Original paper

Thyroid neoplasms – errors of the cytological diagnosis

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Abstract

Objectives: the evaluation of the diagnostic value of a cytological examination and its limitations for the diagnosis of thyroid neoplasms.
Material and methods: From 1995 to 2004 nine hundred ninety eight patients were operated on for nodular lesions of the thyroid gland in our department. Cytological and histopathologic diagnoses were compared retrospectively in all cases where a neoplasm was suspected (true positive, false negative and false positive diagnoses). The verification was carried out independently by two pathologists. It enabled the establishment of interpretation errors (IE). The cases where cytological and histopathologic diagnoses were incompatible were interpreted as a sampling error (SE).
Results: As a result of the verification 45 cytological and histopathologic diagnoses were changed compared with the primary ones. In the analysed material the following diagnoses were put: true positive – 144, true negative – 824, false positive – 12, false negative – 18. The sensitivity of FNAB was 0.89, specificity 0.99, accuracy 0.97 and a positive predictive diagnostic value 0.92. False cytological diagnoses were found in 75 cases (7.5%). In 45 cases (4.5%) a diagnosis was changed compared with a primary one – interpretation error. In the remaining 30 cases (3%) a false diagnosis was caused by a sampling error.
Conclusions: FNAB is an examination of high diagnostic value for the detection of thyroid neoplasms in the hands of an experienced pathologist. False cytological diagnoses comprised only a small part (7.5%) of their total number and were caused by interpretation error in 4.5% and by sampling error in 3.0%. The percentage of interpretation errors can be decreased by a multiple independent assessment of samples.

Key words: thyroid neoplasms, fine-needle aspiration biopsy, diagnostic errors.

Introduction

Fine needle aspiration biopsy (FNAB) is a basic examination used contemporarily for the diagnosis of thyroid pathologies. A generally accepted diagnostic logarithm comprises clinical examination, thyroid ultrasound or/and scintigraphy and compulsory ultrasound-guided FNAB of thyroid nodular lesions. The result of a cytological examination has a crucial influence on the planning of a therapeutic process. If neoplastic lesions are detected cytology makes it possible to establish the extent of thyroid resection.

FNAB has its advantages and disadvantages like other diagnostic methods. Its advantages are as follows: low invasiveness, simplicity and reproducibility, low costs, high sensitivity for the detection of neoplasm [1, 2].

Specific limitations of a cytological examination result from the inadequate diagnostic value of some aspirates (oligocellular) or sampling of a region out of the proper pathology. Such a situation can appear when the following lesions are punctured: cystic lesions, solid lesions with local fibrosis, hyalinisation or calcification, nodular lesions with heterogeneous structure where a neoplasm can comprise only a part of it [1].

False cytological diagnoses based on the assessment of aspirates of low diagnostic value or sampled from non-representative regions are defined as a sampling error.

The second type of an error results from an incorrect microscopic interpretation of a specimen by a pathologist. It is connected with subjectivity of the interpretation of a microscopic picture as a pathologist has to make a choice among various possible diagnoses on the basis of cells having similar structural features. Another reason is a lack of experience. This type of errors is defined as an interpretation error.

High effectiveness of FNAB for the detection of most thyroid neoplasms especially papillary and anaplastic carcinomas is well documented [3, 4]. A well known problem connected with a cytological diagnosis of thyroid pathology is a group of thyroid neoplasms that derive from follicular cells. In these cases on the basis of the microscopic picture of an aspirate it is not able to differentiate unequivocally non-neoplastic or benign lesions from malignant ones. This problem touches especially the differentiation between follicular adenomas and follicular or oxyphilic carcinomas that demand histologic evaluation to make a sure diagnosis that is impossible on the basis of cytology [1, 5, 6]. It causes serious difficulties for the choice of proper surgical treatment. The diagnosis of thyroid carcinoma is an indication for thyroidectomy. The lack of proper pathological diagnosis before surgery induces many surgeons to limit the extent of thyroid resection that exposes some patients to a next surgical procedure (radicalisation) if the carcinoma is diagnosed postoperatively [7-10].

Objectives

1. The assessment of the diagnostic value of FNAB for thyroid pathology.
2. The establishment of most common errors committed in the cytological diagnosis of thyroid neoplasms.

Material and methods

From 1995 to 2004 nine hundred ninety eight patients were operated on for nodular lesions of the thyroid gland in our department. In all cases FNAB was performed before surgery and a routine histopathologic examination after it. Comparing cytological and histopathologic diagnoses two groups of patients were selected: 226 cases with suspected neoplasm diagnosed by cytological and/or histopathologic examination independently of its grade of malignancy (true positive, false positive, false negative cytological diagnoses) and 816 cases where both cytological and histopathologic diagnoses show no neoplastic lesions (true negative diagnoses). To identify false cytological diagnoses in the analysed material a retrospective verification of both cytological and histologic specimens was conducted. To make the verification more objective it was carried out independently by two experienced pathologists. If after the verification a primary diagnosis was changed it was classified as an interpretation error. If a disagreement between cytological and histopathologic diagnoses persisted after the verification it was classified as a sampling error. On the basis of the obtained data the coefficients of the diagnostic value of FNAB for the diagnosis of thyroid neoplasms were calculated.

Results

A simple comparison of cytological and histopathologic diagnoses in the group of 998 patients showed the diagnostic compatibility of both methods in 930 cases, while in the remaining 68 cases the diagnoses were different. Thyroid neoplasms were suspected by cytological and/or histopathologic examinations in 185 cases (FNAB – 150, histopathology – 152 cases). Cytological diagnoses were divided into four groups on the basis of the conducted verification: true positive **(TP)**, true negative **(TN)**, false positive **(FP)**, false negative **(FN)** (Figure 1).

Taking the number of cases in the groups into account the coefficients of the diagnostic value of a cytological examination for the detection of thyroid neoplasms were calculated and they were as follows: sensitivity – 0.78, specificity – 0.96, accuracy – 0.93, positive predictive diagnostic value – 0.78, negative predictive diagnostic value – 0.96.

The reassessment of specimens from 185 patients in whom a neoplasm was diagnosed or suspected both by a cytological and histopathologic examinations was carried out. Specimens out of the group of true negative diagnoses where both cytological and histopathologic examinations show no neoplasia were excluded from the analysis. As a result of the independent verification conducted by two pathologists 45 primary cytological and histopathologic diagnoses were changed. The consequences of the changes are presented schematically in Figure 2.

Most of the changes (17) were made in the FN group where preoperative cytology diagnosed no

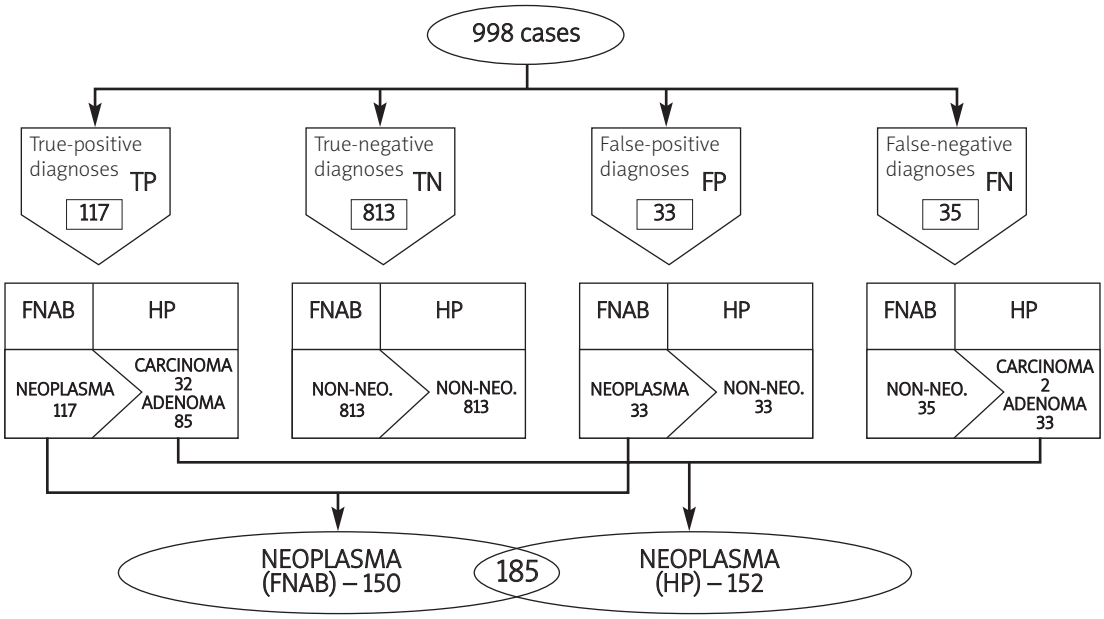

Figure 1. Primary cytological diagnoses in the material of 998 patients

thyroid neoplasm and retrospective reassessment made by two experienced pathologists detected thyroid neoplasia. The cases were finally included into the TP group. The second group, taking the number of cases (14) into account, was the FP one. In this group the primary evaluation of the cytological specimen showed neoplastic lesions which were not detected by a final histopathologic examination. The verification of histopathologic specimens proved the presence of a neoplasm and finally these cases were classified as TP. In 8 cases out of the FP group the verification of cytological and histopathologic specimens did not support the diagnosis of a thyroid neoplasm; they were reclassified as TN. In 4 TP cases both cytological and histopathologic diagnoses of a neoplasm were changed after the verification and these cases were included finally into the TN group. One TN case was reclassified as TP when the verification of a primary negative cytological and histopathologic diagnosis showed the features of thyroid neoplasia. In one TP case after the verification a cytological diagnosis was supported but it was not confirmed by histopathologic findings and the case was finally included into the FP group.

After the verification (Figure 3) the coefficients presented above were recalculated and they appeared to be higher than primarily, that is: sensitivity – 0.89, specificity – 0.99, accuracy – 0.97, positive predictive diagnostic value – 0.92 and negative predictive diagnostic value – 0.98.

75 cases (7.5%) of false cytological diagnoses were finally found in our material. In 45 out of them (4.5 %) an interpretation error was found and after the verification they were classified differently compared with a primary diagnosis. In the remaining 30 cases (3.0%) the error was defined as a sampling error. The cytological and histopatologic diagnoses were still different despite the conducted verification. They were similar to those given primarily and they comprised 12 false positive cytological diagnoses of a thyroid neoplasm and 18 false negative cytological diagnoses of a non-neoplastic lesion. In the cases of a false positive diagnosis a microscopic picture resembled cellular structures characteristic of thyroid neoplasms which caused that all pathologists gave a similar diagnosis while for the false negative diagnoses a microscopic picture did not authorise a pathologist to give a diagnosis of a thyroid neoplasm (diagnostic material of low value, material sampled from an improper region).

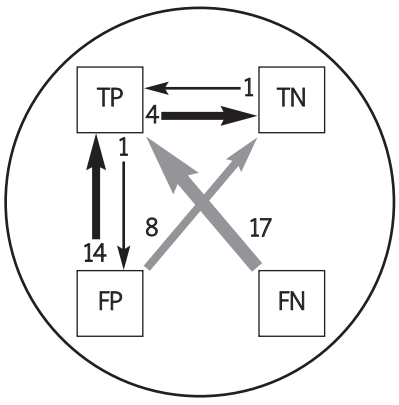

Figure 2. The changes of primary cytological and histopathologic diagnoses after verification

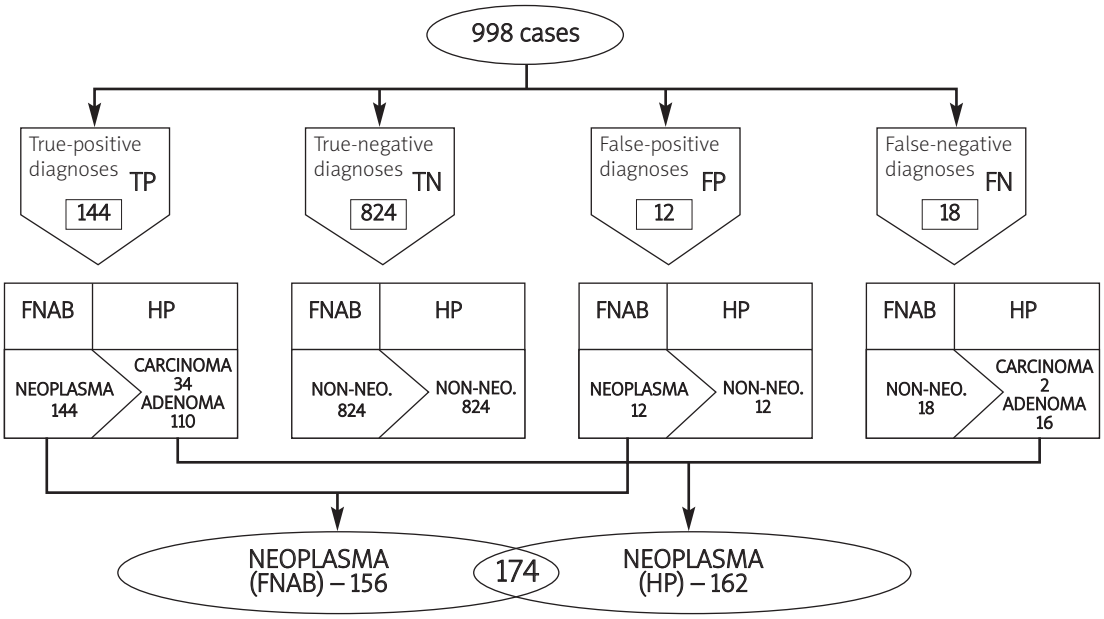

Figure 3. The groups of cytological diagnoses in the material of 998 patients after verification

Discussion

Our study touches upon a problem of errors connected with a preoperative cytological diagnosis of thyroid neoplasms. That is an extremely important issue as they influence a choice of therapy. Preoperative diagnosis of a neoplasm enables to qualify a patient to a surgical treatment and a choice of the adequate extent of resection that meets oncological criteria. Total thyroidectomy is contemporarily recommended in all cases of thyroid carcinoma except for papillary carcinoma $T_{1a}N_0M_0$ where more limited resection is acceptable that is resection of the affected thyroid lobe and the thyroid isthmus. If a neoplasm is suspected by a preoperative cytological examination the smallest acceptable extent of surgery is resection of the affected thyroid lobe and the isthmus [11]. This procedure has one great advantage; if the resection of the remaining thyroid lobe is necessary the procedure is performed within an intact operative field that makes it possible to avoid complications on the side of the primary intervention [8-11]. If thyroid carcinoma is diagnosed by a histopatologic examination and its result is not papillary carcinoma in stage $T_{1a}N_0M_0$ the resection of the remaining thyroid gland should be performed [8, 12].

According to many authors FNAB is characterised by high sensitivity for the detection of most thyroid neoplasms, especially such as: papillary, medullar and anaplastic carcinomas [3-5, 13, 14]. However, as it was mentioned above, follicular and oxyphilic tumours are still an unsolved diagnostic problem for this method as on the basis of cytology only a general diagnosis can be given for these tumours (follicular neoplasm, oxiphilic tumour) without a clear definition of malignant or benign nature of these lesions [1, 2, 5, 10, 15].

Generally, it is assumed that the diagnostic accuracy of FNAB depends on a few factors such as: technical skill at biopsy, experience of a cytopathologist, technical mistakes during cytological smear preparation and false interpretation of the cytological picture [1, 2, 4, 5, 16, 17]. The most frequent reasons for a false diagnosis based on FNAB are as follows:

a) false interpretation of the microscopic picture of an aspirate- interpretation error (caused by a mistake or a lack of experience of a cytopathologist),
b) sampling error caused by the aspiration of a non-representative tissue material that makes it impossible to diagnose a lesion properly as a result of:
   - missing a tumour,
   - biopsy of a material from a non-representative region of a tumour,
   - incorrect preparation of a cytological smear,
   - coexistence of two or more pathologies blurring the cytological picture of a main lesion (e.g. benign neoplasm and chronic inflammation).

A method used in our study enabled the establishment of errors of the cytological diagnosis in our material and their potential implications for patients. In the cases of false positive diagnoses a patient is exposed to a more extensive surgical procedure – thyroidectomy or unilateral lobectomy with a partial resection of the contralateral lobe that is connected with a higher probability of some serious complications such as: recurrent nerve paresis, permanent or transient hypoparathyroidism,

postoperative hypothyroidism [18]. However, even more serious consequences follow false negative diagnoses. A delayed diagnosis of cancer and a delay in the application of an adequate treatment can result in the loss of a chance for a radical cure. If equivocal diagnoses such as: follicular neoplasm or oxiphilic tumour are given a next surgical procedure is necessary (radicalisation) in 5-35% of cases when a postoperative histopathologic examination detects malignancy [6, 8-10, 13, 19]. A false negative diagnosis in the cases of benign neoplasms is of less importance for a patient. A partial resection of the thyroid gland for benign tumours is fully acceptable [11].

On the basis of our material we found that the most frequent reasons for a sampling error were as follows:

- missing a tumour – 44.4%,
- biopsy of a material from a non-representative region of a tumour – 38.9%,
- non-diagnostic material (oligocellular) – 16.7%.

We are of the opinion that conducting of such studies is useful for the education of young cytopathologists and for the establishment of rules of FNAB technique in each division of pathology (multiple control of diagnoses). It could help to define the most frequent mistakes, their causes and to work out some ways to eliminate them in the future that could bring some benefits for patients.

Conclusions

1. FNAB is a method of high diagnostic value in the hands of an experienced pathologist.
2. False cytological diagnoses comprised only a small part (7.5%) of their total number and were caused by interpretation error in 4.5% and by sampling error in 3.0%.
3. The percentage of interpretation errors can be decreased by a multiple and independent assessment of cytological smears by several pathologists.

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