

ROLE OF USING FINE NEEDLE ASPIRATION CYTOLOGY AND FROZEN SECTION EXAMINATION IN THE DIAGNOSIS AND MANAGEMENT OF THYROID NODULES

APPORT DE LA CYTOPONCTION ET DE L'EXAMEN EXTEMPORANÉ DANS LE DIAGNOSTIC ET LA PRISE EN CHARGE DES NODULES THYROÏDIENS

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ABSTRACT

Aim: To study the diagnostic accuracy of fine needle aspiration cytology (FNAC) and intraoperative frozen section (IOFS) for thyroid nodules.

Methods: We reviewed the medical files of 63 patients who underwent surgery for thyroid nodule between January 2016 and December 2019 at our department. All patients included in the study were subjected to both FNA (fine needle aspiration) and intraoperative frozen section (IOFS). We evaluated the sensitivity, specificity, positive and negative predictive value of each of these studies.

Results: The FNAC diagnosis was Bethesda I in 7 cases, Bethesda II in 16 cases, Bethesda III in 19 cases, Bethesda IV in 6 cases, Bethesda V in 5 cases, and Bethesda VI in 10 cases. The malignancy rate was 44%. The malignancy rate for each Bethesda category was: Bethesda II, 2/16 (12.5%), Bethesda III 57%, Bethesda IV 50%, Bethesda V, 100%, and Bethesda VI 70%. The sensitivity, specificity, positive and NPV values for FNAC were respectively 85.7%, 82.3%, 80% and 87.5%. The sensitivity, specificity, PPV and NPV values for IOFS were respectively 42.3%, 100%, 100% and 68%.

Conclusion: Our data showed that FNAC had a better sensitivity and negative predictive value, while the IOFS examination had a better specificity for predicting malignancy. Both FNAC and IOFS are useful in the management of thyroid nodules.

Key words: Thyroid, Thyroid nodule, Fine needle aspiration (FNA), Cytopathology, Thyroid tumor, Ultrasound

RÉSUMÉ

Objectif: Évaluation des performances de la cytoponction et de l'examen extemporané dans le diagnostic des nodules thyroïdiens.

Méthodes: Nous avons examiné les dossiers médicaux de 63 patients opérés pour un nodule thyroïdien entre janvier 2016 et décembre 2019. Tous les patients inclus dans l'étude ont eu une cytoponction et un examen extemporané. Nous avons calculé la sensibilité, la spécificité, la valeur prédictive positive et négative de la cytoponction et de l'examen extemporané.

Résultats: Les résultats cytologiques selon la classification de Bethesda se répartissaient comme suit: Bethesda I dans 7 cas, Bethesda II dans 16 cas, Bethesda III dans 19 cas, Bethesda IV dans 6 cas, Bethesda V dans 5 cas et Bethesda VI dans 10 cas. Le taux de malignité était de 44%. Pour chaque catégorie de Bethesda, le taux de malignité était le suivant: Bethesda II 12,5%, Bethesda III 57%, Bethesda IV 50%, Bethesda V 100% et Bethesda VI 70%. La sensibilité de la cytoponction était de 85,7%, avec une spécificité de 82,3% et des valeurs prédictives positive et négative de 80% et 87,5% respectivement. Pour l'examen extemporané, la sensibilité était de 42,3%, avec une spécificité de 100% et des valeurs prédictives positive et négative de 100% et 68% respectivement.

Conclusion: Nos résultats indiquent que la cytoponction était plus sensible et présentait une meilleure valeur prédictive négative, tandis que l'examen extemporané était plus spécifique dans la prédiction de la malignité. Les deux méthodes, cytoponction et examen extemporané, sont utiles dans la prise en charge des nodules thyroïdiens.

Mots-clés: Thyroïde, Nodule thyroïdien, cytoponction, Cytologie, Tumeur thyroïdienne, Échographie



INTRODUCTION:

Incidence of thyroid nodules has increased in the last decades, affecting 11 – 55% of the general population, mainly due to the diffusion of ultrasound examination of the neck. Thyroid cancer (CT) accounts for only 5-20% of these nodules, which requires an appropriate diagnostic approach in order to avoid unnecessary surgery [1]. Two tools have shown usefulness in management planning. These are preoperative fine needle aspiration (FNAC) and intraoperative frozen section examination (IOFS). IOFS is often used to aid further surgical decision-making at the operating table but its usefulness in the management of thyroid nodules after a FNAC has already been performed continues to be debated.

Aim of this Study:

To study the accuracy of fine needle aspiration cytology (FNAC) and intraoperative frozen section (IOFS) of thyroid nodules by comparing these reports with the final histopathological findings and to determine the role of using both of these methods as investigatory tools in patient management.

METHODOLOGY:

We reviewed the medical records of 63 consecutive patients who underwent surgery for thyroid nodule between January 2016 and December 2019 at our department. Age, sex, thyroid cancer risk factors, compressive symptoms, physical examination findings, sonographic findings and surgical approach were collected for each patient. Pathology reports were reviewed for frozen section examination and final histology. All patients included in the study were subjected to both FNAC (fine needle aspiration cytology) and intraoperative frozen section (IOFS). For nodules classified as EuTirads 2, FNAC was performed before the consultation. FNAC findings were graded according to the Bethesda classification. The data was analyzed by using Statistical Package for the Social Sciences (SPSS) software version 21. For descriptive analysis, we calculated frequencies and percentages for qualitative variables. All statistical tests were bidirectional with a significance level of 0.05. When FNAC was tested, we excluded all cases of non-diagnostic results including Bethesda type I, III and IV, and all cases of suspicious cytology were classified in the malignant group according to ROC curve analysis. Intraoperative FS histological findings were graded as either malignant or benign. Any undetermined cases were included in the benign group. The results from both studies were compared with each other, and also with the final histological results obtained from the surgical specimens. We evaluated the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of each of these studies.

RESULTS:

Among the sixty-three patients, 58 (92%) were female and 5 (8%) were male. The mean age was 45.73 years [17 - 71 years]. One patient had a previous thyroid lobectomy for multinodular goiter and five patients had a history of dysthyroidism. Compressive symptoms were reported

in 3 cases (5%). Thyroid nodules were palpable in 39 cases (62%). All patients had normal TSH levels recorded before surgery. All patients had a preoperative ultrasound examination. For each ultrasound examination, we defined as the dominant nodule the largest one or the one with the most pejorative Eu-Tirads classification. The dominant nodule was classified EuTirads 2 in 2 cases (3.17%), EuTirads 3 in 16 cases (44.44%), EuTirads 4 in 25 cases (39.68%) and

EuTirads 5 in 20 cases (31.74%). Suspicious cervical lymph nodes were revealed by ultrasound in 5 cases (7.93%) (homolateral in 3 cases and bilateral in 2 cases). Preoperative FNAC was performed in all cases according to the recommendations of the EU-TIRADS classification. As shown in Table I, results from cytological reports were classified using Bethesda system 2017: Bethesda I (non diagnostic) in 7 cases (11%), Bethesda II (benign) in 16 cases (25%), Bethesda III (atypia of undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS)) in 19 cases (30%), Bethesda IV (follicular neoplasm (FN) or suspicious for a follicular neoplasm (SFN)) in 6 cases (10%) (Figure1a), Bethesda V (suspicious for malignancy (SM)) in 5 cases (8%) (Figure1b), and Bethesda VI (malignant (M)) in 10 cases (16%)(Figure1c).

Tableau I: Risk Stratification of thyroid nodules with Bethesda category

| Bethesda category | Number of cases (%) |
|---|---------------------|
| I non diagnostic | 7 (11%) |
| II Benign | 16 (25%) |
| III Atypia of undetermined significance or follicular lesion of undetermined significance | 19 (30%) |
| IV Follicular neoplasm or suspicious for a follicular neoplasm | 6 (10%) |
| V Suspicious for malignancy | 10 (16%) |
| VI Malignant | 5 (8%) |
| Total | 63 (100%) |

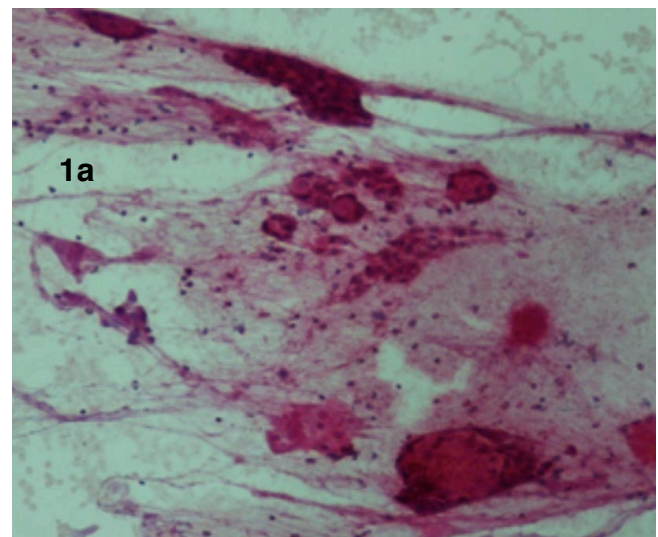


Figure 1a: Cytologic features of follicular neoplasm (bethesda IV). A microfollicular-patterned neoplasm is shown as a cellular follicular aspirate demonstrating microfollicles

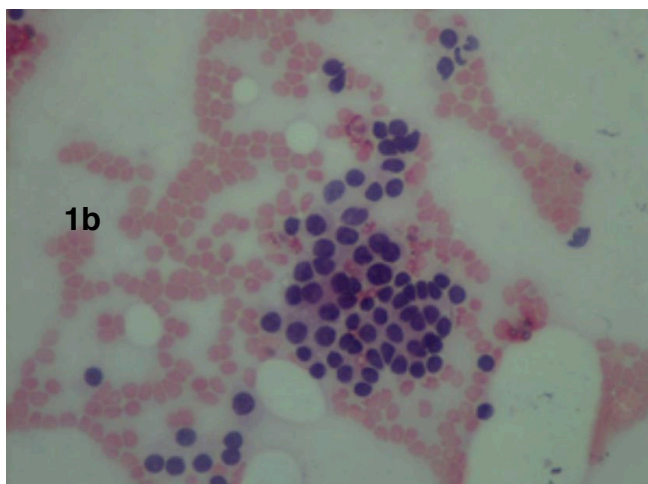


Figure 1b: Cytologic Features of suspicious of papillary carcinoma (Bethesda V). Clusters of follicular cells with round nuclei and minimal size variation and nuclear grooving.

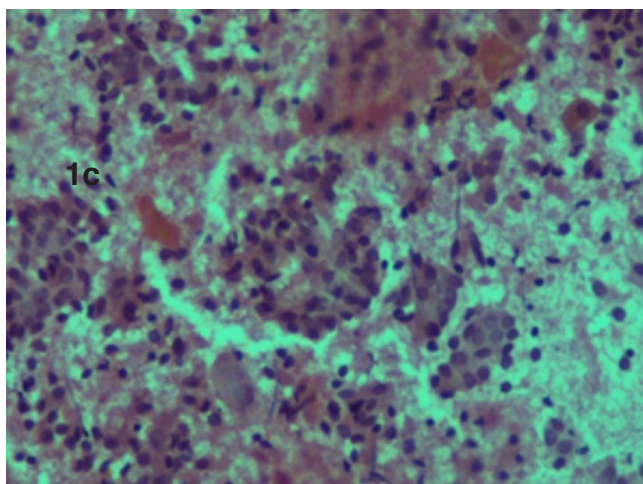


Figure 1c: Cytologic Features of papillary thyroid carcinoma (Bethesda VI). Syncytial clusters of cells with nuclear crowding, anisonucleosis and nucleomegaly (x200). Thick chewing gum colloid (arrow).

Depending on the location and number of thyroid nodules, on the result of IOFS examination and the presence of suspicious lymph nodes on the preoperative imaging and / or on the intraoperative examination, a lobo-isthmectomy or total thyroidectomy was performed. Initially, 44 patients had lobo-isthmectomy and 19 patients had total thyroidectomy for multinodular goiter. For the 44 patients who underwent a lobo-isthmectomy, the IOFS examination was graded as benign in 22 cases, malignant in 8 cases, and inconclusive in 14 cases. A thyroid totalization associated with a bilateral central lymph node dissection was carried out in 8 cases which were graded malignant in the IOFS. In cases of inconclusive results, ipsilateral central neck dissection was performed. The preoperative cytology findings for these cases were: Bethesda II in one case, Bethesda III in 4 cases, Bethesda IV in 2 cases, Bethesda V in 5 cases, and Bethesda VI in 2 cases. For the 19 patients who had a total thyroidectomy and after performing a IOFS, bilateral central lymph node dissection was performed

in 10 cases, in case of a malignant result on IOFS or inconclusive with a doubt about the malignancy in view of the intraoperative findings. Homolateral functional neck dissection was associated in 2 cases in view of the presence on preoperative imaging of suspicious lymph node in the lateral cervical chains.

The intraoperative FS findings were graded as malignant in 12 patients (19%), benign in 28 patients (44%) and inconclusive in 23 patients (37%).

Thyroid malignancies were histologically confirmed in 28 cases (44%). The sensitivity, specificity, PPV and NPV for IOFS (if we consider "inconclusive results" in IOFS findings as "benign") were respectively 42.3%, 100%, 100% and 68%.

To further evaluate the diagnostic efficacy and possible advantages of this study, each cytological grade obtained by FNAC was compared with the correlating histological findings obtained by IOFS and the final histological results (Figure 2). When FNAC was graded as benign, IOFS correctly identified the pathology as benign in 10 cases (Fig. 2a). In this category, the sensitivity, specificity and NPV were respectively 0%, 100%, and 87% for the FS examination. FNAC had a similar NPV of 87%. In the Bethesda 6 category, both fine needle aspiration cytology (FNAC) and intraoperative frozen section (IOFS) diagnosed malignancy in 7 out of 10 cases. In 3 cases, there was a discrepancy between FNAC and IOFS (1 benign case and 2 indeterminate cases). Our management approach was to perform total thyroidectomy without lymph node dissection in cases where IOFS indicated benign findings. In cases where IOFS results were indeterminate, total thyroidectomy with bilateral lymph node dissection was performed. The definitive histological examination revealed papillary carcinoma in 6 cases, medullary carcinoma in one case, vesicular adenoma in 2 cases and lymphocytic thyroiditis in one case. In this category the specificity, sensitivity, PPV and NPV for IOFS were 100%. Next, we examined the value of IOFS in nodules graded as atypical cytology (Bethesda III) (figure 2c), which was the most common cytological findings, accounting for 19 nodules (30%). In this category, the sensitivity, specificity, PPV and NPV were respectively 36%, 100%, 100% and 53% for the IOFS. For the follicular neoplasm or suspected follicular neoplasm category (Bethesda IV) (figure 2d): the malignancy rate was 50%. FS findings revealed malignancy in a third of cases (1/3). In this category, the sensitivity, specificity, PPV and NPV for the FS were respectively 33%, 100%, 100% and 60%. Finally, For the suspected malignancy category (Bethesda V) (figure 2e), the malignancy rate was 100%. The histological type found was papillary carcinoma in 5 cases. IOFS was inconclusive in all 5 cases. It was completed by: a bilateral central neck dissection at the same operating time in 3 cases and two-step surgery with thyroid totalization and contralateral central neck dissection in 2 cases.

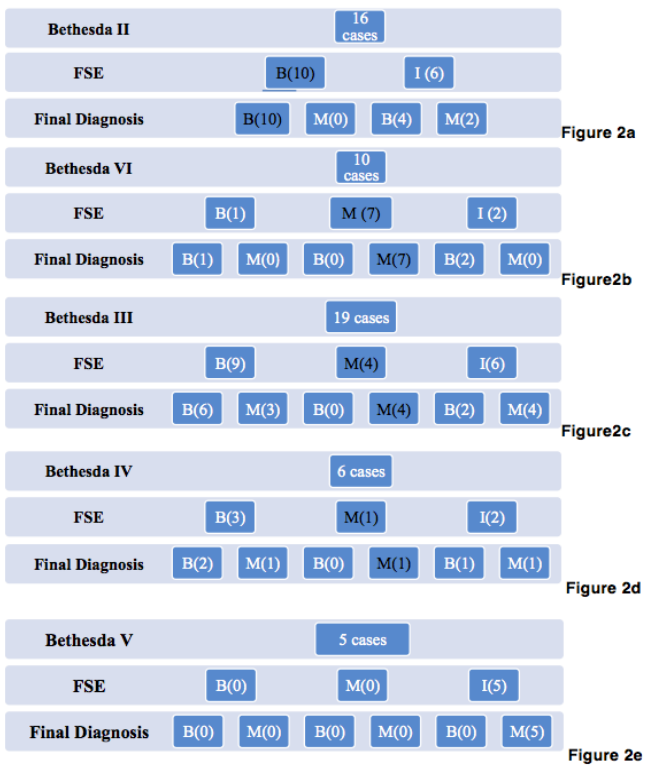


Figure 2: Diagnosis correlation of FNAC, IOFS and final diagnosis. B: Begin, M: Malignant, I: Inconclusive

The final histological examination found a malignancy rate of 44%. Among malignant tumors, the most frequent histological type was papillary carcinoma in 24 cases (85% of malignant tumors), followed by vesicular carcinoma (2 cases), oncocytic carcinoma (1 case) and medullary thyroid carcinoma (1 case). Benign tumors were mainly related to multi-nodular goiter (18 cases) and vesicular adenoma in 10 cases. Other histological types were found: Oncocytic adenoma in 3 cases, thyroiditis in 3 cases and tuberculosis in one case (Table II). Ten cases of vesicular adenoma, identified on definitive histological examination, had benign IOFS results in 7 cases and inconclusive IOFS results in 3 cases. The preoperative cytology was inconclusive in 2 cases, benign in 5 cases, atypia of undetermined significance in one case and malignant in 2 cases. Two vesicular carcinomas were diagnosed as atypia of undetermined significance in one case and follicular neoplasm in one case on preoperative cytology, with an inconclusive IOFS result in both cases.

Tableau II: Type of thyroid carcinoma identified on final diagnosis

| Tumor Type | Number of cases (%) |
|---------------------|---------------------|
| Papillary carcinoma | 24 (85%) |
| Vesicular carcinoma | 2 (7.14%) |
| Oncocytic carcinoma | 1 (3.57%) |
| Medullary carcinoma | 1 (3.54%) |
| Total | 28 |

DISCUSSION

Intraoperative Frozen section (IOFS) in thyroid surgery has been used for over 40 years; on the one hand to obtain a rapid diagnosis of benignity or malignancy and on the other hand to guide the surgical extension; however, its accuracy remains controversial and its place has clearly changed with the appearance of fine-needle aspiration cytology (FNAC). Opinions diverge between performing this examination routinely (however with fewer and fewer followers) and its restricted use to cases with suspicious or uncertain FNA and to guide surgical extension in cases confirmed as malignant by the FNAC.

In our cohort, after excluding the Bethesda III, IV and V category, the sensitivity, specificity, positive predictive value and negative predictive value of FNAC were 85.7%, 82.3%, 80% and 87.5%. For the IOFS examination, considering inconclusive results as benign, the sensitivity, specificity, positive predictive value and negative predictive value were 42%, 100%, 100% and 68% respectively. Thus, the FNAC had a better sensitivity and negative predictive value, while the IOFS examination had a better specificity. For Bethesda categories II, III and IV, frozen section examination had a fairly low sensitivity (varying between 0% and 36%), thus showing the absence of a significant gain in terms of reducing the reoperation rate. For Bethesda category V, frozen section examination had zero sensitivity and negative predictive value, thus showing little contribution in the management of nodules in this category. In contrast, the FNAC had a positive predictive value of 100%. For Bethesda category VI, the frozen section had a specificity of 100% thus exceeding the FNAC. Our management approach was to perform total thyroidectomy without lymph node dissection in cases where IOFS indicated benign findings. In cases where IOFS results were indeterminate, total thyroidectomy with bilateral lymph node dissection was performed.

According to the literature, the contribution of IOFS examination in the management of nodules of an indeterminate nature is debatable. A meta-analysis published in 2008 and other more recent series had highlighted the high rate of false negatives of frozen section examination and therefore its low sensitivity (22-67%) [1-5] involving FNAC and or frozen section in their management pathway were included. FNAC (n = 159). The results of our series agree with those of the literature regarding nodules classified Bethesda II, III and IV, showing the absence of significant contribution from frozen section examination given its low sensitivity. In addition, for follicular lesions, IOFS examination does not allow a gain in terms of diagnostic efficiency and reduction in the rate of reoperation. Lin [2] revealed that IOFS had a sensitivity of 29% for the follicular variant of papillary thyroid carcinoma, whereas its sensitivity for typical PTC was 87%. Also, frozen section examination can make the final histological diagnosis more difficult and less precise [1-6] imposing surgical treatment for definitive diagnosis. Thus, they represent a diagnostic



and therapeutic challenge given the risk of over or under treatment. Several teams continue to perform systematic intraoperative frozen sections (FS).

However, other studies reported the usefulness of IOFS examination in case of suspicious cytology (Bethesda V) and in cases confirmed as malignant (Bethesda VI) by the FNAC in order to guide surgical extension [7-9]. In a retrospective study of 662 patients comparing frozen section and FNAC, Chang et al. showed that the precision of frozen section examination (78.9%) is higher than that of FNAC (21.1%) [10]. A positive frozen section examination is particularly interesting because of the very low rate of false positives of this technique, reaching 0% in some studies with a specificity close to 90% [11–13]. Goemann [14] reported a sensitivity for IOFS examination analysis of 92,5% and a specificity of 100% for nodules of Bethesda category V. Performing an IOFS examination after suspected malignancy (Bethesda V) helps to avoid subsequent totalization surgery and thus reduces health care costs. Thanks to its good specificity and the low rate of false positives, a total thyroidectomy with a lymph node procedure should be performed if this examination is positive. However, in our series, IOFS examination for Bethesda V nodules showed little benefit in view of its low sensitivity. This may be related to the small number of subjects included in our series and also related to the experience of the pathologists.

Consequently, thyroid cytology under ultrasound guidance is an essential asset in the preoperative diagnostic strategy and before any thyroid surgery. In our cohort we found a higher malignancy rate for the Bethesda category II, III, IV and V and a less malignancy rate for the Bethesda VI category comparing to literature [15] (table III). The false negative rate of FNAC reported by most studies is less than 5% [16]. However, it has shortcomings. In the study by ZHU et al [16] involving 2781 patients who had FNAC followed by thyroid surgery, there were 62 false diagnoses on preoperative cytology; 47 false positives and 15 false negatives. False diagnoses in cytology are mainly related to a non-well-targeted sample [17,18], large nodules [19-21], reading errors in the event of follicular lesions [22-27] and thyroiditis [28]. Papillary microcarcinomas and NIFTP-type lesions often escape diagnosis both on preoperative cytology and intraoperative frozen section examination [29,30].

Table III: Malignancy rate according to the Bethesda classification

| Bethesda category | Malignancy rate (Bethesda 2017) [15] | Malignancy rate in our cohort |
|-------------------|--------------------------------------|-------------------------------|
| II | < 3 % | 12.5% |
| III | 6 -30 % | 57% |
| IV | 10-40 % | 50% |
| V | 45-75% | 100% |
| VI | 94-97% | 70% |

CONCLUSION:

Our data showed that FNAC had a better sensitivity and negative predictive value, while the IOFS examination had a better specificity for predicting malignancy. To optimize the preoperative and intraoperative diagnosis of differentiated thyroid carcinoma Both FNAC and IOFS should be taken into account.

Compliance with ethical standards

Conflict of interest: The authors stated that there is no conflict of interest.

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