mp ORL 86 ANGLAIS 207-275(new) 15/02/05 11:33 Page 1

Surgical indications for thyroid nodules

Nicolas Guevara, Laurent Castillo, José Santini.

Otorhinolaryngology - Head and Neck Surgery Department - Pasteur Teaching Hospital - Nice - France.

ABSTRACT

Study objective: Thyroid nodules are so common as to constitute a public health problem. The abundant literature on their diagnostic management reflects the absence of a consensus. Fine-needle aspiration biopsy (FNAB) is the gold-standard diagnostic investigation. The objective of this study was to evaluate thyroid nodule management in our department according to the rules of evidence-based medicine.
Material and methods: We retrospectively reviewed the medical charts of 398 patients managed at our department for thyroid nodules over a 3-year period. Diagnostic performance characteristics were computed for physical findings, radionuclide scanning, high-resolution ultrasonography (HRUS), and HRUS-guided FNAB, using surgical specimen histology as the reference. **Results:** Age older than 70 years; a hard nodule upon palpation; and presence of cervical lymphadenopathy were significantly associated with a diagnosis of cancer. Hypoechogenicity and microcalcifications by HRUS and malignant or suspicious cells by FNAB significantly predicted cancer. Likelihood ratios were similar for FNAB and HRUS. Radionuclide scanning failed to assist in the diagnosis of cancer. **Conclusion:** High-resolution ultrasonography and high-resolution ultrasonography guided fine-needle aspiration biopsy are the best diagnostic tools for differentiating benign nodules from suspicious or malignant nodules. *(Fr ORL - 2005 ; 86 : 1 - 9)*

Keywords: Thyroid nodules, Diagnosis, Evidence-based medicine.

Submitted for publication: April 2004
Accepted for publication: December 2004
Corresponding author: Nicolas Guevara
Service d'ORL et de Chirurgie de la Face et du Cou
Hôpital Pasteur - 30 avenue de la Voie romaine
BP 69 - 06002 Nice Cedex 1 - France
e-mail: nicolas.guevara@wanadoo.fr

mp ORL 86 ANGLAIS 207-275(new) 15/02/05 11:33 Page 2

INTRODUCTION

The management of thyroid nodules has changed considerably in recent years. Before the 1980s, the diagnostic strategy was fairly straightforward. Only palpable nodules were investigated, and radionuclide scanning was used to distinguish hot nodules at low risk of malignancy from cold nodules, which included most malignancies. All palpable cold nodules were removed surgically; only 10% were found to be benign upon histology.

Over the last 25 years, the development of high-resolution ultrasonography (HRUS) and fine-needle aspiration biopsy (FNAB) has provided surgeons with valuable guidance. However, these investigations have been used either selectively on the basis of rational criteria or, more often, according to a school of thought. As a result, a number of complex diagnostic strategies have emerged, and the best strategy is not agreed on. The combined use of several diagnostic investigations has resulted in a substantial cost burden. Furthermore, the widespread use of HRUS as a noninvasive diagnostic tool has led to the diagnosis of nonpalpable thyroid nodules [1-2], which prompt further investigations, generating additional costs and causing psychological stress in patients who usually require no treatment [3].

A rational strategy for managing thyroid nodules is needed to distinguish common benign conditions from malignancy in a highly reliable and cost-effective manner. To this end, a number of guidelines have been developed using the principles of evidence-based medicine.

Evidence-based medicine consists in using the best current evidence to make preventive, diagnostic, and/or therapeutic decisions about the individual patient. This approach was developed in the 1980s by researchers at McMaster University in Hamilton, Canada,[4] who were working on a new teaching strategy based on self-learning by small groups of students closely supervised by a senior tutor, clinical problem-solving as the main focus of training, and use of the best current evidence to guide decisions. In a 1992 article in JAMA [5], evidence-based medicine is described not only as a new teaching approach, but also as a tool for improving the quality of clinical practice. Sackett DL et al. defined evidence-based medicine as the *"conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients"*[6].

In the field of diagnostic management, evidence-based medicine involves an evaluation of diagnostic investigations based on measures that are directly relevant to everyday clinical practice, such as pretest probability, posttest probability, and likelihood ratio. The results of this evaluation help clinicians to select the investigations best suited to each individual patient.

The objective of this study was to evaluate the management of thyroid nodules in our department, using the principles of evidence-based medicine. More specifically, we evaluated the performance of diagnostic investigations in determining which patients with asymptomatic thyroid nodules required surgery.

MATERIAL AND METHODS

We retrospectively assessed surgical decisions in 398 consecutive patients treated surgically for thyroid nodules between January 1, 2000, and December 31, 2002, at the Otorhinolaryngology -- Head and Neck Surgery Department, Pasteur Teaching Hospital, Nice, France.

All surgical decisions were made by the same clinician. Diagnostic investigations were ordered by hospital-based or office-based physicians. HRUS of the thyroid gland was obtained routinely, whereas FNAB was not. When performed, FNAB was done under ultrasound guidance, and each nodule larger than 1 cm in diameter was aspirated three times.

We excluded patients who underwent thyroid procedures during surgery for hyperparathyroidism and those who required thyroidectomy for Graves' disease. We divided the patients into three categories based on the reason for surgery: mechanical complications (compression of the aerodigestive tract), hyperthyroidism (with any pattern of thyroid lesions from solitary nodule to multinodular goiter), and suspected cancer (potentially malignant nodule).

In this last category, which formed the basis for the present study, most of the patients were free of symptoms but required an evaluation of the risk of cancer within the nodule or nodules.

We used a standardized diagnostic strategy, differentiating cases where surgery was mandatory from those where the surgeon or patient deemed that surgery was preferable over other options.

• *Surgery was considered mandatory in patients with any of the following:*

- Serum thyrocalcitonin level greater than

mp ORL 86 ANGLAIS 207-275(new) 15/02/05 11:33 Page 3

10 ng/L, indicating a high risk of medullary thyroid carcinoma or C-cell hyperplasia;
- Malignant or suspicious cells by FNAB;
- A hard nodule to palpation; or a suspicious cervical lymphadenopathy indicating a high risk of cancer.

• *Surgery was deemed preferable over other options, either by the surgeon or by the patients in a number of patients who did not meet the above-listed criteria.*

- The surgeon based this preference on the presence of several factors associated with a high risk of cancer: age younger than 25 years, male gender, immunodeficiency, history of neck irradiation, family history of thyroid carcinoma, nodule larger than 3 cm, and ultrasound showing a solid hypoechoic nodule with uneven contours and microcalcifications (for instance, surgery would be preferred in a man with immunodeficiency and a solid hypoechoic nodule larger than 20 mm in diameter).
- Patients based their preference on their personal opinion that surgery was better than monitoring with repeat FNAB; during a private interview with the surgeon, these patients were fully informed of the advantages and drawbacks of surgery.

We collected detailed descriptive data on the clinical features, laboratory test results, HRUS and FNAB findings, radionuclide scan images, and histology of thyroid nodules treated surgically. We then compared the findings from diagnostic investigations in patients with and without malignant disease as assessed histologically, and we looked for factors significantly associated with malignancy.

Statistics

Associations between histologically documented cancer and each of the qualitative variables (gender, history, clinical features, HRUS findings, FNAB findings, and radionuclide scan findings) were evaluated using the chi-square independence test, or the Fisher exact test when the qualitative variable was dichotomous and at least one of the sample sizes was smaller than 5.
Student's test for unpaired data was used to evaluate associations between histologically documented cancer and quantitative variables (age and nodule size by HRUS).

To assess associations between each HRUS finding and histologically documented cancer, we used logistic regression, in which the independent variable was presence of cancer and the dependent variables were HRUS findings. Variables yielding P values smaller than 0.02 in the univariate analysis were entered into a multivariate model. Crude and adjusted odds ratios (ORs) were computed, with their 95% confidence intervals (95 % CIs), and Wald's test was used to look for significant associations.
The alpha risk was set at 5 %. All tests were two-sided. Statistical tests were run using the SAS software package (SAS Institute Inc. 1996. SAS/Stat Software: Changes and enhancement through release 6.11. Carry, NC, USA).

RESULTS

Descriptive data

During the 3-year period from 2000 to 2002, 398 patients underwent surgery for thyroid nodules at our department. The female-to-male ratio was 3.1/1 (301 women and 97 men) and the age range was 17 to 83 years (mean, 51.8±13.8 years).
Histological examination of the operative specimens found at least one malignant lesion in 68 (17.1%) patients, 50 women and 18 men (ratio 2.8/1).
The reason for surgery was presence of mechanical complications in 53 (13.3%) patients, hyperthyroidism in 68 (17.1%) patients (17 [25%] with solitary nodules and 51 [75%] with more than one nodule), and suspected cancer in 313 (78.6%) patients (with one or more nodules).

Of the 68 patients with at least one malignant lesion, 48 had cancer tissue within the nodule investigated preoperatively, 19 had cancer discovered at another site during surgery, and 1 had both. All patients without cancer in the nodule investigated preoperatively were included in the "benign lesion category", as this was the only nodule relevant to the evaluation of preoperative diagnostic investigations (Table I).
Of the 14 patients with high serum thyrocalcitonin levels, 4 had papillary carcinomas discovered intraoperatively outside the investigated nodule.
Of the 69 patients with cancer, 51 (73.9%) had papillary adenocarcinomas (31 [60.8%] in the investigated nodule and 20 [39.2%] elsewhere), 12 (17.4%)

mp ORL 86 ANGLAIS 207-275(new) 15/02/05 11:33 Page 4

had vesicular cancer (all in the investigated nodule), 5 (7.25%) had medullary thyroid carcinoma, and 1 (1.45%) had anaplastic cancer.

Table I. Reasons for surgery and histological diagnoses in 313 patients referred to our head and neck surgery department for thyroid nodules. ***Some patients in the mandatory surgery group had more than one criterion: 24 met both physical and FNAB criteria, 2 met both laboratory test and FNAB criteria, and 3 met all three criteria.***

		Benign (n %)	Malignant (n %)
Mandatory surgery	Laboratory tests	8 (57.1 %)	6 (42.9 %)
	FNAB	50 (63.3 %)	29 (36.7 %)
	Physical findings	55 (67.9 %)	26 (32.1 %)
	At least one of the three criteria	**101 (72.1 %)**	**39 (27.9 %)**
Preferred surgery	Surgeon's preference	95 (90.5 %)	10 (9.5 %)
	Patient's preference	68 (100 %)	0 (0 %)
	Total	**163 (94.2 %)**	**10 (5.8 %)**

FNAB: fine-needle aspiration biopsy
Significant factors are in bold type

Univariate analysis of factors potentially associated with malignancy

For this analysis, we excluded the 14 patients with high serum thyrocalcitonin levels. Thus, 299 patients were included, of whom 69 had cancer. Tables II and III report results for patient-related factors and physical findings.

As shown in Table IV, one patient was excluded from the analysis of HRUS features; this patient had suspicious cervical lymphadenopathy, no nodule visible by HRUS, and a 7-mm papillary cancer by histology. In the 298 other patients, four HRUS features were studied: hypoechogenicity, microcalcifications, uneven contours and size of nodules.
Nodule size failed to discriminate between benign and malignant nodules. Mean size was 25.5 mm for benign nodules and 23.1 mm for malignant nodules (p=0.33). The proportion of nodules larger than 30 mm was similar for benign nodules (29/195, 14.87%) and malignant nodules (13/102, 12.75 %) (OR, 0.8 ; 95 % CI, [0.4-1.7], P=0.6).

Table II: Univariate analysis of patient-related risk factors potentially associated with thyroid cancer

		Cancer rate (%)	Odds ratio	95% confidence interval	p value
Age	**≤ 70 years** **≥ 70 years**	**12.20** **35.70**	**4**	[1.70-9.40]	**0.0025**
Gender	Male Female	17.65 13.40	1.38	[0.67-2.87]	0.38
Immunodeficiency	No Yes	14.10 22.20	1.70	[0.35-8.65]	0.62
Family history of thyroid cancer	No Yes	13.42 29.40	2.70	[0.89-8.02]	0.08
Family history of benign thyroid nodules	No Yes	14.10 15.05	1.10	[0.54-2.16]	0.82

Significant factors are in bold type.

Table III: Univariate analysis of physical findings potentially associated with thyroid cancer

		Cancer rate (%)	Odds ratio	95% confidence interval	p value
Number of nodules	Solitary nodule Goiter with two or more nodules	18.20 12.23	1.60	[0.82-3.02]	0.17
Hard and/or immobile nodule	No Yes	**9.30** **30.14**	**4.20**	[2.15-8.25]	**<0.0001**
Suspicious cervical lymphadenopathy	No Yes	**13.36** **57.14**	**8.65**	[1.86-40.12]	**0.01**

Significant factors are in bold type.

mp ORL 86 ANGLAIS 207-275(new) 15/02/05 11:33 Page 5

Table V reports the risk of cancer according to the number of HRUS criteria; 2 patients were excluded, 1 with no nodule visible by HRUS (see above) and 1 with anaplastic cancer infiltrating the entire thyroid gland; this left 297 patients. In the multivariate analysis of HRUS features, hypoechogenicity and microcalcifications were significantly associated with cancer, whereas uneven contour was not.

Tc99m radionuclide scanning was performed in 128 (42.8%) of the 299 patients. Histological findings according to radionuclide scan findings are reported in Table VI. Radionuclide scan findings were not associated with malignancy (P>0.05).

FNAB was done in 136 (45.5 %) of the 299 patients (Table VII). Patients with inconclusive FNAB findings were excluded from the analysis. When computing sensitivity and specificity, we pooled patients with malignant cells and those with suspicious cells (papillary or vesicular cancer) into a single group. *Sensitivity* was 92.9 % (26/28), *specificity* was 49.5 % (47/95), *positive predictive value* was 35.1 % (26/74), and *negative predictive value* was 95.9 % (47/49). The *false-negative rate* was 4.1 % (2/49) and the *false-positive rate* was 64.9 % (48/74). Among patients with malignant cells or suspicious follicular or papillary cells by FNAB, 35.1% had cancer; among patients with normal FNAB findings, 4.1 % had cancer. This difference was highly significant (OR, 12.7; 95 % CI, 2.9-56.7; P<0.0001).

Table IV: Univariate and multivariate analyses of associations between high-resolution ultrasonography findings and cancer in the investigated nodule. ***Ultrasound features:***
dependent variable = presence of malignant tissue in the investigated nodule
independent variable = presence of hypoechogenicity, microcalcifications, or uneven contours

		Univariate analysis			Multivariate analysis		
		OR	**95% CI**	**p value**	**OR**	**95% CI**	**p value**
Hypoechogenicity	no	1.0		**<0.0001**	1.0		**0.0004**
	yes	5.2	[2.6-10.9]		**4.2**	[1.9-9.5]	
Microcalcifications	no	1.0		**<0.0001**	1.0		**<0.0001**
	yes	7.2	[3.5-14.5]		**6.2**	[2.9-13.3]	
Uneven contours	no	1.0		**0.0004**	1.0		0.27
	yes	4.0	[1.8-8.5]		1.7	[0.7-4.1]	

OR: odds ratio; 95%CI: 95% confidence interval
Significant factors are in bold type.

Table V: Cancer rate according to the number of high-resolution ultrasonography features predicting malignancy

Number of ultrasonography features	Benign n	Malignant n (%)*
0	148	4 (2.6 %)
1	79	20 (20.2 %)
2	23	12 (34.3 %)
3	5	7 (58.3 %)

* : p<0,0001.

Table VI: Distribution of cancers according to radionuclide scan findings

Radionuclide uptake	Benign n	Malignant n (%)
Hot nodule	11	2 (15.4 %)
Cold nodule	94	9 (8.70 %)
Normal uptake	11	1 (8.33 %)

Table VII: Distribution of results of fine-needle aspiration biopsy

	Fine-needle aspiration biopsy findings					
		Benign	Incon-clusive	Suspicious follicular	Suspicious papillary	Malignant
Final histological diagnosis	No cancer	47	10	44	4	0
	Cancer	2 (4 %)	3 (23 %)	7 (13.7 %)	12 (75 %)	7 (100 %)

mp ORL 86 ANGLAIS 207-275(new) 15/02/05 11:33 Page 6

Table VIII: Likelihood ratios for patient-related factors, physical findings, and findings from high-resolution ultrasonography and fine-needle aspiration biopsy.

	Se	Sp	1-Sp	Positive likelihood ratio	Negative likelihood ratio
Patient-related and physical findings					
Male vs. female	27.91	78.13	21.87	1.28	0.92
Age < 70 y vs. ≥ 70 y*	23.26	92.97	7.03	3.31	0.83
Family history of thyroid cancer	11.63	95.31	4.69	2.48	0.93
Family history of benign thyroid nodules	32.56	69.14	30.86	1.06	0.98
Hard/immobile nodule*	51.16	80.08	19.92	2.57	0.61
Suspicious cervical lymphadenopathy*	9.30	98.83	1.17	**7.95**	**0.92**
Ultrasound findings					
Hypoechogenicity*	72.09	66.67	33.33	2.16	0.42
Microcalcifications*	48.84	88.24	11.76	4.15	0.58
Uneven contours*	30.23	90.20	9.80	3.08	0.77
Size: < 3 cm vs. ≥ 3 cm	30.95	65.10	34.90	0.89	1.06
0 criteria vs. 1 or more	90.70	58.04	41.96	2.16	**0.16**
0 or 1 criterion vs. 2 or more	44.19	89.02	10.98	4.02	0.63
0, 1, or 2 criteria vs. 3 criteria	16.28	98.04	1.96	**8.31**	0.85
Hypoecho. + Microcalc. vs. other	32.56	94.90	5.10	**6.39**	0.71
Hypoecho. + uneven contours vs. other	27.91	92.55	7.45	3.75	0.78
Microcalc. + uneven contours vs. other	16.28	97.65	2.35	**6.92**	0.86
Fine-needle aspiration biopsy findings					
M+SF+SP vs B	92.86	49.47	50.53	1.84	**0.14**
M+SP vs B	90.50	92.20	7.80	**11.60**	**0.10**

Se: sensitivity; Sp: specificity; M: malignant; SF: suspicious follicular; SP: suspicious papillary; B: benign
** Statistically significant (P<0.01) by univariate analysis.*

Likelihood ratios for factors associated with malignancy

The results are reported in Table VIII. The results should be interpreted as follows: for instance, presence of microcalifications by HRUS was 4.15 times more common in patients with than without cancer, whereas absence of microcalcifications was 1.72 times less common among patients with than without cancer (« cancer » being defined as malignant tissue within the investigated nodule). Likelihood ratio values in the 5-10 range or the 0.1-0.2 range indicate large differences in likelihoods.

DISCUSSION

The analysis of our diagnostic strategy and its comparison to recommendations issued by the French national agency for medical evaluation (ANDEM, Agence Nationale pour le Développement de l'Évaluation Médicale) [7] highlights recent changes in the management of thyroid nodules, with HRUS and FNAB gradually superseding radionuclide scanning. These changes are consistent with earlier work showing that FNAB is the diagnostic investigation with the highest yield [8-9] and that HRUS may be as useful as FNAB in evaluating thyroid nodules for cancer.

mp ORL 86 ANGLAIS 207-275(new) 15/02/05 11:33 Page 7

The prevalence of malignant thyroid lesions in our series of patients treated surgically over a 3-year period was 17.1% when both microscopic and macroscopic cancers were included. A far lower prevalence was reported by the French Society for Otorhino-laryngology in 1995 (7.56%) [10], and among 366 patients managed between 1995 and 1997 at our department, the prevalence of cancer was 12.8%, [11], although no differences were noted over time in the distribution of histological types. This increase in the cancer rate among patients referred to head and neck surgeons probably reflects better patient selection. Thus, after exclusion of cancers discovered outside the investigated nodule (5%) and patients who preferred surgery over monitoring, the cancer rate in our study was 20% (49/245).

As with all retrospective studies of surgical patients, selection bias occurred in our study, as only patients referred to a head and neck surgery department were included. To minimize selection bias, we included all patients who underwent thyroid surgery rather than only those patients with a strong suspicion of cancer: thus we included 69 patients (21.7% of our population) who were offered monitoring but preferred surgery; none of these 69 patients had cancer.

We selected patients for surgery based on ANDEM recommendations and on our personal experience [7, 11- 12]. Since 2000, we use a standardized selection procedure, which has benefited from recent advances in HRUS and FNAB. Furthermore, we use clinical features and the results of HRUS and FNAB to distinguish patients in whom surgery is mandatory from those in whom other options exist. However, among the criteria used in our study, several failed to predict cancer in the present study.

Computing the positive and negative likelihood ratios for each criterion, which reflect usefulness in everyday clinical practice, supplied us with valuable information.

Presence of a criterion associated with a likelihood ratio greater than 5 strongly supports a need for surgery. For instance, assuming that the baseline prevalence of cancer is 4% (prevalence of cancer among patients with thyroid nodules), a likelihood ratio of 5 on the Fagan nomogram [13] yields a posttest probability of cancer greater than 20%.

The positive likelihood ratios were 7.95 for a suspicious cervical lymphadenopathy and 11.6 for FNAB findings certainly or possibly indicating papillary carcinoma. Thus, surgery is mandatory in patients with either criterion.

In contrast, a hard nodule, which indicated that surgery was mandatory in our strategy, had a positive likelihood ratio of only 2.57. A plausible explanation is that nodules accompanied with macrocalcifications or thyroiditis are frequently hard or immobile yet usually benign. Although FNAB may correct the diagnosis in some patients, calcified nodules may be difficult to aspirate and should in this case be removed surgically. FNAB findings suggesting follicular cancer had a very low positive likelihood ratio, so that the overall positive likelihood ratio of FNAB was only 1.84. However, because FNAB was highly sensitive, it had an excellent negative likelihood ratio, of 0.14. A negative likelihood ratio lower than 0.2 strongly supports nonsurgical management. FNAB showing only benign cells was 7.1 times (1/0.14) more common in patients with than without cancer. Again assuming a baseline prevalence of thyroid cancer of 4% and using the Fagan nomogram, a negative likelihood ratio lower than 0.2 indicates a posttest likelihood of cancer lower than 1%. Thus the risk of finding malignant tissue within a nodule that produces benign FNAB results is smaller than 1%.

HRUS was performed routinely in our patients and often contributed to the therapeutic decision (mandatory surgery or surgeon's preference). Our likelihood ratio evaluation indicated that HRUS was almost as useful as FNAB. Although no single HRUS criterion was conclusive and nodule size was unrelated to cancer risk, concomitant presence of both criteria independently associated with cancer (hypoechogenicity and microcalcifications) had a positive likelihood ratio of 6.39, indicating that surgery was mandatory. On the opposite, absence of all three HRUS criteria had a negative likelihood ratio of 0.16, nearly identical to the value for benign FNAB findings (0.14). Thus, a "benign" HRUS pattern can be defined.

Using the same standardization system as with FNAB results, HRUS results could be categorized according to the risk of cancer (malignant, suspicious, or benign; or low, intermediate, or high risk). Studies having a satisfactory level of evidence found that several HRUS criteria, used alone or in combi-

mp ORL 86 ANGLAIS 207-275(new) 15/02/05 11:33 Page 8

nation, were associated with a diagnosis of cancer [14-18]. However, no diagnostic classification of HRUS findings has been developed to date.

CONCLUSION

The risk of cancer in a thyroid nodule is evaluated on the basis of physical findings and diagnostic investigations, most notably FNAB and HRUS. FNAB is currently the gold standard investigation and should be performed routinely.

Recently developed immunohistochemical and genetic techniques for examining FNAB specimens may produce nearly 100% reliability in the near future. Technical advances in HRUS have benefited the diagnosis of thyroid nodules. HRUS can be expected to remain a key tool for assisting in surgical decisions. It extends physical findings and constitutes the first step in the evaluation of gross nodule appearance. However, HRUS remains unstandardized and heavily operator-dependent, explaining why a diagnostic classification has yet to be developed.

REFERENCES

1. Ross DS. Nonpalpable thyroid nodules-managing an epidemic. J Clin Endocrinol Metab. 2002; 87: 1938-1940.
2. Tan GH, Gharib H, Reading CC. Solitary thyroid nodule. Comparison between palpation and ultrasonography. Arch Intern Med. 1995; 155: 2418-2423.
3. Meier CA. Thyroid nodules: pathogenesis, diagnosis and treatment. Baillieres Best Pract Res Clin Endocrinol Metab. 2000; 14: 559-575.
4. Neufeld VR, Woodward CA, Mac Leod SM. The McMaster MD program: a case study of renewal in medical education. Acad Med. 1989; 64: 423-432.
5. Evidence-Based Medicine Working Group. Evidence-based Medicine. JAMA 1992; 268: 2420-2425.
6. Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. BMJ 1996; 312: 71-72.
7. ANDEM. La prise en charge diagnostique du nodule thyroïdien. Recommandations pour la pratique clinique. Paris: Agence Nationale pour le Développement de l'Evaluation Médicale-Service des Etudes; décembre 1995.
8. Feld S. AACE clinical practice guidelines for the diagnosis and management of thyroid nodule.American Association of Clinical Endocrinologists. American College of Endocrinology. Endocr Pract. 1996; 2: 80-84.
9. Singer PA, Cooper DS, Daniels GH, et al. Treatment guidelines for patients with thyroid nodules and well-differentiated thyroid cancer. American Thyroid Association. Arch Intern Med. 1996; 156: 2165-2172.
10. Cannoni M, Demard F. Les nodules thyroïdiens. Du diagnostic à la chirurgie. Paris: Arnette Blackwell; 1995.
11. Castillo L, Haddad A, Meyer JM, Sadoul JL, Santini J. Predictive malignancy factors in thyroid nodular disease. Ann Otolaryngol Chir Cervicofac. 2000; 117: 383-389.
12. Guevara N, Meyer JM, Castillo L, et al. Indications opératoires pour pathologie nodulaire de la thyroïde. Revue officielle de la Société Française d'O.R.L. 2000; 75: 21-24.

mp ORL 86 ANGLAIS 207-275(new) 15/02/05 11:33 Page 9

13. Fagan TJ. Nomogram for Bayes' theorem. N Engl J Med. 1975; 293: 257.
14. Koike E, Noguchi S, Yamashita H, Murakami T, Ohshima A, Kawamoto H, Yamashita H. Ultrasonographic characteristics of thyroid nodules: prediction of malignancy. Arch Surg. 2001; 136: 334-337.
15. Peccin S, de Castsro JA, Furlanetto TW, Furtado AP, Brasil BA, Czepielewski MA. Ultrasono-graphy: is it useful in the diagnosis of cancer in thyroid nodules? J Endocrinol Invest. 2002; 25: 39-43.
16. Leenhardt L, Menegaux F, Fran B, et al. Selection of patients with solitary thyroid nodules for operation. Eur J Surg. 2002; 168: 236-241.
17. Kim EK, Park CS, Chung WY, Oh KK, Kim DI, Lee JT, Yoo HS. New sonographic criteria for recommending fine-needle aspiration biopsy of nonpalpable solid nodules of the thyroid. AJR Am J Roentgenol. 2002; 178: 687-691.
18. Papini E, Guglielmi R, Bianchini A, et al. Risk of malignancy in nonpalpable thyroid nodules: predictive value of ultrasound and color-Doppler features. J Clin Endocrinol Metab. 2002; 87: 1941-6.