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ORIGINAL ARTICLE

# Methodology for evaluation of malignancy screening in surgical thyroid gland disease

**Vladimir Rubio,[a,*] José Manuel Tamarit,[b] Nuria Baviera,[c] Sergio Fernández,[d] Paloma Estrems,[b] Teresa Seijas,[b] Celia López,[b] and José Dalmau[b]**

[a]*Servicio de ORL, Hospital de Torrevieja, Alicante, Spain*
[b]*Servicio de ORL, Hospital Universitario Dr. Peset, Valencia, Spain*
[c]*Servicio de ORL, Hospital de Vinaroz, Castellón, Spain*
[d]*Servicio de Medicina Preventiva, Hospital Padre Jofré, Valencia, Spain*

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**KEYWORDS**
Surgical thyroid gland disease;
Thyroid gland cancer;
Fine-needle aspiration;
Extemporaneous biopsy

**Abstract**
*Introduction:* We review a methodology for detection of malignancy in thyroid gland surgery, comparing clinical exploration, ultrasonography, gammagraphy, fine-needle aspiration (FNA), and extemporaneous biopsy with the definitive pathological results.
*Material and methods:* We carried out a retrospective study on a sample of 433 (n=433) patients who had been intervened due to thyroid gland disease at the same ENT centre between 1999 and 2004. We collected information focusing on the characteristics of cervical exploration, ultrasonography, gammagraphy, FNA, extemporaneous biops,y and definitive pathological results.
*Results:* With n=433, the male/female ratio was approximately 1/9 (m/f, 1/9), the average age was 45.5 years (range, 13-87) and there was 20.3%of referred family history of thyroid gland disease; the cervical exploration, ultrasonography, and gammagraphy were not good tests for the screening of malignancy; FNA and extemporaneous biopsy offered 74% and 81% of sensitivity (Sn), and 73% and 92% of specificity (Sp) in the detection of malignancy. The specific sensitivities towards papillary carcinoma of FNA and extemporaneous biopsy were 81% and 88%, while they were 66%and 62.5%, respectively, for follicular carcinoma.
*Conclusions:* FNA has good sensitivity in clinical suspicion of thyroid papillary carcinoma, although it should be complemented by extemporaneous biopsy due to its better specificity. In the case of follicular carcinoma, there is a tendency towards conservative treatment, without carrying out extemporaneous biopsy previously and with reoperation in case of definitive malignancy.


*Corresponding author.
*E-mail address:* vladirubi@hotmail.com (V. Rubio).

**PALABRAS CLAVE**
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Punción-aspiración con aguja fina;
Biopsia extemporánea

**Evaluación metodológica para detección de malignidad en patología quirúrgica tiroidea**

**Resumen**
*Introducción:* Presentamos una revisión metodológica para detección de malignidad en cirugía tiroidea, comparando la palpación, la ecografía, la gammagrafía, la punción- aspiración con aguja fina (PAAF) y la biopsia extemporánea con la anatomía patológica definitiva.
*Material y métodos:* Realizamos un estudio retrospectivo sobre una muestra de 433 (n=433) pacientes intervenidos quirúrgicamente por patología de la glándula tiroides en un mismo centro de ORL desde 1999 a 2004. Realizamos recogida de datos centrándonos en las características de la palpación cervical, la ecografía, la gammagrafía, la PAAF, la biopsia extemporánea y la anatomía patológica definitiva.
*Resultados:* Con n=433 pacientes, la relación hombres/mujeres fue de 1/9 aproximadamente (m/f: 1/9), la edad media fue de 45,5 anos, con un rango comprendido entre 13 a 87 anos, y con un 20,3%de antecedentes de enfermedad tiroidea referidos; la palpación cervical, la ecografía y la gammagrafía resultaron pruebas de escaso valor para la detección de malignidad; la PAAF y la biopsia extemporánea nos aportaron un 74 y un 81% de sensibilidad y un 73 y un 92% de especificidad para la detección de malignidad. La sensibilidad específica para carcinoma papilar de la PAAF y la biopsia extemporánea fueron del 81 y del 88%, mientras que para el carcinoma folicular fueron del 66 y del 62,5% respectivamente.
*Conclusiones:* La PAAF es sensible en la sospecha clínica del carcinoma papilar de tiroides, aunque se debe complementar con la biopsia extemporánea por su mayor especificidad. Ante el carcinoma folicular hay tendencia al tratamiento conservador, sin realización de biopsia extemporánea y reintervención ante malignidad definitiva.


## Introduction

Surgical thyroid pathology usually represents a high percentage of otolaryngology surgery in many centres. Its diagnosis and indication depend on complementary techniques that often refine and sometimes decide the treatment and subsequent quality of life for patients. From the classical scintigraphy with metastable technetium 99 or iodine 131/123 to positron emission tomography or single photon imaging or imaging techniques such as ultrasound, computed tomography or magnetic resonance, the diagnostic spectrum is very broad, and availability in the healthcare environment often marks use and performance. The technique of fine-needle aspiration (FNA) and intraoperative biopsy are more efficient diagnostic techniques for detection of malignancy, especially FNA, whose routine performance has reduced the number of unnecessary thyroid surgeries.[1] To conduct an analysis of the method for malignancy diagnosis in surgical pathology of the thyroid gland, we performed a review of thyroid operations, focusing on the value of palpation, ultrasound, scintigraphy, FNA, and extemporaneous biopsy in comparison with the definitive pathology.

## Material and methods

We carried out a retrospective study on a sample of 433 patients undergoing thyroid pathology surgery in an otolaryngology centre from 1999 to 2004. We collected data (Table 1) from each patient concerning affiliation, age, gender, family history of thyroid disease, presentation of the disease, symptoms, prior medical treatment, cervical palpation and characteristics of nodular palpation, ultrasound nodular characteristics, scintigraphic nodular features, FNA, type of surgery and need for neck treatment (with or without cervical node emptying), location and number of parathyroid glands found, extemporaneous biopsy, definitive anatomical pathology, surgical complications, reoperation for malignancy of the definitive anatomy, prior suspicion of malignancy and cause for suspicion of malignancy (malignant or inconclusive FNA, rapid growth, suspicious exploration or others). However, for the present study, we focused on the results of cervical palpation, ultrasound, scintigraphy, FNA and extemporaneous biopsy compared with definitive anatomical pathology to evaluate the sensitivity (Sn) and specificity (Sp) of these tests for preoperative malignancy diagnosis. The data processing was performed with SPSS version 12 and Epidat 3.1 programs.

## Results

The sample size was of 433 patients intervened for surgical thyroid pathology, with a male/female ratio of 1.2/8.7, average age of 45.5 years and range from 13 to 87 years. The sampling distribution by age ranges showed 2.1% younger than 19, 30.5% between 20 and 39, 45.3% between 40 and 59, and 21.5% of 60 years or more. Up to 20.3% of patients referred family history of thyroid disease, the presentation was as single nodule in 45.3% of cases, multinodular goitre (MNG) in 35.1%, Graves' disease in 12.2%, toxic nodule

**Table 1** Main variables collected for the study

| | |
|---|---|
| Patient affiliation | |
| Age | |
| Gender | |
| Family history of thyroid disease | |
| Mode of presentation of disease | Single nodule |
| | Multinodular goitre |
| | Graves-Basedow disease, toxic nodule |
| | Others |
| Symptoms | Hyperthyroidism |
| | Subclinical hyperthyroidism Hypothyroidism |
| | Euthyroidism |
| Prior medical treatment | Antithyroids |
| | Radioactive iodine |
| | Thyroid hormones |
| Cervical palpation | Not palpable |
| | Single nodule (measurement) |
| | MNG (measurement of major nodule) |
| | Diffuse goitre |
| Characteristics of nodular palpation | Soft, firm, or hard |
| | Adhered or mobile |
| Characteristics of nodular ultrasound | Homogeneous or heterogeneous |
| | Size of nodule (larger in MNG) |
| | Solid or cystic |
| | Presence of calcifications |
| Characteristics of nodular scintigraphy | Hypercapturing or hypocapturing |
| | Homogeneous or heterogeneous capture |
| Diagnostic approximation by FNA | Benign |
| | Malignant |
| | Doubtful |
| | Inadequate material for diagnosis |
| Extemporaneous biopsy | Benign |
| | Malignant |
| | Deferred |
| Definitive anatomical pathology | Adenoma |
| | MNG |
| | Papillary carcinoma |
| | Follicular carcinoma |
| | Medular carcinoma |
| | Anaplastic carcinoma |
| | Papillary microcarcinoma |
| | Hurthle cell carcinoma |
| | Others |

FNA indicates fine needle aspiration; MNG, multinodular goitre.

in 4.6%, and as other presentations in 2.8%. The final anatomical pathological result showed 12% malignancy (52 cases) versus 88% benign cases, of which 28% were adenomas and 52.3% were MNG. Malignant cases (12%) were due to papillary carcinoma in 7.4% (61.6% of all malignant tumours), follicular carcinoma in 2.1% (17.5% of carcinomas), papillary microcarcinoma in 2.8% (23.3%), Hurthle cell carcinoma in 0.2%, and small cell sarcoma in 0.2% of cases; there were no cases of medullar or anaplastic carcinoma during this period. The gender/malignancy ratio in males was 8.9% of malignant cases versus 12.5% in females, with no statistical significance; and the relationship age/malignancy by age range was 0% in children under 19 years old, 13% between 20 and 39, 8.7% between 40 and 59, and 19.4% of age 60 or older, with a statistical significance of 0.04. We established the relationship palpation/malignancy for hard and adhered nodular palpation as single variables and then requiring the 2 criteria (Table 2) with n=323 descriptions, which offered sensitivity (Sn) = 42.86%, specificity (Sp) = 88.96%, positive predictive value (PPV) = 36.73%, and negative predictive value (NPV) = 91.24% for hard nodule; Sn = 14.29%, Sp = 97.51%, PPV = 46.15%, and NPV = 88.39% for adhered nodule, and Sn = 42.86%, Sp = 87.9%, PPV = 34.62%, and NPV = 91.14% when requiring both criteria, with no statistical significance. The ultrasound study showed a malignancy rate over 384 cases of 14.1% in single node, of

**Table 2** Sensitivity and specificity values found on cervical palpation with hard and adhered nodules

| Palp hard / adhered | Def PA (B/M) | | Total |
|---|---|---|---|
| | Benign | Malignant | |
| Yes | 34 | 18 | 52 |
| No | 247 | 24 | 271 |
| Total | 281 | 42 | 323 |

Sensitivity, 42.86; specificity, 87.9.
Positive predictive value, 34.62; negative predictive value, 91.14.
B indicates benign; Def PA, definitive anatomical pathology; M, malignant; Palp, palpation.

**Table 3** Relationship between solid nodule in ultrasound and malignancy in definitive anatomical pathology

| Solid nodule in ultrasound | Def PA (B/M) | | Total |
|---|---|---|---|
| | Benign | Malignant | |
| Yes | 269 | 39 | 308 |
| No | 32 | 1 | 33 |
| Total | 301 | 40 | 341 |

Sensitivity, 97.5; specificity, 10.63.
Positive predictive value, 12.66; Negative predictive value, 96.96.
B indicates benign; Def PA, definitive anatomical pathology; M, malignant.

**Table 4** Relationship between decreased scintigraphy and definitive malignancy

| Decreased scintigraphy nodule | Def PA (B/M) | | Total |
|---|---|---|---|
| | Benign | Malignant | |
| Yes | 310 | 32 | 242 |
| No | 79 | 3 | 82 |
| Total | 289 | 35 | 324 |

Sensitivity, 91.4; specificity, 27.33.
Positive predictive value, 13.23; negative predictive value, 96.34.
B indicates benign; Def PA, definitive anatomical pathology; M, malignant.

10.3% in MNG, and 4.3% in diffuse goitre. For solid versus non-solid nodule, with n=341, the malignancy rate was 12.7% versus 3% respectively. The ultrasound data in cases of solid nodularity offered Sn=97.5%, Sp=10.63%, PPV=12.66% and NPV=96.96%, with no statistical significance (Table 3). Comparing the size of nodules in ultrasound and palpation with criteria for malignancy, the benign nodules were larger, without statistical significance (3.3 cm in benign vs 3.2 cm in malignant, as an ultrasound average, and 3.1 vs 2.9 cm on palpation).

The scintigraphic study, with n=324 cases, showed 13.2% malignancy in hypocapturing nodule compared to 3.7% in non-hypocapturing, with Sn=91.4%, Sp=27.3%, PPV=13.23% and NPV=96.34 %, with a significance of 0.009 (Table 4).

**Table 5** Relationship between FNAB and definitive anatomical pathology

| FNAB B versus S/M | Def PA (B/M) | | Total |
|---|---|---|---|
| | Benign | Malignant | |
| Yes | 177 | 11 | 188 |
| No | 65 | 32 | 97 |
| Total | 242 | 43 | 285 |

Sensitivity, 74.42; specificity, 73.14.
Positive predictive value, 32.99; negative predictive value, 94.15.
B indicates benign; Def PA, definitive anatomical pathology; FNAB, fine-needle aspirative biopsy; M, malignant; S, suspicious.

**Table 6** Relationship between extemporaneous biopsy and definitive anatomical pathology

| Extemporaneous B versus S/M | Def PA (B/M) | | Total |
|---|---|---|---|
| | Benign | Malignant | |
| Yes | 199 | 7 | 206 |
| No | 17 | 31 | 48 |
| Total | 216 | 38 | 254 |

Sensitivity, 81.58; specificity, 92.13.
Positive predictive value: 64.58; negative predictive value: 96.6.
B indicates benign; Def PA, definitive anatomical pathology; M, malignant; S, suspicious.

We collected n=285 cases of FNA, grouping variables in benign versus suspicious/doubtful for malignancy and malignant, eliminating inadequate punctures, with Sn=74.42%, Sp=73.14%, PPV=32.99%, and NPV=94.15% (Table 5).

The intraoperative biopsy, with n=254 cases, was grouped into benign and malignant or deferred, with Sn=81.58%, Sp=92.13%, PPV=64.58%, and NPV=96.6% (Table 6), with a concordance index of 0.38 with FNA as per the kappa test.

Of all the interventions, 45% were total thyroidectomy, 42.7% were hemithyroidectomy with extemporaneous biopsy, 5.5% were subtotal thyroidectomy, 3.9% were hemithyroidectomy, and 2.5% were hemithyroidectomy with isthmusectomy, with 3.5% of reoperations (n=16 cases). In the reoperations, 10 cases were after hemithyroidectomy with extemporaneous biopsy (4 follicular carcinomas, 3 papillary carcinomas, 1 papillary microcarcinoma, 1 small cell sarcoma, and 1 Hurthle cell carcinoma); 2 cases were papillary carcinomas after hemithyroidectomy; and there was 1 papillary microcarcinoma in hemithyroidectomy with isthmusectomy, 1 papillary microcarcinoma in subtotal thyroidectomy, and 2 cases in total thyroidectomy with adenopathies after surgery and cervical lymph node dissection (due to 1 papillary carcinoma and 1 follicular carcinoma).

## Discussion

The descriptive analysis conducted in our study showed values similar to those collected by other authors such as Lopez et al,[2] with 902 thyroidectomies and 14.3% of malignant disease; of these, 74.42% were papillary carcinomas, 14.73% were follicular carcinomas, 3.87% medullary carcinomas, 3.1% anaplastic carcinomas, 3.13% Hurthle cell carcinomas, and 0.75% lymphomas.

The diagnostic-therapeutic algorithm for thyroid surgical pathology varies depending on each centre according to the possibilities for further testing. Clinical examination provides signs that can suggest malignancy, usually in specific cases of advanced disease, with nodal and/or extraglandular involvement and recurrent invasion. The detection of hard nodules adhered to planes on palpation is insufficient for the detection of malignancy, as other authors have pointed out,[3-5] although most reported studies offer exploratory retrospective data, in the absence of protocolised prospective studies that are well-defined and have unified exploratory criteria.

The availability of thyroid ultrasound scans and scintigraphy provided us with data of high Sn for the detection of malignancy, but low Sp in cases of hypocapturing solid nodule; in our study, these are therefore not suitable screening tests for malignancy, as referred by other authors.[3,6] In our study, the hypocapture of nodules was significant for malignancy with 13.2%, versus non-hypocapture with 3.7%. Although scintigraphy is becoming an obsolete technique, this is not the case with thyroid ultrasound, with high resolution in nodular detection, and Sn and Sp of up to 80% and 90%, respectively, and used by radiologists with great experience.[5]

FNA is considered the gold standard test for screening of malignancy in thyroid pathology.[7] To carry out our analysis, the FNA variable was grouped into benign (which included cytological descriptions of cyst, colloid, or thyroiditis) and malignant together with suspected malignancy (which included follicular proliferation and Hurthle cell proliferation). We obtained results of Sn=74% and Sp=73% for detection of malignancy in all thyroid surgical pathology for study. In the case of papillary carcinoma (n=31), the aspiration was malignant in 15 cases, doubtful in 7, and benign in 5 cases (4 cases without puncture). Grouping malignant with doubtful for malignancy, we obtained a specific Sn of 81% for papillary carcinoma; of the follicular carcinomas (n=9), 2 had FNA of malignancy, 3 were benign, and 4 were doubtful, with a specific Sn from FNA for follicular carcinoma of 66% Our results contrast with those published by other authors, with Sn from the FNA for thyroid carcinoma ranging between 52.6% and 89% to 90% 95%.[7-10]

The intraoperative pathological study was grouped into benign and malignant or delayed result, with Sn=81.58% and Sp=92.13% Considering the cases of papillary carcinoma, the result was malignant in 18 cases, benign in 3 and there were 4 deferred cases (it was not performed in 6 cases), with a specific Sn of 88%. For follicular carcinomas studied, 3 offered a result of malignancy in extemporaneous biopsy, 3 were benign and 2 were deferred (1 without study), with specific Sn of 62.5%. Thus, in our study, FNA provided information for malignancy screening although Sp was not sufficient, requiring extemporaneous biopsy for suspected malignancy, with higher Sn and Sp for the papillary carcinoma, as supported by other authors,[4] compared with studies with higher Sn for FNA, which advocate the performance of total thyroidectomy after a positive FNA of malignancy.[11-13] Follicular carcinoma is more problematic at the time of diagnosis, with a lower Sn both in aspiration and in intraoperative biopsy; in our study, there was a higher rate of reoperations (44%) than papillary (16%), after the false negative or delayed result of an extemporaneous biopsy during hemithyroidectomy. In this sense, some authors advise against extemporaneous biopsy when there is a FNA of follicular proliferation, performing simple hemithyroidectomy and a second surgical procedure if malignancy is proven in the definitive anatomical pathology.[44]

## Conclusions

1. In our study, clinical examination is not useful in assessing malignancy risk, as corroborated by previous studies.
2. Scintigraphy is a very sensitive test but not specific in our data, in cases of hypocapturing and solid nodule, and it is not a good techniques for malignancy screening, although scintigraphic hypocapture did increase the risk of malignancy significantly.
3. FNA gave us Sn=74% and Sp=73%, while the extemporaneous biopsy offered Sn=81.5% and Sp=92%, thus being the best test to confirm/rule out malignancy in our study. FNA is sensitive in clinical suspicion of papillary thyroid carcinoma, although according to our results it should be complemented with extemporaneous biopsy due to its higher Sp. Follicular carcinoma presents more diagnostic difficulty, with a tendency, according to some authors, to conservative treatment compared to FNA with follicular proliferation, without intraoperative biopsy and reoperation in case of a real positive in the definitive anatomy.
4. In our study, age over 60 years significantly increased the risk of malignancy. Male gender, age below 19 years and nodular size did not seem to increase risk.

## Conflict of interests

The authors declare no conflict of interests.

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