

Low false-negative rate of cytology in thyroid nodules ≥ 4 cm

Baixa taxa de falso-negativo da citologia em nódulos tireoidianos ≥ 4 cm

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ABSTRACT

Objective: To report the results of cytology and histology obtained for a series of systematically resected thyroid nodules ≥ 4 cm. **Methods:** A group of 151 patients with thyroid nodules ≥ 4 cm was submitted to surgery despite the cytology result. **Results:** Malignancy was confirmed histologically in 22.5% of the patients. Excluding cases of insufficient material, cytology was benign in only 3/31 carcinomas (90.3% sensitivity). The frequency of malignancy was 35% among nodules with indeterminate cytology (follicular neoplasm), and there was a predominance (77%) of papillary carcinoma. The negative predictive value of benign cytology was 96.4%. **Conclusions:** The false-negative rate of cytology in thyroid nodules ≥ 4 cm does not justify systematic resection of these nodules in asymptomatic patients with benign cytology. *Arq Bras Endocrinol Metab.* 2009;53(9):1143-5

Keywords

Thyroid nodule; cytology; benign

RESUMO

Objetivo: Reportar os resultados da citologia e da histologia em uma série de nódulos tireoidianos ≥ 4 cm sistematicamente ressecados. **Métodos:** Foram submetidos à cirurgia 151 pacientes com nódulo tireoidiano ≥ 4 cm, a despeito do resultado da citologia. Apenas a histologia referente a este nódulo foi considerada nos resultados. **Resultados:** Malignidade foi confirmada histologicamente em 22,5% dos pacientes. Excluindo os casos com material insuficiente, a citologia foi benigna somente em 3/31 carcinomas (sensibilidade 90,3%). A frequência de malignidade foi de 35% nos nódulos com citologia indeterminada (neoplasia folicular), predominando o carcinoma papilífero (77%). O valor preditivo negativo da citologia benigna foi 96,4%. **Conclusões:** A taxa de falso-negativo da citologia em nódulos tireoidianos ≥ 4 cm não justifica a ressecção sistemática destes em pacientes assintomáticos com citologia benigna. *Arq Bras Endocrinol Metab.* 2009;53(9):1143-5

Descritores

Nódulo da glândula tireoide; citologia; benigna

INTRODUCTION

Fine-needle aspiration cytology (FNAC) is the best method for the definition of the nature of thyroid nodules. Although the false-negative rate of FNAC is low, especially when guided by ultrasound, these cases are clinically relevant, since a delay in the diagnosis of malignancy and, consequently, in surgery may compromise the prognosis of the patient (1,2). The concern that a thyroid nodule might be malignant despite benign cytology is even greater for nodules measuring ≥ 4 cm. Compared to smaller nodules, the false-negative rate of FNAC seems to be higher in these cases

(3-5) and, when malignant, these nodules present a higher chance of metastasizing and a poorer prognosis (2,6). Thus, a delay in treatment may have a major impact. In this respect, some investigators recommend surgery for nodules ≥ 4 cm (3-5), irrespective of the cytology result. This approach has so far also been used at our service. However, data regarding this recommendation are controversial and show that the sensitivity of FNAC is not compromised in the case of larger nodules (7-10).

The objective of the present study was to report the results of FNAC and the histology obtained for a series of

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consecutive patients with thyroid nodules ≥ 4 cm systematically resected.

METHODS

All patients examined in this study between 2003 and the conclusion of this study (2008), who had thyroid nodules ≥ 4 cm on ultrasound and no contraindication/refusal of surgery were submitted to nodule resection despite the FNAC result – which was only used for definition of the extent of surgery. Eight of 162 patients had a contraindication to surgery and 3/162 refused surgery. These patients were excluded. The final sample consisted of 151 patients (111 women; age range: 12 to 80 years; median: 50 years). None of the patients had a family history of medullary or papillary carcinoma (in the latter case, at least two first-degree relatives) or had been previously exposed to neck radiation. Paralysis of the vocal cord ipsilateral to the nodule was not confirmed in ten patients who reported persistent hoarseness of recent onset. The study was approved by the Research Ethics Committee.

Sonography was performed with a linear multifrequency 10 to 12 MHz transducer for morphological analysis and the images were analyzed by experienced professionals. FNAC was performed with a 22-gauge needle and a 5- or 10-mL syringe. The smears were stained with hematoxylin-eosin and analyzed by pathologists experienced in thyroid pathology. Only the histological diagnosis of thyroid nodules ≥ 4 cm was considered for analysis.

RESULTS

The results of cytology and histology are shown in table 1. The most relevant findings regarding thyroid nodules ≥ 4 cm were the following:

- malignancy was histologically confirmed in 22.5% of cases;
- excluding cases of inadequate cytology, cytology was benign in 3/31 carcinomas (90.3% sensitivity);
- the negative predictive value of benign cytology was 96.4%;
- 35% of the nodules with indeterminate cytology (follicular neoplasm) were malignant.

DISCUSSION

In the present study, the rate of malignancy in thyroid nodules ≥ 4 cm was approximately 20%, in agreement

Table 1. Frequency of malignancy in thyroid nodules ≥ 4 cm according to cytology result

Cytology result	Malignancy (%)	Histological type
Malignant or suspicion of PTC	15/15 (100)	15 PTC
Indeterminate (follicular neoplasm)	13/37 (35)	7 FVPTC, 3 PTC, 1 FTCm, 2 FTCa
Inadequate	3/15 (20)	2 PTC, 1 FTCa
Benign	3/84 (3.6)	2 FVPTC, 1 FTCm
Total	34/151 (22.5)	9 FVPTC, 20 PTC, 5 FTC

PTC: papillary thyroid carcinoma; FVPTC: follicular variant of papillary thyroid carcinoma; FTCm: minimally invasive follicular thyroid carcinoma; FTCa: angioinvasive follicular thyroid carcinoma.

with previous studies, in which nodules of this size were also systematically resected (4). Since smaller nodules were not routinely resected in the present study or in the series of McCoy and cols. (4), it is not possible to state that a size ≥ 4 cm really increases the risk of malignancy. Studying consecutive cases of thyroidectomy for nodular disease, Meko and Norton (3) did not observe a difference in the rate of malignancy between nodules $<$ or ≥ 3 cm, which was about 20% for both. McHenry and cols. (8) showed that malignant nodules were even smaller than benign ones, with a mean size of 3.3 cm *versus* 4.4 cm. In contrast, Kuru and cols. (9) diagnosed carcinoma in 24% of nodules ≥ 4 cm *versus* 12% of nodules < 4 cm in a series of 662 thyroidectomies for nodular disease.

When cytology was indeterminate (follicular neoplasm), histology revealed malignancy in 35% of cases (versus 23.5% in nodules < 4 cm, with the same cytological result and systematically operated at Santa Casa de Belo Horizonte during the period of this study – unpublished data). Nodule size has been confirmed as a predictor of malignancy in cases with indeterminate cytology in most series, but not in all (11). Most (77%) carcinomas in nodules with indeterminate cytology (follicular neoplasm) were papillary and not follicular carcinomas. Similar findings have been published recently by Rago and cols. (12) for a large series.

Porterfield and cols. (7) retrospectively examined 597 patients with nodules ≥ 3 cm and benign cytology. No additional thyroid malignancies were identified during an average follow-up period of three years. A definitive histological diagnosis was available for 145 (20%) patients, who underwent thyroidectomy: one (0.7%) was false-negative. Kuru and cols. (9) reported false-negative rates of cytology of 1.3% and 4.3% for nodules < 4 cm and ≥ 4 cm, respectively ($p = 0.9$). In contrast, McCoy and cols. (4) found a false-negative

rate of cytology of 13% in nodules ≥ 4 cm. According to the authors, this rate is high enough to recommend routine surgery in these cases. In our series, the sensitivity of FNAC in nodules ≥ 4 cm was 90%, and the negative predictive value of benign cytology was 96.4%.

In conclusion, the false-negative rate of cytology in larger nodules alone is not high enough to justify routine surgery and we therefore have changed our management of these patients. Although uncommon (only 3.6%), false-negative results of cytology exist and, together with the fact that the tumors are ≥ 4 cm (associated with a poorer prognosis when carcinomas), require a close follow-up of patients with benign cytology who are not submitted to surgery with thyroidectomy being necessary in the case of growth of the nodule. In view of the differences between series (3-5,7-10), each center should determine its own false-negative rate of FNAC in large thyroid nodules and should define patient management based on this rate.

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