [8, 12, 14, 17, 36].

Our results show that with four variables it is possible to classify the patients with a sensitivity of 96% and a specificity of 73%. A 96% sensitivity instead of a 100% sensitivity was obtained using the CVP because a patient with a malignant tumor was always misclassified. This outlying patient was a female, with negative cytologic result, without irregular margin on the 99m Tc scan and whose nodule was not solid according to the ultrasound examination. This observation suggests that it is never possible to achieve a sensitivity of 100%. It could also justify the strategy of Hoffmann *et al.* [12] and Mellière *et al.* [38] who operate on all thyroid nodules. Nevertheless, the misclassification of a very small number of malignant nodules has limited practical consequences because each patient who is not operated on is regularly followed.

In our department, the decision for surgery is now assessed according to the value of the logistic function calculated with 'cytologic result', 'sex', 'irregular margin' and 'homogeneous' variables. Patients who do not undergo surgery are reexamined every year.

The variables included in our logistic function and their regression coefficients may not necessarily be the same for another population. Clinical, cytologic, scintigraphic and ultrasound variables are operator-dependent. The accuracy of these investigations may vary from one medical center to another. Thus, it would be preferable for each individual medical staff to determine its own logistic function.

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APPENDIX

The logistic function is the probability of benignity and is given by:

$$\text{Logistic function} = \frac{\exp(B_0 + \sum_{i=1}^{P} B_i X_i)}{1 + \exp(B_0 + \sum_{i=1}^{P} B_i X_i)}$$

where: P is the number of significant variables in the model, X_i is the value of the ith variable, B_i is the value of the regression coefficient of the ith variable and B_0 is a constant.

The sensitivity is the probability of a test being positive in a disease patient. It is estimated by the ratio of the number of true positives (correctly diagnosed disease patients) and the total number of disease patients.

The specificity is the probability of a test being negative in a non-disease patient. It is estimated by the ratio of the number of true negatives (correctly diagnosed non-disease patients) and the total number of non-disease patients.

The receiver operating characteristic (ROC) [24, 25] curve is the plot of the values of the sensitivity vs. the values of (1 − the specificity) obtained for different threshold values.