Research, Society and Development, v. 11, n. 7, e12311729440, 2022
(CC BY 4.0) | ISSN 2525-3409 | DOI: http://dx.doi.org/10.33448/rsd-v11i7.29440

Sensitivity and specificity of fine needle aspiration biopsies performed in patients undergoing thyroidectomy

Sensibilidade e especificidade das punções aspirativas por agulha fina realizadas em pacientes submetidos à tireoidectomia

Sensibilidad y especificidad de las punciones aspirativas con aguja fina realizadas en pacientes sometidos a tiroidectomía

Received: 04/20/2022 | Reviewed: 04/29/2022 | Accept: 05/13/2022 | Published: 05/17/2022

Lucas Ribeiro Canedo
ORCID: https://orcid.org/0000-0001-7548-663X
Hospital Regional da Asa Norte, Brazil
E-mail: lucasrcanedo@outlook.com
Victor Mateus Xavier de Santana
ORCID: https://orcid.org/0000-0002-3160-1242
Hospital Regional da Asa Norte, Brazil
E-mail: victormxs@gmail.com
Rhenan dos Reis
ORCID: https://orcid.org/0000-0001-5874-3008
Hospital Regional da Asa Norte, Brazil
E-mail: rhenanreis@outlook.com
Wendel dos Santos Furtado
ORCID: https://orcid.org/0000-0002-5535-6712
Hospital Regional da Asa Norte, Brazil
E-mail: wsfdriju@terra.com.br
Adriana Araújo do Nascimento
ORCID: https://orcid.org/0000-0002-6305-049X
Hospital Regional da Asa Norte, Brazil
E-mail: driaraujo_endo@hotmail.com
André Luiz Aquino de Carvalho
ORCID: https://orcid.org/0000-0003-3179-2322
Hospital Regional da Asa Norte, Brazil
E-mail: andrerush26@gmail.com

Abstract
Objective: To identify the sensitivity and specificity of Fine-Needle Aspiration Biopsies (FNAB) performed at Hospital Regional da Asa Norte (HRAN) for the diagnosis of thyroid cancer in patients submitted to thyroidectomy. Methods: This was an observational and analytical study, which analyzed medical records of patients submitted to FNAB at HRAN from April 2015 to December 2021. The data were descriptively analyzed using the SPSS 2.0 program, and using the ROC Curve, considering a p value <0.05 as statistically significant. Results: 699 patients were submitted to FNAB. 62 patients were undergoing biopsy and surgery after. FNAB sensitivity and specificity were 90.32% and 83.87%, respectively (p <0.001). Most patients were females (96.78%), aged > 60 years (32.25%) and were submitted to total thyroidectomy (66.12%). Among the analyzed cytopathological samples, the Bethesda II classification predominated (25.80%), followed by class V (22.58%). In the histopathological analysis, the predominant diagnosis was papillary carcinoma (43.54%) followed by goiter (38.70%). Among classes I and II, only one sample was considered malignant after the histopathological analysis. Among class III samples, 22.22% were, in fact, malignant lesions. Among the samples suspected of malignancy (Bethesda IV, V and VI), there was a progressive increase in the rate of cancer diagnosis, of 62.50%, 85.71% and 100%, respectively. The FNAB results showed an accuracy of 87.09%. Conclusions: The results of this study are compatible with the findings in the literature. Thus, FNAB remains the gold standard for the analysis of thyroid nodules until another more sensitive and specific method is described.
Keywords: Thyroid Neoplasms; Thyroidectomy; Fine Needle Aspiration Biopsy.

Resumo
Objetivo: Identificar a sensibilidade e especificidade das Punções Aspirativas por Agulha Fina (PAAF) realizadas no Hospital Regioal da Asa Norte (HRAN) para o diagnóstico do câncer de tireoide em pacientes submetidos à tireoidectomia. Métodos: Estudo observacional e analítico, no qual foram analisados prontuários dos pacientes

submetidos à PAAF no HRAN, de abril de 2015 a dezembro de 2021. Os dados foram analisados através do programa SPSS 2.0, de forma descritiva e pela Curva de ROC, considerando o valor p<0,05 como significativamente estatístico. Resultados: 699 pacientes foram submetidos à PAAF. 62 pacientes foram submetidos à biópsia e cirurgia após. A sensibilidade e especificidade das PAAF foram de 90.32% e 83.87%, respectivamente (p<0,001). A maioria dos pacientes era do sexo feminino (96.78%), com idade superior a 60 anos (32.25%) e foi submetida à tireoidectomia total (66.12%). Nas amostras citopatológicas estudadas, a classificação Bethesda II predominou (25.80%), seguida pela classe V (22.58%). Já na análise histopatológica, o diagnóstico predominante foi carcinoma papilífero (43.54%) seguido do bócio (38.70%). Dentre as classes I e II, apenas uma amostra foi considerada maligna após análise histopatológica. Dentre a classe III, 22.22% eram, de fato, lesões malignas. Dentre as amostras sugestivas de malignidade (Bethesda IV, V e VI), houve progressivo aumento na taxa de câncer, com 62.50%, 85.71% e 100% respectivamente. A PAAF mostrou acurácia de 87,09% Conclusões: Os resultados obtidos neste estudo são compatíveis com os achados na literatura. Assim, a PAAF continua a ser o padrão ouro para avaliação de nódulos tireoidianos até que outro método mais sensível e específico seja descrito.
Palavras-chave: Neoplasias da Glândula Tireoide; Tireoidectomia; Biópsia Aspirativa por Agulha Fina.

Resumen

Objetivo: Identificar la sensibilidad y especificidad de las punciones aspirativas con aguja fina (PAAF) realizadas en el Hospital Regioal da Asa Norte (HRAN) para el diagnóstico de cáncer de tiroides en pacientes sometidos a tiroidectomía. Métodos: Estudio observacional y analítico, en el que se analizaron prontuarios de pacientes sometidos a PAAF en el HRAN, desde abril de 2015 hasta diciembre de 2021. Los datos fueron analizados mediante el programa SPSS 2.0, de forma descriptiva y por la curva ROC, considerando el valor de p <0,05 como estadísticamente significativo. Resultados: 699 pacientes fueron sometidos a PAAF. 62 pacientes fueron sometidos a biopsia y cirugía después la sensibilidad y especificidad de la PAAF fueron del 90.32 % y 83.87%, respectivamente (p<0,001). La mayoría de los pacientes eran mujeres (96.78%), mayores de 60 años (32.25%) y se les realizó tiroidectomía total (66.12%). En las muestras citopatológicas estudiadas predominó la clasificación Bethesda II (25.80%), seguida de la clase V (22.58%). En el análisis histopatológico el diagnóstico predominante fue carcinoma papilar (43.54%) seguido de bocio (38.70%). Entre las clases I y II, solo 1 muestra se consideró maligna después del análisis histopatológico. Entre la clase III, el 22.22% eran, de hecho, lesiones malignas. Entre las muestras sugestivas de malignidad (Bethesda IV, V y VI), hubo un aumento progresivo de la tasa de cáncer, con 62.50%, 85.71% y 100% respectivamente. La FNA mostró una precisión del 87,09% Conclusiones: Los resultados obtenidos en este estudio son consistentes con lo encontrado en la literatura. Por lo tanto, FNA sigue siendo el estándar de oro para la evaluación de nódulos tiroideos hasta que se describa otro método más sensible y específico.
Palabras clave: Neoplasias de la Glándula Tiroides; Tiroidectomía; Biopsia con Aguja Fina.

1. Introduction

Thyroid cancer is the eighth most common malignancy in the female gender and the most common in the endocrine system (DeLelis et al., 2004; Rago & Vitti, 2022; Holt, 2021; Nguyen et al., 2015). Its incidence is approximately 11 cases per 100,000 inhabitants, being accountable for approximately 0.5 deaths for the same population (approximately 0.4% of all deaths from neoplasia worldwide) (Mazzaferri, 1993; Power et al., 2019; DeGroot & Pacini, 2012; Ferlay et al., 2015).

The diagnosis is extremely dependent on technology, a fact that may explain its higher incidence in high-income countries, when compared to middle and low-income ones (Ali, 2011). In Brazil, for instance, there is an estimated number of 9,610 new cases of thyroid cancer for the 2018-2019 biennium (Forman et al., 2014; La Vecchia et al., 2015;; Santos, 2018).

Considering the estimate that approximately 20% of adults submitted to a routine thyroid ultrasound evaluation will be diagnosed with a thyroid nodule, the major challenge is the differentiation of benign lesions (which correspond to approximately 90% of cases) from malignant ones (Ali, 2011; Mazzaferri, 1993; Quaglino et al., 2017). Currently, the gold standard for this screening is the fine-needle aspiration biopsy (FNAB), which is a safe, efficient and economically viable diagnostic tool (DeGroot & Pacini, 2012; Forman et al., 2014; La Vecchia et al., 2015; Ferlay et al., 2015; Santos, 2018; Quaglino et al., 2017; Gharib et al., 2006; Hassel et al., 2011; Bongiovanni et al., 2012).

Aiming to standardize the information provided by the samples collected during the fine-needle aspiration biopsies (FNABs), as well as the consequent medical conducts, the Bethesda system (Table 1) was created, which describes 6 categories that stratify the risk of malignancy of the biopsied nodule (Ali, 2011; Cibas & Ali, 2009; Kim et al., 2017). Since its

implementation, many studies have shown that the Bethesda system has improved the diagnostic quality, decreasing the number of ambiguous diagnoses, increasing the positive predictive value of malignancy in the thyroid glands submitted to surgery and decreasing the rates of surgery in benign thyroid nodules (Bongiovanni et al., 2012; Horne et al., 2012).

Table 1 – Risk of Malignancy for each Bethesda Category and Management.

Classification	Description	Risk of Malignancy (%) with NIFTP(ª)	Risk of Malignancy(%) Without NIFTP(b)	Management Options
I	Nondiagnostic	5%-10%	5%-10%	Repeat FNA with ultrasound guidance
II	Benign	0-3%	0%-3%	Clinical and radiologic Follow-up
III	Atypia/follicular lesion of uncertain significance	6%-18%	10%-30%	Repeat Biopsy, Molecular testing, Surgery
IV	Follicular neoplasm/suspicious for follicular neoplasm	10%-40%	25%-40%	Molecular testing, Surgery
V	Suspicious malignancy	40%-60%	50%-75%	Near-total Thyroidectomy or lobectomy
VI	Malignant	94%-95%	97%-99%	Near-total Thyroidectomy or Lobectomy

Source: The Bethesda System for reporting thyroid cytopathology (Cibas & Ali, 2017). FNA: Fine Needle Aspiration. NIFTP: NonInvasive Follicular Thyroid Neoplasm with Papillary-like nuclear features. (ª) Risk of malignancy if the NIFTP category is used (i.e., NIFTP nodules are not considered malignant). (b) Risk of malignancy if the NIFTP category is not used (ie, NIFTP nodules are considered malignant).

As for the malignant lesions, they can be classified into 3 distinct groups, with the first being well-differentiated carcinomas, including the papillary and the follicular types, with papillary carcinomas being the most common histological type (50 to 80% of cases), followed by the follicular type (15 to 20% of cases); the second, which comprises poorly differentiated carcinomas, includes the medullary type; and the third is the undifferentiated carcinoma, including the anaplastic type (DeLelis et al., 2004).

The main objective of this study is to identify the sensitivity and specificity of the cytological analysis performed through FNABs in the detection of thyroid cancer in patients submitted to thyroidectomy at HRAN. The secondary objectives were to describe the age and gender profile of the patients submitted to thyroidectomy, as well as the findings of the preoperative FNABs in the study population, comparing them with the histological findings of the surgical specimens. The positive predictive value, negative predictive value and accuracy of the FNABs were calculated. The study also aims to verify the prevalence of the main histopathological findings of the study population and to correlate them with the FNAB results. Considering that the misdiagnosis of thyroid cancer can lead the patient to undergo a thyroidectomy without an actual indication and that the diagnostic delay can lead to a worse prognosis in patients with malignant neoplasms, the present study aims to evaluate the effectiveness of FNABs performed at Hospital Regional da Asa Norte (HRAN) for thyroid cancer detection (Cibas & Ali, 2009; Cibas & Ali, 2017; Cibas et al., 2013; Eszlinger et al., 2014).

2. Methods

This was a cross-sectional, observational, analytical and retrospective study, developed at the Service of General

Surgery, Service of Endocrinology and Service of Pathology at Hospital Regional da Asa Norte, in the city of Brasília, Federal District, Brazil.

The medical records of patients submitted to FNAB from April 2015 to December 2021 were evaluated; therefore, a census of the total number of medical records was carried out, which corresponded to a total number of 699.

Medical records of patients submitted to FNABs at the Endocrinology Service of the Hospital Regional da Asa Norte during the selected period were included in the study.

Medical records that did not include an adequate description of the FNAB analysis were excluded, as well as those that did not adequately describe the histological analysis after the thyroidectomy.

Because it depends on the correct documentation of the patients' information in the medical records, the study has an information bias. Aiming to reduce this bias as much as possible, only one person was in charge of the selection of medical records to be included in the SPSS program, discarding those without validated data. The appropriate reference for exams and a data collection instrument that included all variables were also utilized.

The risk of selection bias was minimized owing to the rigorous selection of individuals, excluding from the statistical analysis those who did not include the desired variables.

It was not possible to extrapolate the results to the entire population of patients with thyroid diseases submitted to thyroidectomy, as it is possible there are differences between this sample and those not included in the study.

The independent study variables that were analyzed included: age, gender and surgical procedure. The dependent study variables comprised the cytological categories of the Bethesda Classification and the following histopathological diagnoses: Hürthle cell adenoma, follicular adenoma, thyroiditis goiter, another benign disease, papillary carcinoma, follicular carcinoma and medullary carcinoma.

The cytological and histological diagnosis of benign or malignant thyroid diseases provided the dependent variables analyzed in this study.

The obtained information was inserted in a database, developed using the Microsoft Excel program. Subsequently, they were exported to the SPSS-2.0 program, where they were analyzed. The qualitative variables were described using absolute and relative frequencies and the ROC curve to calculate Sensitivity and Specificity. The level of significance was set at $p < 0.05$.

The research project was sent to the Research Ethics Committee through Plataforma Brazil, in compliance with Resolution n. 466/12 of the National Health Council (CNS, Conselho Nacional de Saúde) and the ethical principles of beneficence, non-maleficence, justice and autonomy of the Guidelines and Regulatory Norms of Research involving human beings. The analysis of the medical records of patients treated at the Endocrinology Service and submitted to a thyroid FNAB was started after the study approval by the Research Ethics Committee (REC), under CAAE number 17630019.4.0000.5553 (updated in 2020, based on the consubstantiated Opinion number 3,972,128), and consent by HRAN technical director via the assent form. The data that comprise this investigation was obtained exclusively from these patients' records.

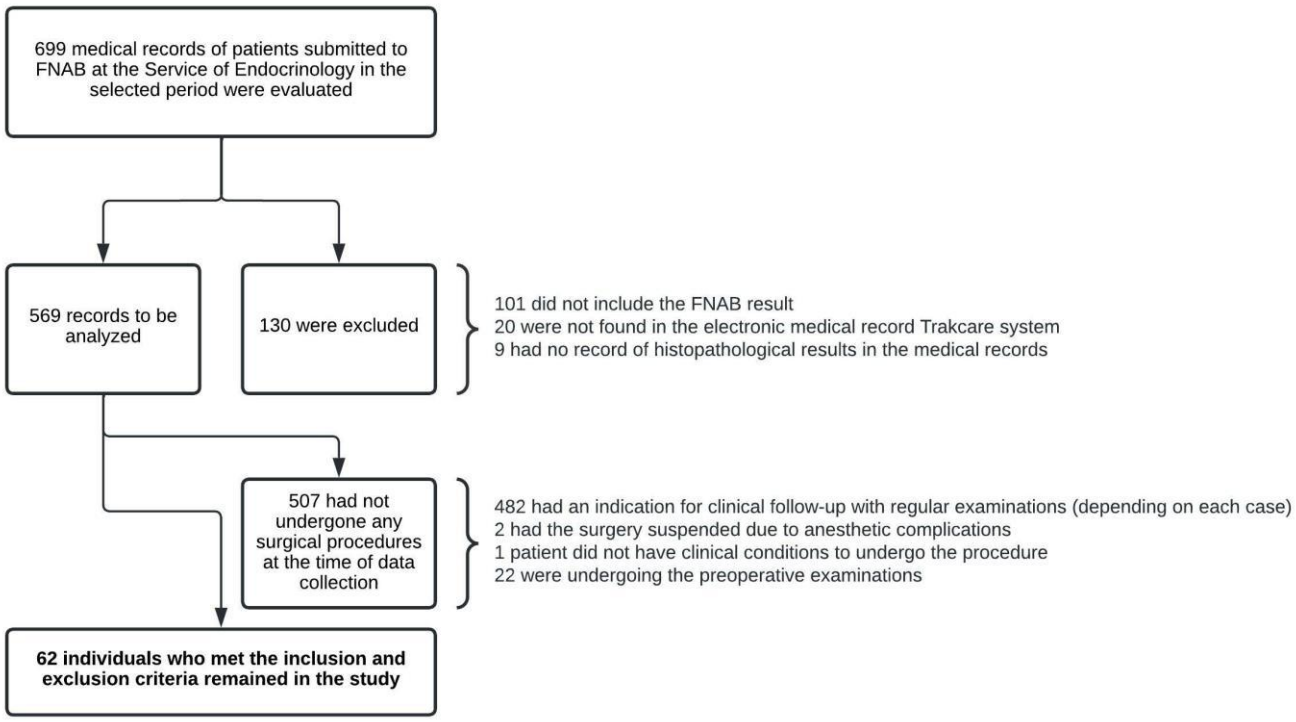
The researchers declare no conflicts of interest related to the present study. The waiver of the Free and Informed Consent Form was requested, as data collection was performed exclusively from medical records and test results of participants who are not hospitalized or who were no longer treated at the institution during the data collection period (research carried out with retrospective data obtained from a secondary database).

The risks inherent to the research are minimal and related to data exposure, which will be controlled by maintaining the anonymity and confidentiality of the participants' data throughout all steps of the research.

3. Results

To obtain the 62 samples analyzed in this study, 699 medical records of patients submitted to FNAB at the Service of Endocrinology in the selected period were evaluated. Of these, 130 were excluded (20 were not found in the electronic medical record Trakcare system, 101 did not include the FNAB result, 9 had no record of histopathological results in the medical records), leaving 569 records to be analyzed. Of these, 507 had not undergone any surgical procedures at the time of data collection – 482 had an indication for clinical follow-up with regular examinations (depending on each case), 2 had the surgery suspended due to anesthetic complications, 1 patient did not have clinical conditions to undergo the procedure and 22 were undergoing the preoperative examinations. Thus, after analyzing the inclusion and exclusion criteria, 62 individuals who met the inclusion and exclusion criteria remained in the study.

Figure 1. Shows the flowchart of the current job.



Source: Figure created by authors (2022).

The final sample consisted of 62 patients, 96.78% females and 32.25% aged 60 years or over, as shown in Table 2.

When analyzing the sociodemographic profile, we observed that most patients were aged ≥ 60 years (32.25%) and the vast majority was females (96.78%).

Table 2 – Description of the age and gender profile of patients submitted to FNAB at the Service of Endocrinology at Hospital Regional da Asa Norte from April 2015 to December 2021.

Variables	N	%
Age (years)		
< 20	2	3.22
20 to 29	2	3.22
30 to 39	12	19.35
40 to 49	17	27.41
50 to 59	9	14.51
≥ 60	20	32.25
Gender		
Female	60	96.78
Male	2	3.22
Total	62	100

Source: Table created by the authors (2022)

When analyzing the sociodemographic profile, we observed that most patients were aged ≥ 60 years (32.25%) and the vast majority were females (96.78%).

Table 3 shows the clinical profile of the study population, showing the types of surgeries performed, the cytopathological analysis of the thyroid glands and histopathological analysis of the surgical specimens obtained during the thyroidectomy.

Of patients submitted to surgical procedures, most of them underwent total thyroidectomy (66.12%). Of all the FNABs performed, most samples were classified as Bethesda II (25.80%), followed by class V (22.58%). Regarding the histopathological analysis of these same thyroid glands, now as surgical specimens after the thyroidectomy, 27 were diagnosed with papillary carcinoma (43.54%), followed by goiter, a benign condition that represented 38.70% of the assessed thyroid glands.

When comparing the procedures performed with the histological types, it is verified that most (68.29%) of the total thyroidectomies were performed due to the presence of cancer and that 18 (85.71%) of the 21 partial thyroidectomies were performed for benign lesions.

Table 3 – Aspects related to the clinical profile of patients submitted to FNAB at the Service of Endocrinology at Hospital Regional da Asa Norte, from April 2015 to December 2021

Variables	N	%
Surgical procedure / Histological Type		
Total thyroidectomy / Cancer	41 / 30	66.12 (68,29)
Partial thyroidectomy / Benign lesion	21 / 18	33.88 (85,7)
Bethesda		
I	4	6.45
II	16	25.80
III	9	14.51
IV	8	12.90
V	14	22.58
VI	11	17.74
Histopathological analysis		
Hurthle cell adenoma	2	3.22
Follicular adenoma	5	8.06
Goiter	24	38.70
Thyroiditis	0	0
Another benign disease	0	0
Papillary carcinoma	27	43.54
Follicular Carcinoma	4	6.45
Total	62	100

Source: Table created by the authors (2022).

As for the description of suspected malignancy prevalence in the cytological analysis of the performed FNABs, the values are shown in Tables 4 and 5.

Only one of the cytological analyses classified as I and II had a malignancy classification in the histological analysis. Among class III, which means the results show atypia or follicular lesion with undetermined characteristics, 22.22% were malignant lesions according to the histological analysis. From cytological classification IV, there is a gradual suspicion of malignant disease – which was in fact accompanied by the result of the histological analyses (which were 62.50% malignant for this class, 85.71% for class V and 100% of malignant cases for class VI).

Table 4 – Prevalence of malignancy in each cytological group.

Classification (BETHESDA)	N/total	%
I	0/4	0
II	1/16	6.25
III	2/9	22.22
IV	5/8	62.50
V	12/14	85.71
VI	11/11	100

Source: Table created by the authors (2022)

Among the histological groups with a high probability of malignancy (Bethesda IV, V and VI), the most prevalent histological diagnosis was Papillary Carcinoma. Among those with a low probability of malignancy (Bethesda II and III), the most frequent diagnosis was Goiter. In patients with indeterminate samples (Bethesda I), there were no samples suggestive of malignancy.

Among the cytological analyses suggestive of malignancy, 84.84% were actually malignant on the histopathology. Among the cytological analyses suggestive of benign lesions, 89.65% had a benign result on the histological analysis.

Table 5 – Results of the FNAB diagnostic tests.

	Malignant Cytology	Benign Cytology	TOTAL
Malignant Histology	28	5	33
Benign Histology	3	26	29
TOTAL	31	31	62

Source: Table created by the authors (2022).

As a result of the diagnostic tests related to the FNABs, a sensitivity of 90.32% and specificity of 83.87% were obtained. The test accuracy was 87.09%. These results are shown in Table 6.

Table 6 – Summary of FNAB diagnostic tests

Sensitivity	Specificity	PPV	NPV	Accuracy	p-value
90.32%	83.87%	84.84%	89.65%	87.09%	P < 0.001

Source: Table developed by the authors (2022).

4. Discussion

Considering that 482 patients (84.71% of the 569 evaluated ones) had an indication for clinical follow-up, as the lesions were probably benign alterations in the FNABs, this value is in agreement with the literature, which shows that approximately 90% of the cytological findings in the FNABs correspond to benign lesions (Mazzaferri, 1993; Ali, 2011; Quaglino et al., 2017). Regarding the sociodemographic profile, most of the participants were over 60 years old (32.25%), in agreement with the current data, which show a higher incidence of thyroid nodules with increasing age (Reiners et al., 2004). Another relevant sociodemographic data was the participant's gender: 96.78% were females, which is not in agreement with the current literature. While this study found a proportion of 31 females for each male participant, the Framingham study found a proportion of approximately 4.3 women with thyroid nodules for each man. This difference may be related to the male population's culture of low self-care, as men are less likely to seek health services in Brazil (Levoreto et al., 2014), as well as the small sample used in the present study.

Of the patients submitted to some type of surgical procedure, 66.12% underwent total thyroidectomy. Of these, 68.29% received a diagnosis of cancer at the histopathological analysis; on the other hand, 18 (85.71%) of the 21 partial thyroidectomies were performed in patients with benign lesions. This proportion shows a good quality of the indications related to the procedures, since the suspected malignant lesions were mostly treated through a total thyroidectomy, whereas those considered benign allowed the partial preservation of the gland, improving patient quality of life in the postoperative period. We can avoid unnecessary surgeries for diagnostic purposes, as well as morbidity and excessive expenses, as already

mentioned in the literature. (Holt, 2021; Steinmetz-wood et al., 2022). Other authors bring this concern for a more precise surgical indication through the repetition of punctures of the nodules to confirm the malignancy of the same, in addition to using other diagnostic methods such as molecular tests to identify false-negatives in FNA (Houdek et al., 2021; Köseoglu et al., 2021; Steinmetz-Wood et al., 2022; Zhao et al., 2022).

Considering the current scientific situation, the expected proportion of FNABs with a benign result was approximately 90% (Mazzaferri, 1993; Ali, 2011; Quaglino et al., 2017). In the present study, this proportion was 46.77%. This difference can be attributed to the selection bias, since only patients submitted to a surgical procedure were included in the study and, in most cases, lesions with a high probability of being benign (Bethesda II and III) are followed clinically, without the need for any surgical procedure (Cibas et al., 2009). Three samples were considered unsatisfactory in repeated biopsies and the patients underwent a diagnostic thyroidectomy.

Among the lesions considered benign at the histopathological analysis, most (82.75%) corresponded to Goiter, whereas among the malignant ones, more than half (81.81%) corresponded to Papillary Carcinoma. These prevalence rates are similar to those found by Roseti et al., who demonstrated that the presence of goiter corresponded to the majority (72.2%) of benign lesions and Papillary Carcinoma predominated (68.4%) among the malignant ones.

It is known that from the Bethesda group IV onward there is a progressive increase in the risk of malignancy (Cibas et al., 2009). Regarding the risk of malignancy in each histological group, this trend persisted, with histological types considered malignant in classes IV, V and VI of 62.50%, 85.71 and 100% of the samples, respectively.

Finally, in our series, the FNAB showed a sensitivity of 90.32%, a specificity of 83.87% and an accuracy of 87.09% for the detection of thyroid cancer. A similar design study obtained results of 84.3%, 76.5% and 79.7%, respectively – similar to those found in the present study. Concerning FNAB as a diagnostic method, together with patient history, physical examination, laboratory and imaging exams, this biopsy is shown to be an effective tool for conduct decision-making. Many studies have shown that the FNAB – associated with the Bethesda classification – has satisfactorily improved the diagnostic quality, reducing the number of ambiguous diagnoses (Kim et al., 2017; Bongiovanni et al., 2012; Vander et al., 1968; Medeiros-neto et al., 1998; Roberti & Rapoport, 2005; Girardi et al., 2005; Horne et al., 2012).

Nevertheless, considering the particularities of the studied population and the relatively small sample size, it is not possible to extrapolate the results obtained in this study to other population groups, even though the analysis of the data found they are in agreement with the national and international literature in almost its entirety (Escalante & Anderson, 2022; Köseoglu et al., 2021; Mezei et al., 2021; Steinmetz-Wood et al., 2022). This concordance reflects the study methodological rigor, starting from the cross-sectional design with strict criteria aiming to reduce the risk of bias, as well as the instruments developed especially for the present study, which reduced the vulnerabilities related to data loss and interpretation bias.

Other factors that have reduced the bias also need to be considered. Among them, we can mention the stringent practices related to data collection, application of the methodology and interpretation of data to rule out the possibility of information errors.

On the other hand, there were limitations that escaped our control. Among them, it is necessary to highlight the lack of information in some medical records and the sample size, which prevented the formation of more significant groups and the performance of more discriminant and consistent statistical analyses.

5. Conclusion

Finally, considering the obtained data, the sensitivity, specificity, positive and negative predicted values of the FNABs (90.32%, 83.87%, 84.84% and 89.65% respectively), as well as the accuracy of 87.09%, it can be concluded that the present data corroborated what is described in the literature and reaffirm that, to date, there is no economically viable method

to replace FNABs as the gold standard for thyroid nodule differentiation.

We warn that the misdiagnosis of thyroid cancer can lead the patient to perform a thyroidectomy without a real indication and that the delay in diagnosis can lead to a worse prognosis in patients with malignant neoplasms, we confirm that the effectiveness of FNAs for the detection of thyroid cancer thyroid can solve some of these problems. We agree with the literature and based on our results when FNA is indicated as the best method for screening and monitoring thyroid nodules.

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