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The role of fine-needle aspiration biopsy in the diagnosis of malignant tumors

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Abstract

Cytopathology and histopathology play a key role in the process of diagnosing oncological diseases and premalignant conditions. Fine-needle aspiration (FNA) is one of the techniques used for obtaining biopsy of a wide variety of body tissues, causing patients minimal discomfort. Therefore, it is often considered to be the best strategy for investigating and diagnosing some precancerous or potential malignant lesions. Being successful as a means of confirming the clinical suspicion of metastatic recurrence in the cases of an already known cancer, the interest has further focused on the preliminary diagnosis of various types of benign or malignant tumors. In cases of inoperable tumors, this technique is useful for formulating the final diagnosis. FNA biopsy proved its effectiveness as a highly accurate, cost-effective, and safe technique, with potential high diagnostic yield. Immunohistochemistry, used as an additional tool to classical histopathological examination, remains a very practical and reliable technique that promises good results especially in determining the site of origin within metastatic disease.

Keywords: diagnosis, cytopathology, histopathology, immunohistochemistry, fine-needle aspiration, metastasis.

Introduction

Cancer is considered to be a leading cause of mortality, globally, in countries of all income levels. A large proportion of these diseases can be prevented by different measures, including early detection, and promoting a healthy lifestyle. In addition, the burden of suffering can be reduced with early appropriate treatment [1]. Gastrointestinal (GI) cancer ranks first for annual number of deaths. The patients between 6th and 8th decades of life are the most affected [2]. Often the diagnosis is made in advanced stages when oncological disease has a reserved prognosis due to incomplete response to therapy [3]. One of the main objectives in oncological research is to develop new methods for the early diagnosis of premalignant and malignant lesions, with greater benefits for the patients and also regarding the costs [4].

Cytopathology and histopathology play a key role in the process of diagnosing oncological diseases and premalignant conditions. Fine-needle aspiration (FNA) is one of the techniques used for obtaining biopsy of a wide variety of body tissues, causing patients minimal discomfort. Therefore, it is often considered to be the best strategy for investigating and diagnosing some precancerous or potential malignant lesions [5]. FNA is a minimally invasive procedure, therefore this is a widely used technique despite known limitations of clinical inadequacy considered to be between 9% to 34% for breast and thyroid lesions and even 50% for assessment of endobronchial and deep abdominal lesions [6–9].

Two main microscopic methods are used for diagnostic purposes: the histopathological (HP) examination – the only one able to allow a certain diagnosis – and the cytological examination – meant to provide a probability diagnosis. Immunohistochemistry (IHC) represents a complementary method to the classical histological examination, widely contributing to the diagnosis of poorly differentiated tumors [10].

It may be also used to confirm the origin of metastasis originating from the primary tumor that was already diagnosed [11]. Conceptually, needle biopsies can be labeled as inadequate, partly adequate, or entirely adequate for the supposed diagnostic purpose. In order to be considered ideal, a needle biopsy sample must present some characteristics: the sample must reflect lesion localization, must contain cells and cell component for intended assessment, must contain cell representative of the lesion and where possible must contain predominantly lesional tissue. Most commonly, FNA biopsy (FNAB) provides sufficient cells for one or two slides. Even if the tissue architecture is not seen properly, the simple existence if tumoral cells may be enough for cellular evaluation [12]. Smears are categorized according to their cellularity in the following way: high cellularity – having at least one or two slides with over 5000 cells, moderate cellularity – having

between 1000 and 5000 cells, and low cellularity – having less than 1000 cells. Despite this rather elevated cellular requirement, the sequencing is effective approximately 50% of the time. Considering this, it is widely recognized and accepted that the cellularity of the tumoral lesion as well as the operator's manual dexterity are two fundamental limitations of FNA [13]. FNAB is considered to be, theoretically, more advantageous than core needle biopsy (CNB) regarding the IHC assessment for biomarkers, as the entire cells can be observed with minimal post-biopsy processing [14, 15]. The washout fluid resulting from FNAB may be used to evaluate the IHC markers in order to diagnose specific entities, as follows: in samples collected from lymph nodes, thyroglobulin analysis is used for diagnosis of metastatic thyroid carcinoma and calcitonin analysis for the diagnosis of medullary thyroid carcinoma [16–18]. Table 1 includes some of the most common IHC markers, frequently used in pathology laboratories that are found to be helpful in characterizing cell differentiation [19, 20].

Table 1 – ***Organ-specific IHC markers***

Primary site	IHC markers
Breast	ER, PR, CK7, CK20, GATA3, E-cadherin, HER2
GI tract	CEA, CK7, CK20, CDX2
Liver	Hep-Par1, AFP, CK7, CK20, pan-CK AE1/AE3
Pancreas	Pan-CK AE1/AE3, CK7, CK20, CA19-9, CEA
Lung	TTF-1, CK7, CK20, CEA, S100
Prostate	PSA, CK7, CK20, NKX3.1
Kidney	EMA, CD10
Thyroid	TTF-1, thyroglobulin, calcitonin, CEA
Urothelium	CK7, CK20
Lymphoma	LCA, CD3, CD20, CD30, Bcl-2
NE tumors	Chromogranin, synaptophysin, CD56
Melanoma	S100, HMB-45, MART1
Sarcoma	Vimentin, S100, CD117 (c-kit), CD34, α-SMA, desmin

α-SMA: Alpha-smooth muscle actin; AFP: Alpha-fetoprotein; Bcl-2: B-cell lymphoma 2; CA19-9: Carbohydrate antigen 19-9; CD: Cluster of differentiation; CDX2: Caudal-type homeobox 2; CEA: Carcinoembryonic antigen; CK: Cytokeratin; EMA: Epithelial membrane antigen; ER: Estrogen receptor; GATA3: GATA-binding protein 3; GI: Gastrointestinal; Hep-Par1: Hepatocyte-paraffin 1; HER2: Human epidermal growth factor receptor 2; HMB-45: Human melanoma black-45; IHC: Immunohistochemistry; LCA: Leukocyte common antigen; MART1: Melanoma antigen recognized by T-cells 1; NE: Neuroendocrine; PR: Progesterone receptor; PSA: Prostate-specific antigen; TTF-1: Thyroid transcription factor-1.

If used by an experienced team, FNA is a valuable appendix to the diagnostic tools, especially for neoplastic pathologies. Diagnostic accuracy is over 80% for the majority of indications of this technique [21]. FNA is considered to be a safe procedure due to its remarkably low risk of morbidity (0.98%) and mortality (0.02%). This method provides information in order to determine the benign or malignant nature of a tumor and also provides clues for establishing further investigations, thus saving time and resources [22].

Aim

The objective of this study was to assess the pathological and IHC profile of biopsy material obtained by FNA from a wide variety of body tissues, aiming to identify the utility of IHC markers in diagnosing the metastasis and determining their origin. Secondly, we aimed to evaluate the effectiveness of this method in sampling adequate material for HP examination. Also, we aimed to describe particularities of morphological and IHC findings and to emphasize their relevance compared to data from the other studies.

Patients, Materials and Methods

Five-year retrospective cross-sectional research was performed on the database from the Archives of Pathological Anatomy Service, Emergency County Hospital Bihor, Oradea, Romania, analyzed between January 2017 and May 2021. The biopsy material was sampled from the patients admitted in the Medical and Gastroenterology Clinics with the presumptive diagnosis of malignant tumor. Clinical and HP characteristics including demographics, tumor location and other details like recurrence suspicion were gathered from the patient's medical records. The samples were completely processed and examined according to the general protocol of examination. The results were analyzed using Statistical Package for the Social Sciences (SPSS) software. A statistically significant level was considered $p \leq 0.05$. The results of our study were compared to the existing literature from *PubMed* database.

Results

In the presented study there were analyzed a number of 174 samples collected from 135 patients. At the time of diagnosis, the patients were between 27 and 83 years old (62.44±12.45 years). Most patients in the study were males compared to females (63% *vs.* 37%, respectively $p<0.0001$). It was a significant difference between male and females regarding the age (62.42±2.51 years for males and 61.20±2.48 for females, $p=0.007$).

Regarding the distribution by decades, most patients had ages specific to the 7th decade (44 cases, a percentage of 32.6%, $p=0.0001$). The organs with the highest frequency of FNAB punction were, in a descending order: liver, lymph nodes, pancreas, adrenal glands (Figure 1).

From all the samples analyzed in the study, 146 (83.8%) were adequate for HP diagnosis, while 28 (16.2%) ($p<0.001$) were constituted from insufficient material and were considered inadequate to formulate a final diagnosis based on them. The inadequate samples were collected most frequently from the liver (nine cases, representing 6.2% from all the biopsies), followed by the pancreas (seven cases, representing 4.8% from all the biopsies) (Figure 2).

Around 70% from all the adequate samples taken in study were confirmed to be malignant (102 samples that contained malignant evidence and 44 samples without malignant evidence – inflammatory or granulomatous tissue and cells with characteristics suggestive of benign tissue) (Figure 3). Analyzing the concordance between clinical and HP diagnosis, we found a high similarity (71.03%, $p<0.001$).

The IHC techniques were used in almost 60% of samples, and a percentage of 74% of these samples were found to be malignant, meaning a number of 64 samples (Figure 4).

Of these 64 samples, obtained from a wide variety of body tissue, 34 (53.12%) were represented by metastatic tissue. Hoping to find the tissue of origin, regarding to these metastatic samples, the IHC markers were tested positive and were helpful, the tissue of origin being specified in 91.18% of cases (Figure 5).

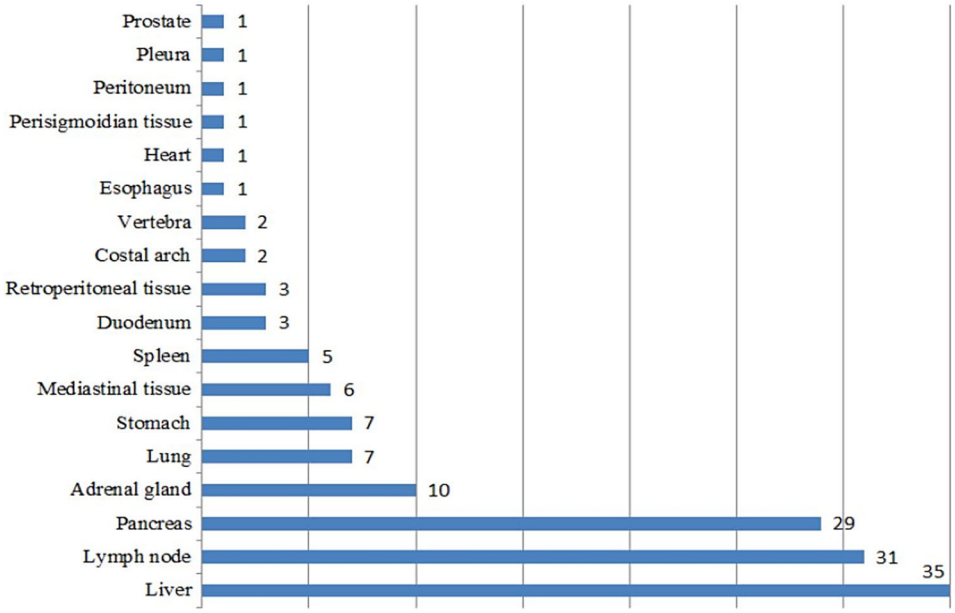

Figure 1 – ***The distribution frequency of the sampling site.***

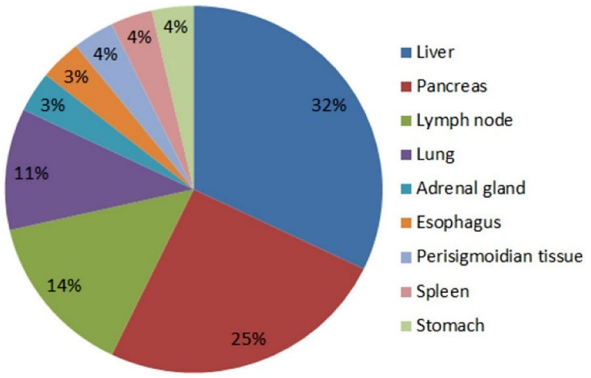

Figure 2 – ***The share of sites in inadequate sample cases.***

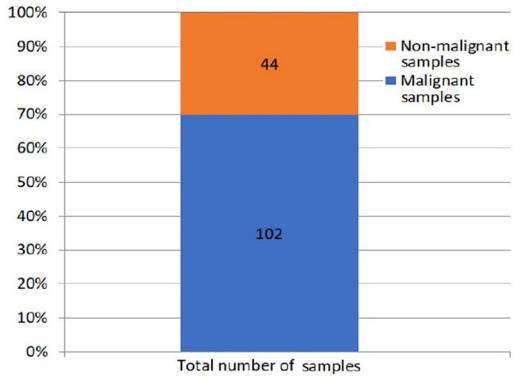

Figure 3 – ***The share of malignant and non-malignant from the adequate samples analyzed.***

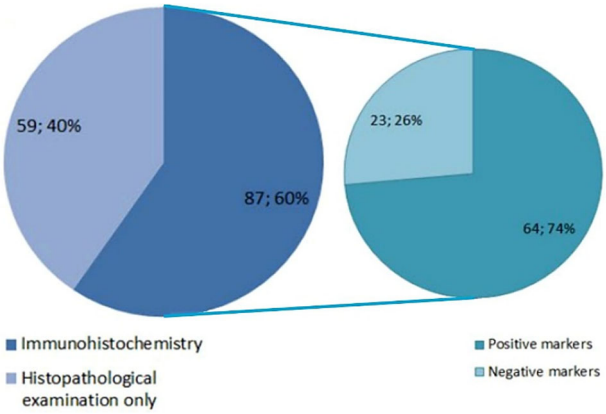

Figure 4 – ***The share of positive and negative markers used for immunohistochemistry (IHC) examination.***

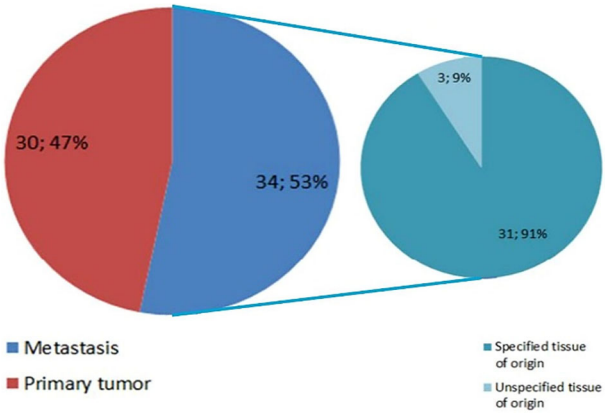

Figure 5 – ***The share of cases where IHC markers were helpful to specify the origin of metastasis.***

IHC is a tool for surgical pathology. Diagnosis should be based on Hematoxylin–Eosin (HE) morphology, with confirmation by IHC or molecular testing. A stain/result is not just positive or negative, we need to focus on the types of cells that are immunoreactive and determine if they are tumor cells, inflammatory cells, normal cells, or stromal cells; comparing the results to an HE-stained section or a negative control of the same block may be helpful.

IHC markers expressed in metastatic tumors obtained from diverse locations were helpful to identify the origin of the primary tumor. These are presented in the microscopic images: GATA-binding protein 3 (GATA3), one of six members of the GATA family of transcription factors, represents a nuclear marker expressed in many epithelial neoplasms including most breast and urothelial (Figure 6A); estrogen receptor (ER) is usually expressed in breast and endometrium, relatively specific for breast origin (but numerous exceptions); it predicts response to Tamoxifen or other anti-estrogens and it is also a prognostic marker for survival (ER+ is favorable) (Figure 6B); caudal-type homeobox 2 (CDX2) is a homeobox gene that encodes a nuclear transcription factor critical for intestinal embryonic

development (it can be used to determine the origin of metastatic adenocarcinoma as part of panel) (Figure 6C); NKX3.1 is an amino acid transcription factor protein that is expressed in the prostate, important in development of prostate epithelium and ducts and traditionally used as a diagnostic biomarker for prostate carcinoma and other metastatic lesions originating in the prostate (Figure 6D); human epidermal growth factor receptor 2 (HER2) detects evidence of protein overexpression *via* evaluation of the membranous immunostaining in the breast tumor cells (Figure 6E); thyroid transcription factor-1 (TTF-1) is an exclusively nuclear marker preferentially expressed in thyroid and lung (Figure 6F).

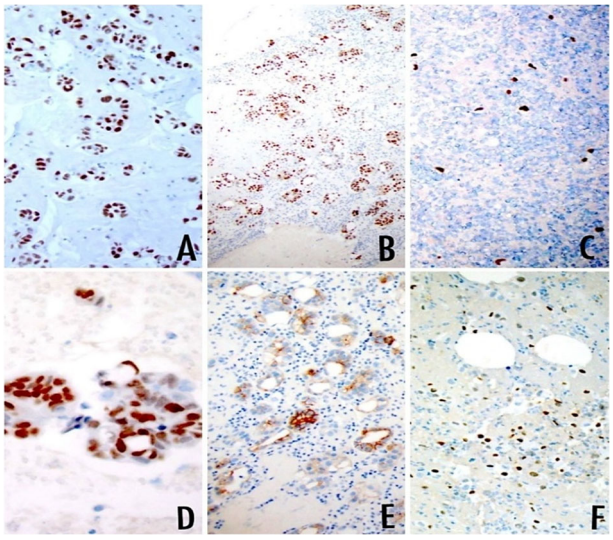

Figure 6 – ***Immunohistochemical staining of metastatic tumors in diverse sites: (A) Micrograph with GATA3 nuclear immunostaining (×400) highlighting clusters of ECs in a patient with metastatic BC to the pleura (GATA3 is a nuclear marker, more sensitive than GCDFP-15 or mammaglobin for metastatic BC immunostaining); (B) Clusters of ECs with moderate ER nuclear expression (×200) in a patient with metastatic BC to the mediastinal tissue (ER is used by pathologists in BC, to predict response to Tamoxifen or other anti-estrogens; it is relatively specific for breast origin in metastatic sites); (C) CDX2 immunostaining (×200) highlighting ECs in a patient with metastatic gastric carcinoma to the peritoneum (CDX2 is a fairly specific marker of gastro-intestinal origin for adenocarcinoma; it can be used to determine origin of metastatic carcinoma as part of a panel); (D) NKX3.1 nuclear immunostaining (×400) highlighting cluster of ECs in a patient with metastatic prostate carcinoma to the vertebra; (E) Clusters of ECs with incomplete HER2 membrane immunostaining (×200) in a patient with metastatic BC to the mediastinal tissue [HER2 testing must be performed on every primary invasive carcinoma and on a metastatic site (if stage IV); anti-HER2 therapy (Trastuzumab/Herceptin) plus chemo-therapy reduces recurrence, metastases and mortality in HER2 gene amplified BC patients; anti-HER2 therapy may improve survival in metastatic disease]; (F) TTF-1 nuclear immunostaining (×200) highlighting ECs in a patient with metastatic lung adenocarcinoma to the mediastinal tissue. BC: Breast carcinoma; CDX2: Caudal-type homeobox 2; ECs: Epithelial cells; ER: Estrogen receptor; GATA3: GATA-binding protein 3; GCDFP-15: Gross cystic disease fluid protein-15; HER2: Human epidermal growth factor receptor 2; TTF-1: Thyroid transcription factor-1.***

In order to avoid bleeding and implicitly the artifacts, the biopsies were targeted taken, ultrasound (US)-guided, by an internal medicine doctor. Two to eight biopsy fragments were sampled for each patient and approximately 10 images were recorded. All the biopsies were analyzed by a pathologist specialized in FNAB cytology. Strong nuclear GATA3 positivity was detected in the metastatic breast carcinoma to the pleura (Figure 6A) that was also positive for ER (Figure 6B). ER nuclear expression was also detected in a metastatic breast tumor to the mediastinal tissue, liver, and mediastinal lymph node. Although it was expected to be tested negative or downregulated in the metastatic lesion, the immunostaining for NKX3.1 protein was positive in a metastatic prostate tumor to vertebra (Figure 6D). TTF-1 immunostaining was positive in metastatic lung adenocarcinomas to the mediastinal tissue (Figure 6F) and also in one mediastinal tumoral mass. This was also positive for synaptophysin and chromogranin, which led to the necessity of differential diagnosis with a neuroendocrine tumor (NET).

Discussions

FNAB was initially conceived as a means of confirming the clinical suspicion of metastatic recurrence in the cases of an already known cancer, thus avoiding the patient's submission to surgery. Being successful in this aim, the interest has further focused on the preliminary diagnosis, before surgical management, of various types of benign and malignant tumors. In cases of inoperable tumors, this technique is useful for formulating the final diagnosis [23].

Firstly, in terms of applicability, FNA is a useful method for sampling superficial lesions, generally found in the skin, subcutaneous tissue, soft tissue, thyroid, breasts, salivary glands, and lymph nodes. Secondly, but with a similar importance, deep structures of the body can also be sampled by FNA, additionally using modern imaging techniques for guidance, mainly ultrasonography and computed tomography [24, 25]. Using these means, transthoracic and/or trans-peritoneal biopsy of deeply located structures is possible. Such samples can be obtained from the lung, mediastinum, abdominal organs, and retroperitoneal organs, deep areas of the head and neck and even from the bone. In addition, US-guided FNA can also be performed using endoscopic techniques, mainly in cases of pancreatic mases or its adjacent tissues [26–28]. Some steps are essential to follow in order to perform a successful FNA: establishing that FNA is warranted as a certain indication, obtaining the consent of the patient, preparing the equipment, positioning the patient, and immobilizing the lesions, sampling the targeted lesion adequately, preparing the sample for evaluation and providing post-procedure instruction to the patient [29, 30].

FNA technique has some well-defined advantages: it is a minimally invasive technique, which involves low costs and provides diagnosis information in a short time. Besides this, in most cases, if performed by an experienced operator, the accuracy of the method in providing an unequivocal diagnosis is close to that of the classical HP examination. In addition, FNA is used for both superficial and deep lesions, with a low risk of developing post-procedural complications [31–33].

FNA is burdened by certain limitations, such as the fact

that the results and the diagnostic accuracy are dependent on the quality of the sample, adequate preparation and experience of the operator are necessary to obtain an optimal sample. Furthermore, being known that many pathological processes have a heterogeneous structure, thus it is possible that the obtained sample not to be representative for the entire lesion; multiple attempts may help in this regard, but their number must be limited by the need to minimize trauma [34, 35].

Regarding the risks and complications that FNA involves, for the superficial lesions were reported post-procedural local pain, bleeding, and bruising. More serious complications have been reported depending on the area of interest: major hemorrhage, septicemia, biliary peritonitis, acute pancreatitis, and pneumothorax. Exceptional cases of death during FNA of a tumor localized in the carotid artery wall complicated with arterial dissection have been reported [36–38]. The risk of spreading malignant cells along the path of the needle is very low when using fine needles, between 0 and 0.009%. This risk increases proportionally with the depth of the lesion, the diameter of the needle and the number of passages performed [39–41]. Recent studies have demonstrated that endoscopic ultrasound (EUS)-guided FNA is a procedure involving a low risk of causing bacteremia and infectious complications when used for solid tumors of inferior GI tract. As a result, in such cases, the use of antibiotics for the 3[42].

In our study, 174 FNA biopsies were obtained from 18 sites: liver (35), lymph nodes (31), pancreas (29), adrenal glands (10), lungs (7), stomach (7), mediastinum (6), spleen (5), retroperitoneum (3), duodenum (3), vertebra (2), costal arch (2), myocardium, pleura, prostate, peritoneum, perisigmoidal tissue, and esophagus (1). The liver is the most frequently sampled internal solid abdominal organ, similar fact to the other studies carried out in this regard. The percentage of 83.3% of biopsies adequate for examination is consistent with the data from the literature, in several studies the adequacy of the method being reported between 57% and 87% [43–46]. IHC markers were used in the majority of malignant samples, increasing the accuracy of diagnosis. Our study revealed a frequency of positive IHC markers corresponding mostly with the data from the literature [19, 47–50].

Conclusions

FNAB proved its effectiveness as a highly accurate, cost-effective, and safe technique with potential high diagnostic yield. When performed by an experienced practitioner, this technique is a minimally invasive approach for establishing the initial pathological diagnosis of a primary benign or malignant mass, to confirm the existence of metastatic tumors and also, to prove the recurrence of a localized neoplasia. In some situations, particularly for deep biopsies, patients with an advanced grade of disease, with multiple comorbidities, are unable to tolerate surgery, thus the only method available to diagnose them is to repeat the needle biopsy. For these patients, this minimally invasive needle biopsy attitude is extremely valuable in terms of lowering anxiety and increasing confidence in their caregivers. It offers an adequate sample in order to formulate a conclusive diagnostic and speeds up the evaluation process. A substantial proportion of primary and metastatic lesions can be precisely subtyped by FNA cytopathology. In developing countries, FNA continues to be preferred as biopsy method due to the considerably reduced cost. Furthermore, IHC remains a very practical and reliable technique as an additional tool to classical HP examination that promises good results especially in determining the site of origin within metastatic disease. Future developments in needle biopsy instruments, enhanced techniques for managing needle biopsy specimens and innovations in analytical and IHC testing are anticipated to be essential for an accurate diagnose in precision medicine era.

Conflict of interests

The authors declare that they have no conflict of interests.

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