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Cytological vs Histological Evaluation of Percutaneous Biopsies

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Abstract. Fine-needle aspiration cytology yields sufficient diagnostic accuracy to compete with histology from punch biopsy for cancers of the lung and the prostate. For tumors of the breast, pancreas, thyroid, salivary glands, and kidneys, fine-needle aspiration cytology yields sufficient sensitivity and specificity when performed preoperatively; the exact tumor typing will follow surgical excision. In palpable lymph nodes, adrenals, and lungs, fine-needle aspiration biopsy is sufficient if metastases from a known primary tumor are suspected. Indications for punch biopsies and histological investigation are tumors of the liver, posterior and anterior mediastinum, retroperitoneum, soft tissues, and bone. In these conditions, cytological investigation alone provides insufficient typing accuracy. Suspected lymphomas in a retroperitoneal or mediastinal location should be punctured and may be classified from punch biopsies if the node is not easily reached by surgery. There are no indications for percutaneous biopsies in tumors of the skin, testes, and ovaries. Percutaneous fine-needle aspiration biopsies in general are associated with significantly lower complication rates than punch biopsies.

Key words: Percutaneous biopsies—Cytology—Histology

Adequate tumor therapy depends upon a precise microscopic typing or histogenetic classification. Even for tumors that are to be removed operatively, it is often necessary to know their precise typing and grade of malignancy as the surgical strategy may depend on this information. Intraoperative frozen sections are reported to meet this demand so far, although at least 2–3% of the resulting diagnoses are incorrect [1]. Furthermore, the duration of the operation may be increased 10–30 mins by this procedure. The modern and serious alternative for intraoperative frozen section diagnoses and for exploratory operations are percutaneous punch and needle biopsies.

The first person to describe diagnostic needle punctures of tumors was Lebert in 1851 [2]. In 1853, Paget in London aspirated cells from breast tumors for diagnostic purposes [3]. In 1912 and 1919 the German hematologist Hirschfeld [4, 5] reported on the diagnosis of cutaneous lymphomas and other tumors. Mannheim [6], also a German hematopathologist, published a report on "The significancy of tumor punctures for tumor diagnosis," in which he used a needle 1 mm in diameter. The founders of modern aspiration techniques were the American surgeon Martin and his technician Ellis [7, 8]. Between 1940 and 1950, a European school of fine-needle aspiration biopsy developed whose pioneers were the Dutch hematologist Lopez-Cardozo [9, 10] and the Swedish internist Söderström [11, 12]. Franzen from Sweden [13] developed a device for one hand fine-needle aspiration biopsy. Zajicek [14, 15] published the book *Aspirations Biopsy Cytology* which was the first solid basis for routine diagnostic application of that technique. The Swedish urologist Esposti [16] demonstrated that the transrectal fine-needle aspiration biopsy of the prostate revealed the same diagnostic accuracy as the histological diagnosis from core biopsies. Löwhagen [17], a Swedish pathologist, reached a high diagnostic accuracy for fine-needle aspiration from thyroid nodules.

The borders between cytological diagnoses on smears and histological diagnoses on sections are indistinct. Yet, cytological experience is essential to reach a high diagnostic accuracy in the histological evaluation of tiny biopsies. The introduction of the Menghini needle to obtain liver biopsies resulted in an accumulation of a rich histo- and cytopathological

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experience in the diagnosis of liver lesions [18]. A similar "diagnostic culture" on percutaneous core biopsies has only been established for the prostate using the Trucut needle (Travenol) [19], and for the lung [20].

Types of Biopsies

Two types of biopsy can be distinguished on the basis of the material obtained: fine-needle aspiration biopsy (FNAB) and punch biopsy. The first uses needles with a 0.6–1.25 mm outer diameter. Cells for cytological evaluation are aspirated under low pressure with a 10 or 20 ml syringe, moving the needle back and forth within the lesions (needling). Special pistol-shaped syringe holders are available to perform the puncture and aspiration procedure with one hand only. The resulting material is blown out on glass slides and smears are made under slight pressure. They should be very thin and homogenous to prevent cellular overlap. The slides should be air dried, if they are to be stained according to May Grünwald Giemsa, or fixed with 96% alcohol (spray), if they are to be stained according to Papanicolaou or with hematoxylin-eosion. The cytopathologist decides which staining and fixation technique will be performed. We prefer air-dried smears from lymph nodes, thyroid, spleen, salivary glands, and effusions. Short needles (2.5–7.5 cm length) with 0.64–0.75 outer diameters (22–23 gauge) are used for superficially located palpable nodules (thyroid, lymph nodes, breast, skin). Long needles (8–10 cm) with a mandrin with 0.8–0.9 mm outer diameter (spinal needles) are recommended for deeply located lesions and punctures under CT or ultrasound guidance (lung, mediastinum, retroperitoneum, liver, pancreas).

Punch biopsy uses cutting needles with variable outer diameters (0.85–2.1 mm). With smaller needle sizes very thin tissue cores are obtained by a combined cutting and suction procedure. The tissue cores are investigated cytologically and histologically. The thinner needles contain a stylet and bear two sharp incisors at their tip [21]. The needle is pushed to the front of the lesion, the stylet is then removed, low pressure is produced with a syringe, and the needle is advanced with revolving movements. With larger needle sizes (Trucut, Travenol, 2.1 mm) tissues cores of 2 mm diameter are cut by an outer hollow needle using the front piece of the inner needle as a stylet.

The pathologist must decide which size tissue core will best answer the clinician's diagnostic questions. A needle diameter <1.0 mm, for example, is unsuitable for the biopsy of diffuse kidney lesions; glomeruli disintegrate from the tissue section. Thin core biopsies <2 mm are not suitable for immunohistochemical evaluations because of antigen-smearing effects along the surface of the cut tissue. Tissue material has to be formalin fixed (4% formaldehyde in buffered aqueous solution).

Fine-needle aspiration biopsies allow only cytological evaluation of cells. Diagnostically, most relevant nuclear and cytoplasmic details can be examined best when careful alcohol fixation or air drying is performed instead of formalin fixation which produces shrinking artifacts. Additional immunological investigations may be performed on cytological smears, although such procedures often require repetion of fine-needle biopsy to obtain sufficient cells for immunocytochemical reactions. Additional techniques such as DNA cytometry or image analysis may better be performed on cytological rather than histological specimens.

Because the tissue texture as an important diagnostic parameter is lost in fine-needle aspirations, the accuracy of the tumor typing is often worse in cytological specimens. Yet, for some organs, cytological criteria are sufficient for precise tumor typing of cancers of the prostate and the lungs, for example. In these organs, pretherapeutic percutaneous FNAB is widely used and generally accepted as sufficiently accurate.

Applying cytological criteria and diagnostic experience to minute tissue samples (core biopsies) increases the diagnostic accuracy that can be achieved with these specimens. This means that core biopsy specimens are best evaluated by cytopathologists. Histological evaluation of percutaneous core biopsies is well established for tumors of the liver [18], the prostate [19], and the lungs [20].

Risk of Tumor Spread

It has been proven that tumor cells may escape into blood vessels by normal motion of the individual and by manual examination of a tumor. A local spread within the needle tract has sometimes been observed microscopically but local growth has seldom been described. Kato et al. [22] reported on one case of a local implant metastasis in 1,246 fine-needle aspirations of lung tumors (0.08%). Nordenström and Bjork [23] reported only one definite (and one probable) case of needle track implantation in a series of 4,000 percutaneous lung biopsies on 2,500 patients. Up to 1977, 2 cases of needle tract seedings following fine-needle aspiration of renal tumors had been described [24]. The small number of tumor cells released may be the cause for the rare occurrence of needle tract metastases. For 370 women who under-

went fine-needle aspirations of breast cancers, no difference in survival probability was found compared to 370 women who had no needling of their breast tumors [25]. A vascular spread of tumor cells with resulting metastasis following fine-needle aspiration of tumors has not yet been proven [26]. The risk of provoking metastases is theoretically greater with larger needle diameters, however.

Variables of Diagnostic Results

Diagnostic Dimensions

On one hand, diagnostic precision increases with the amount of material obtained and is higher for histological compared with cytological evaluation. On the other hand, the complication rate may increase with increasing needle size and with the amount of removed material. Therefore, the clinician has to weigh the desired diagnostic accuracy against the discomfort for the patient which has to be minimized. In order to minimize the complication rate the clinician must first ask the diagnostic questions that have to be answered by the pathologist. These questions refer to the following diagnostic dimensions: benignity or malignancy, histogenetic tumor classification, grading of tumor malignancy, and therapy monitoring. Not always are all of these questions asked simultaneously, for example, the histogenetic tumor classification that follows evaluation of the resected mass or is known from a previous resection. Further, the radiologist must consider if the questions can be answered for the organ under investigation with sufficient accuracy by investigating cytological material only, or if the pathologist needs histological material. To decide on that question, he or she must know the current diagnostic sensitivities, specificities, and typing accuracies for histological and cytological investigations which are very different for every organ [27].

Table 1. Diagnostic sensitivity, specificity and typing accuracy of fine-needle aspiration biopsy for various sites and organs according to the literature

Organ/site	Sensitivity (%)	Specificity (%)	Typing accuracy (%)
Breast	94.0 [44] aol	99.2 [44] aol	
Kidney	87.0 [47] aol	99.1 [47] aol	
Liver	94.0 [50]	98.9 [49]	
Lung	99.0 [34][a]	94.3 [34][a]	84.6 [34][a]
Lymph nodes	93.8 [54] aol	96.5 [54] aol	59 [54]
Mediastinum	94.5 [37][b]	100 [37][b]	95.6 [37][b]
Pancreas	87.0 [53] aol	99.0 [52]	
Prostate	82.7 [30] aol	97.2 [30] aol	
Salivary glands	72.0 [54] aol	97.0 [54] aol	52.0 [54]
Soft tissues	89.0 [55]	95.5 [55]	
Thyroid	87.0 [54]	88.3 [54]	60.0 [54]

(aol = average of the literature)
Sensitivity represents the percentage of malignant tumors correctly identified in the biopsy specimen. Complementary to it is the false-negative rate, which is composed of the false-negatives caused by the radiologist missing the target with the needle and by the pathologist not identifying tumor cells. Specificity represents the percentage of benign lesions correctly identified as benign. Complementary to it is the false-positive rate, which is caused exclusively by the cytopathologist's misinterpretation of abnormal cells. Typing accuracy refers to the percentage of malignant tumors that were correctly classified histogenetically in the biopsy material
[a] CT-guided puncture
[b] Site-oriented needle selection and CT-guided puncture

Accuracy of Conventional Histology

Despite common opinion, the figures of diagnostic validity do not add up to 100% for histology. The diagnostic accuracy of intraoperative frozen section diagnoses according to extensive investigations reaches only 97–98% [1]. The histological diagnosis of breast cancer in young women may reveal a 17–19% false-positive [28, 29]. The false-positive rate of prostatic punch biopsies amounts to about 2%, the false-negative rate about 7% [30]. The histological accuracy for nonsmall cell bronchial carcinomas in bronchial biopsies was found to be only 95% for squamous cell carcinomas, 67.3% for adeno carcinomas, and 56% for giant cell carcinomas (P. Dalquen et al., unpublished data). The reproducibility of the histological Kiel classification of malignant lymphomas amounts to only 79% [31]. The reproducibility of the histological grading of breast cancer malignancy according to Bloom and Richardson [32], adopted by the WHO, is only 69% [33].

Accuracy of Conventional Cytology

The typing accuracy of cytology is mostly limited compared with that of histology (Table 1). Generally, rare tumors are cytologically classified with insufficient accuracy, whereas frequently occurring tumors are more often typed correctly. For a few organs, cytology yields a typing accuracy compara-

ble to that of histology so that operative therapy may be performed on the basis of the cytological diagnosis (e.g., small cell vs nonsmall cell lung cancer, cancers of the prostate). The sensitivities and specificities of guided fine-needle aspirations with cytological evaluation are generally rather high and compare favorably with those of conventional histological investigations of punch biopsies (Table 1), [27]. Inadequate cytological or histological material does not have to be interpreted as "negative," but can be classified as "insufficient," and then the biopsy has to be repeated unless the diagnosis could be established by other means. However, in many statistical evaluations the inadequate samples are summed up with the negatives. We do not share the common opinion that cytologically negative diagnoses usually have to be regarded as unreliable. If the radiologist is sure that he hit the relevant focal lesion and the cytopathologist was able to make a cytological diagnosis corresponding to a focal disease (e.g., giant cell granuloma, scar tissue, necrosis or infarction, bleeding, abscess) the cytological diagnosis is valid. Yet, if the pathologist described merely normal cells from the respective organ, the FNAB has to be regarded as not representative [34]. The proportion of inadequate aspirates is dependent on the training of the physician and may reach 55% for the prostate, 34% for the breast, and 24% for the thyroid if performed by unexperienced personnel [35].

Combined Histological and Cytological Material

Combined investigation of histological and cytological material has sporadically been advocated [36]. If there is any advantage it is from the higher representativity of the combined material. If tiny tissue specimens are inspected from the histological and cytological point of view by the same observer who is a cytopathologist, it is not necessary to send the tissue specimen to a histopathologist and a cell specimen to a cytologist. Air-dried touch preparations from lymph node biopsies, when investigated cytologically, are supplementary to histological and immunhistochemical investigations and may be helpful in typing malignant lymphomas.

Site-oriented Needle Aspiration

The diagnostic accuracy increases if the needle size is chosen according to the tumors. Although all compartments of the mediastinum are accessible for fine needles, it can be predicted that cytology will fail to correctly diagnose certain lesions. Therefore, the well-known predilection of specific entities in certain mediastinal compartments and their suitability for cytological examination have to be taken into account when choosing the needle size. In the posterior and anterior mediastinal compartments, many noncarcinomatous tumors are found which will not be accurately classified by cytology. Core biopsies are recommended in these regions if a safe access route is available. In the middle mediastinum, the subcarinal region, and the hila, bronchogenic cancers, sarcoidosis, and malignant lymphomas are the most common entities and they are usually correctly identified cytologically. Fine needles may be used for lesions in these compartments. In our series this type of "site-oriented needle selection" yielded a sensitivity and specificity of 100% each in 125 core biopsies and a sensitivity of 94.5% and a specificity of 100% in 103 fine-needle aspirates of the mediastinum. No complication occurred with large core biopsies. The typing accuracy was 96.8% in histological and 97.1% in cytological diagnoses [37]. If the pathologist admittedly does not arrive at a precise tumor diagnosis from biopsy material, then a larger biopsy specimen should be obtained operatively.

Immunohistocytochemistry

Immunohistochemistry increases the tumor typing accuracy achieved by histological investigation of punch biopsies (>2 mm). Most immunological reactions may nowadays be performed on formalin-fixed and paraffin-embedded tissue. This technique may rarely be applied to cytology because of the limited cellular material.

Unfixed, native histological or cytological material is needed in only a few special cases when immunoreactions with antibodies not suitable for paraffin-sections have to be performed. Usually the pathologist will inform the clinician in these cases. If in non-Hodgkin lymphomas a subclassification of T-cells is requested, the proliferative fraction of a tumor using the Ki67 antibody or the epidermal growth factor (EGF) should be quantitated, and native unfixed tissue or cell material will be requested. The same holds for the immunohistochemical quantitation of estrogen and progesterone receptors in breast cancer tissue.

When native fresh tissue has to be transported to the pathologists laboratory in order to perform special immunohistochemical stains (e.g., subclassification of lymphomas) the material need not be suspended in saline or other solution, but merely kept cool (on ice) on a moist piece of gauze.

In most cases it makes no difference to the pathologist whether a punch biopsy is long and narrow

or short and wide. The larger the tissue area under investigation, the more representative the diagnosis will be. However, immunohistochemical reactions can only be performed on biopsies wider than 2 mm. Antibody smearing effects prohibit the immunological investigation of smaller biopsies.

DNA Cytometry

Meanwhile, preoperative diagnostic DNA measurements may be requested on needle biopsy material in selected tumors and stages as the results may influence the operative strategy. In colonic cancer, the pre- or intraoperatively determined DNA-ploidy level highly influences the surgical procedure of tumor resection [38]. In breast cancer, breast saving operations may be restricted to low stage cases with low DNA grades of malignancy [39]. In prostatic cancers, the therapy of incidental tumors mainly depends on the DNA ploidy level. Precise diagnostic DNA measurements of tumor populations may best be performed on fine-needle aspirations independent from the type of prefixation using modern TV-image analysis systems [40, 41].

Quick Stains in Cytology

We do not recommend the application of quick stains to cytological material as they always represent minor staining quality and thus decrease the diagnostic accuracy. The combination of scanty cellular material with insufficient staining quality will result in diagnostic errors. If an intraoperative cytological diagnosis is urgently requested, quick stains may be used as an exemption [42].

Informing the Pathologist

The probabilities of a correct cytological or histological diagnosis will significantly increase if the radiologist informs the pathologist about his/her differential diagnoses. Clinical information motivates the pathologist and increases diagnostic accuracy. Especially for the rational application of various immunohistochemical stains (panel) to classify tumors of unknown origin and type, it is essential for the pathologist to know the clinicians differential diagnoses.

Organ-specific Indications

Bones

FNAB of bone lesions is not well established. Usually histopathologists request larger tumor biopsies combined with the respective x-ray films to diagnose and classify bone tumors [43]. If a bone metastasis from another primary tumor is suspected, bore biopsies with an outer diameter of about 2 mm will suffice to identify the primary tumor. In sclerotic bone lesions, bore biopsies are contaminated by bone meal obscuring the surface of the tissue. Therefore, drill needle diameters smaller than 3 mm should not be used. If a bone primary tumor is suspected, several larger biopsies combined with the respective x-ray films should reach the pathologist.

Breast

FNAB plays an important role in the preoperative evaluation of breast nodules together with palpation and mammography (so-called triple diagnosis). On average, the specificity is 96.5% [44]. A positive cytological diagnosis means operative resection and additional frozen section evaluation of the nodule. As the sensitivity of FNAB is only 84.5% on average [44], a negative cytological diagnosis is only valid when the radiological findings are also normal. The sensitivity of FNAB of the breast can be significantly increased using stereotactic guidance [45]. Precise histological tumor typing will be performed on the resected mass. Punch biopsy with histological investigation may be discussed as an alternative to operative resection in the evaluation of cytologically or radiologically doubtful or suspicious cases [46]. Preoperative nuclear DNA measurements on FNAB smears may significantly influence the radicality of the operative resection of low stage nodules (breast-preserving operation) [39].

Kidney

FNAB of focal solid kidney lesions yields sufficient sensitivity and specificity (99%) to indicate surgical resection in tumor cell-positive cases [47]. As a precise classification will be performed after the histological investigation of the resected tumor, an exact typing is not necessary preoperatively. Aspiration biopsy of kidney cysts is not indicated as imaging techniques can exclude a malignant component with the same sensitivity as cytology does [48].

Liver

FNAB with cytological evaluation is sufficient to clarify focal liver lesions when a metastasis of a known primary tumor with a high index of live metastases is suspected. The false-positive rate of 1.1% of FNAB is within the acceptable limit [49]. Sensitiv-

ity of FNAB is similar to that of punch biopsy, if both methods are performed under ultrasound or CT guidance (94% [50]). The differentiation between a focal nodular hyperplasia and a liver cell adenoma is not possible cytologically. If a focal liver lesion has to be investigated without a known primary tumor, punch biopsy is advocated, which allows additional immunohistochemical investigation thus increasing the probability of correct tumor typing.

Lung

Coin lesions of the lungs are the domain of FNAB under CT guidance, as the complication rate is low (8%), the sensitivity (99.0%) and specificity (94.3%) rather high, and the typing accuracy sufficient [34]. The therapeutically relevant distinction between small-cell and nonsmall-cell carcinomas is cytologically possible in 95% of patients [51]. Negative cytological diagnoses are reliable provided they are in agreement with radiological findings. Positive cytological diagnoses with tumor typing indicate surgical resection of low-stage nonsmall-cell carcinomas and chemotherapy or radiation for high stage nonsmall-cell and all stages of small-cell carcinomas. Cytological diagnosis of focal benign lung disease can be highly accurate with FNAB if the microscopical findings are in agreement with the radiological findings [34]. Exact typing of benign lung tumors is usually not requested. If an access route through unventilated lung is possible, punch biopsy may be performed, resulting in somewhat higher accuracy of the histological investigation. The identification of the original primary tumor may require a punch biopsy of lung metastases, and immunohistochemical stains may help to type the lesion.

Lymph Nodes

FNAB of lymph nodes is only indicated if metastases are suspected.The accuracy of cytology to diagnose and type malignant lymphomas is insufficient when compared with histology from punch biopsies or resected lymph nodes. If an enlarged lymph node easily accessible to surgery is to be examined to exclude a malignant growth, it should be resected and formalin fixed after a touch preparation has been performed from the cut surface. If major surgery is requested to reach a lymphoma, at least two punch biopsies should be obtained to diagnose and type a malignant lymphoma. The usual immunohistochemical markers necessary for typing lymphomas can be found on paraffin-embedded materials. If typing is not achieved, additional unfixed material may be requested by the pathologist. A problem may arise in identifying Hodgkins disease from punch biopsies because the diagnostic Hodgkin or Sternberg Reed cells may not be incorporated in the biopsy (geographic error). Additional biopsies [2–4] will increase the sensitivity in this situation.

Mediastinum

The choice of the adequate needle size for puncturing mediastinal lesions depends on the compartment involved. In those regions where metastases of lung cancers and sarcoidosis are frequently encountered (hilum, subcarinal region, middle mediastinum) and access routes are more risky, FNAB is indicated as it can identify and type these diseases with sufficient accuracy (95.6%) [37]. In other mediastinal compartments, teratomas, lymph nodes, lymphomas, soft tissue and other tumors are frequent, and these cannot be sufficiently typed by cytology alone. Punch biopsies should be requested to diagnose these lesions.

Ovary

Ovarian tumors should not be punctured because the possibility of peritoneal tumor spread exists. As malignant ovarian tumors are resected, they will be precisely classified after the operation.

Pancreas

Punch biopsy has no role in the diagnostic evaluation of pancreatic lesions. The complication rate (acute necrotizing pancreatitis and fistulae) is too high compared with pre- and intraoperative FNAB under ultrasound or CT guidance. As the specificity of the cytological diagnosis is high (99%) [52], a positive diagnosis means operative resection is indicated. Intraoperative frozen section diagnosis should confirm the cytological diagnosis of malignancy to avoid overtreatment. As the sensitivity of the cytological diagnosis of pancreatic lesions is only 87% [53], a negative diagnosis is only valid in accordance with other clinical findings. The final histogenetic tumor classification will be performed on the resected material.

Retroperitoneum

If a safe dorsal access route is possible to reach a retroperitoneal mass, it is advisable to obtain punch biopsies to achieve a sufficiently high typing accu-

racy. FNAB may only be indicated if a retroperitoneal metastasis of a known primary tumor or a malignant lymphoma is suspected. However, subtyping of lymphomas may be problematical on cytological smears.

Salivary Glands

Solitary nodules in salivary glands are targets for FNAB using ultrasound guidance. Positive cytological diagnoses mean operative resection as the average specificity in the literature is high (97%) [54]. Resected nodules should be investigated also by intraoperative frozen section to avoid overtreatment. Exact tumor typing will be performed on the resected material as the cytological tumor typing is not sufficient (52%) [54]. Negative cytological diagnoses are only reliable and acceptable in accordance with other clinical findings as the average sensitivity is only 72% [54]. Punch biopsy is not indicated in salivary gland tumors.

Thyroid

Punch biopsy is not indicated in the diagnostic evaluation of thyroid nodules. Instead, FNAB is the method of choice to clarify the nature of scintigraphically cold nodules. Cytologically positive lesions (average specificity 88.3%, [54]) have to be operatively resected and histologically investigated. Cytologically negative diagnoses are reliable only when in agreement with other clinical findings (average sensitivity in the literature is 87%) [54]. Follicular adenomas and carcinomas cannot be distinguished either by cytology or by intraoperative frozen section, but will be identified only as "follicular neoplasias." The cytological typing accuracy of thyroid tumors is 60% as a mean [54]. Definite histogenetic tumor typing must be performed on the resected material. FNAB under ultrasound guidance may detect tiny carcinomas, which will be identified histologically only by step sectioning of the resected material.

Soft Tissue

Soft tissue tumors are the domain of punch biopsy, if a preoperative diagnosis is requested, as the sensitivity (89%) and specificity (95.5%) [55] of FNAB are low and the typing accuracy is insufficient. Histological investigation of biopsies allows a sufficiently precise preoperative diagnosis and typing of these lesions. DNA cytometry can increase the sensitivity and specificity of FNAB of soft tissue tumors [56].

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