REVIEW Libri Oncol., Vol. 42 (2014), No 1-3, 15 – 22

ROLE OF CYTOLOGY IN DETECTION AND TREATMENT OF BREAST TUMORS

VESNA RAMLJAK, IVA BOBUŠ KELČEC and MERDITA AGAI MUHAXHIRI

Department for Cytology, University Hospital Center Sestre milosrdnice, Zagreb, Croatia

Summary

Fine-needle aspiration cytology (FNAC) is an established, highly accurate, and cost-effective method for diagnosing lesions in the breast. The method is minimally invasive without unwanted side efect. FNAC forms part of the triple assessment of breast lesions and has a high accuracy and sensitivity in dedicated centres. Method as a part of triple assessment has provide its value in describing the findings most accurately. The diagnostic impact depends on experience of the operator, quality of preparation and diagnostic skills of the cytopathologist. Inadequate sampling with FNAC is particulary seen in collagenous lesions and in submitted specimens sampled by physicians lacking experience with the FNAC procedure. The highest accuracy is achived at centres with multidisciplinary approach.

The majority of European countries use similar reporting system for breast FNAC (C1-C5), in keeping with European guidelines for quality assurance in breast cancer screening and diagnosis. A clear reporting system ensures that an unequivocal cytological diagnosis of malignancy is reliable, and in cases where mammography/ultrasonography and clinical examination are in agreement with FNAC, frozen section examination is unnecessary.

The issue of optimal sampling to obtain adequate cell material in sufficient quantity is of paramount importance when assessing the accuracy of FNAC. The inadequate rates in FNAC from different sources are lowest when FNAC is performed by a cytopathologist and highest when done by a non-cytopathologist. The multidisciplinary approach is necessary to amplify FNAC quality and to reduce its diagnostic limits. Only when this model of activity is not available, the role of FNAC is less effective and the addition of core biopsy (CB) to FNAC should be considered. CB as an alternative diagnostic modality should be used advisedly, in situations where it is more likely to yield diagnostic information, e.g., in the diagnosis of impalpable masses, microcalcifications or a clinically apparent malignancy where preoperative chemotherapy is planned. CB should not be used as a substitute for poor performance at FNAC. The methods are not mutually exclusive.

KEY WORDS: *breast, aspiration cytology, breast tumors, diagnosis*

ULOGA CITOLOGIJE U OTKRIVANJU I LIJEČENJU TUMORA DOJKE

Sažetak

Aspiracijska citologija tankom iglom (FNAC) je utemeljena, visoko pouzdana i jeftina metoda u dijagnostici lezija dojke. Metoda je minimalno invazivna bez neželjenih nuspojava. Sastavni je dio tzv. trojnog pristupa u dijagnostičkoj obradi lezija dojke, te u specijaliziranim centrima ima visoku pouzdanost i senzitivnost. Također je unutar trojnog pristupa dokazala svoju vrijednost mogućnošću da izrazito pouzdano okarakterizira promjene. Dijagnostički učinak ovisi o iskustvu liječnika koji izvodi postupak, kvaliteti obrade materijala te dijagnostičkim vještinama citopatologa. Neadekvatni uzorak se najčešće susreće u kolagenoznim lezijama,komplex sklerozirajućim promjenama te u oskudnosti primljenih materijalima od strane liječnika koji izvode punkciju, a nemaju dovoljno iskustva s procedurom. Najviša razina pouzdanosti postiže se u centrima s multidisciplinarnim pristupom. Većina europskih zemalja koristi isti sustav pisanja citoloških nalaza vezanih za dijagnostiku dojke (C1-C5), koristeći se smjernicama za osiguravanje kvalitete u probiru i dijagnostici karcinoma dojke. Jasni sustav pisanja nalaza time osigurava pouzdanost nedvojbene citološke dijagnoze maligniteta, te u slučajevima kada je ona u skladu s radiološkim nalazima (mamografijom/ultrazvukom), kao dio trojnog pristupa nije potrebna hitna, intropera-

tivna patohistološka dijagnostika.Optimalno prikupljanje materijala radi dobivanja adekvatno celularnog uzorka, je od ključne važnosti za pouzdanost aspiracijske citologije(FNA). Nivo neadekvatnog materijala je najniži kada postupak izvodi citopatolog, a najveći kada ga izvode liječnici drugih specijalnosti. Multidisciplinarni pristup je neophodan za povećanje kvalitete metode te za reduciranje njenih dijagnostičkih ograničenja. Samo u slučajevima kada ovakav model pristupa nije dostupan, uloga citologije (FNA) je manje učinkovita te se treba uzeti u obzir biopsija širokom iglom (CB). CB je alternativni dijagnostički modalitet, te se treba koristiti ciljano, u situacijama kada je izvjesnije da će omogućiti bolju dijagnostičku informaciju, npr. u slučajevima kada se radi o nepalpabilnim promjenama, mikrokalcifikatima, te u slučajevima klinički jasnog malignog procesa gdje se planira preoperativna kemoterapija. CB se ne treba koristiti kao alternativa slabo izvedenoj citološkoj punkciji, te se navedene dvije metode međusobno ne isključuju.

KLJUČNE RIJEČI: *dojka, aspiracijska citologija, tumori dojke, dijagnoza*

INTRODUCTION

Breast cancer is the lading cause of death among women. Incidence of breast cancer is rising in developed countries and the overall survival also shows a rising trend (1,2).

The introduction of breast screening programmes increased the use of minimally invasive diagnostic methods. True fine needles aspirations for breast diagnostics were first introduced in the Karolinska Hospital in Stockholm. Franzen, who was an oncologist, introduced standard May-Grunwald Giemsa stains on air –dried to allow rapid analysis . Despite their success, it was not until 1980s that fine needle aspiration cytology (FNAC) became widely used. Probably due to lack of confidence in the sensitivity and specificity of the procedure, fear of tumor implantation in the needle track, law-suits, and surgeons preferring histological biopsy for diagnosis (3). Now, FNAC is widely accepted technique and management of palpable and non-palpable breast lesions due to its simplicity, accuracy and utility for avoidance more invasive procedures.

The use of FNAC varies considerably in different centers. FNAC is commonly used as part of the triple diagnostic triad, along with clinical breast examination and radiology immaging (mammography and ultrasonography). The diagnostic accuracy is close to 100% when all three modalities favor a benign or a malignant diagnosis (4). Therefore, fine needle aspiration (FNA) and core biopsy are now universally accepted as methods that virtually eliminate the need for open biopsy or frozen sections in diagnosis of breast cancer. Nevertheless, growing number of analysis needed enlarged the faced cytologist/pathologist with certain challenges such as the reduced size of material obtained and wide variety of breast lesions that may be identified.

Fine needle aspiration cytology

Fine-needle aspiration cytology in Croatia was the first diagnostic method. According to the Croatian society for clinical cytology working Group guidelines, cytology report for breast tissue includes: adequacy of aspirated tissue, a description of the cells and tissue examined, cytological diagnosis, followed by patohistological confirmation of unclear, suspicious and malignant lesions. Cytology report should include information about tumor grade as a method of predicting histological grade and biological behaviour. The aim is to achieve the highest treatment accuracy (5).

Various cytological scoring systems exist. They are based on different characteristics such as: cell cohesion, cellular pleomorphism, presence or lack of myoepithelial cells, mitotic count, nuclear pleomorphism, presence of nucleoli and chromatin structure. Application of different cytological scoring methods as presented in table 1. and comparison with histological score as a golden standard, has proved that Robinson's method of cytological scoring is easy to use and highly correlates with histological score. Therefore it is a commonly used method for cytological scoring of breast cancer (6-9)

Robinson's method encompasses six criteria presented in table 1. Each of the mentioned criteria is assigned a number from 1 to 3. The sum of numbers attached to each of the mentioned criteria represents tumor grade; grade I: sum of 6-11, grade II: sum of 12-14, grade II: sum of 15-18. When comparing with other scoring systems, Robinson's method includes more criteria and excludes necrosis and mitotic count which are diffi-

Table 1.

ROBINSON'S METHOD OF CYTOLOGICAL GRADING

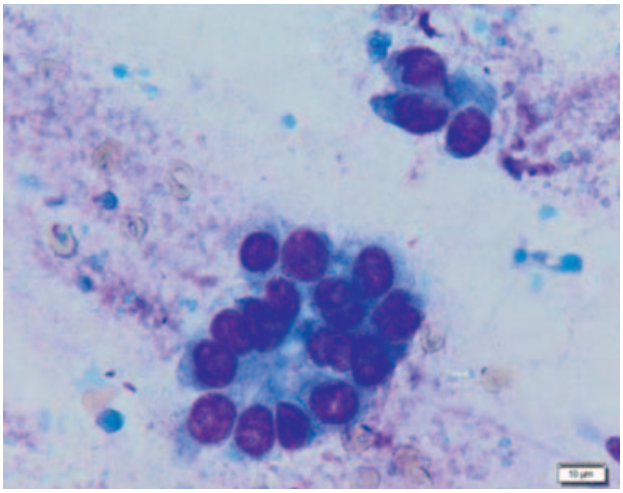
	Count 1	Count 2	Count 3
Cohesion	Cells mainly grouped	Mixed	Cells mainly isolated
Cell size	1-2 x E	3-4 x E	≥ 5 x E
Cell uniformity	monomorphism	moderate	pleomorfism
Nucleoli	invisible	barely visible	prominent
Nucleus margins	smooth	Frilled	protruded, irregular
Cromatine	vesicular	granular	lumpy

cult to detect in cytological specimen and hence provide unreliable information (9).

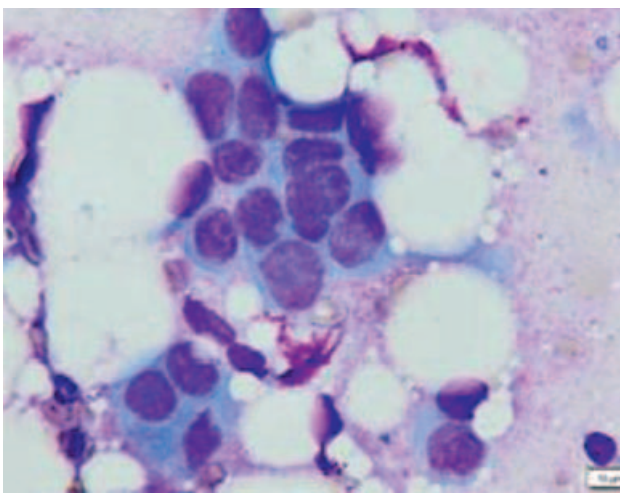
FNAC is performed with fine needle under ultrasound guidance. After the cells are withdrawn by aspiration they are spread on a glass slide, they are air-dried and stained using May Grünwald-Giemsa method. The advantages of FNA are: quick, cheap and safe procedure with no need for local anaesteshia, minor complications and the results are rapidly available (10). Disadvantages are incomplete assessment of the tissue (when compared with histology) due to reduced cellularity in certain lesions (radial scar, lobular cancer and invasive breast cancer with sclerosis) (11). The diagnostic sensitivity, diagnostic specificity, overall accuracy, and the pseudo-negative and pseudo-positive results of FNAC for diagnosing breast carcinoma are 97.72%, 99.4%, 97.94%, 2.28%, and 0.6%, respectively. The results depend upon the skills and education of the aspirator. Inadequate rates (IR) in FNAC from different sources were compared by singh et al. The rates were lowest when FNAC was performed by a cytopathologist (12%) and highest when done by a non-cytopathologist (32%) (12).

Main problems are when there is equivocal/borderline cytological diagnoses and that cases always require a diagnostic biopsy. About good/satisfactory breast FNAC we can talk when there is < 10 % unsatisfactory/nondiagnostic and when is a low percentage of equivocal/borderline diagnoses (10-15 %).

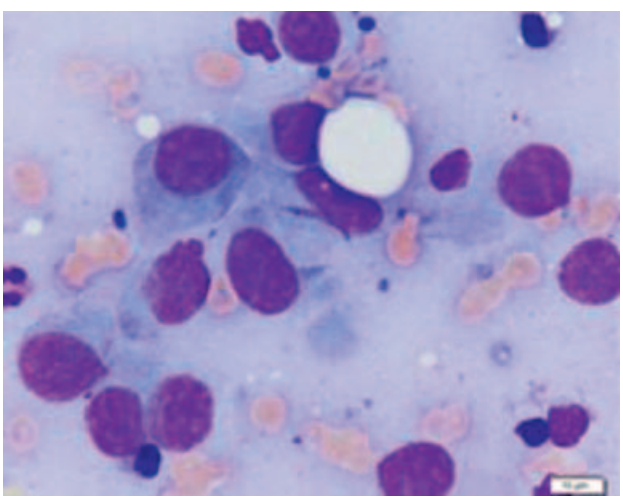
Aspirator skill is reflected mainly in the inadequacy rate which varies from < 5 % to 40%



Gradus I



Gradus 2.



Gradus 3

Figure 1-3. Citology smears of invasive breast carcer graded according to Robinson's scale

Some of the *suspicious* cases are also caused by suboptimal smear quality.

Reporting of Breast FNAC

The majority of European countries use the following reporting terminologies according to European guidelines for quality assurance in breast cancer screening and diagnosis C1-C5:

C1 – insufficient material/no diagnosis (unsatisfactory)
C2 – benign;
C3 – equivocal (probably benign) (PBD without atypia), including
  – Columnar cell lesion/hyperplasia without atypia
  – Intraductal hyperplasia, adenosis, sclerosingadenosis, cellular papillary lesion
C4 – suspicious NOS; PBD with atypia including
  – Consistent with non high-grade DCIS/ADH
  – Columnar cell hyperplasia with atypia
  – Consistent with papillary (intracystic) carcinoma in situ,cannot evaluate invasiveness
C5 – carcinoma NOS including
  – High-grade DCIS, cannot evaluate invasiveness
  – Invasive carcinoma (13,14)

This categorization helps cytopathologist to define the uncertain areas, and the clinicians to offer further investigation like excisional biopsy judiciously. This categorization was initiated by the national coordinating committee for breast screening and the UK national breast screening program and serves as a common dialect among all breast health care professionals involved in breast management. (13)

A clear reporting system ensures that an unequivocal cytological diagnosis of malignancy is reliable, and in cases where mammography/ultrasonography and clinical examination are in agreement with FNAC, frozen section examination is unnecessary. (13)

Adequate FNAC

The adequacy of FNAC is dependent on multiple factors. The rate of inadequate aspiration ranges from 0.7% to 25.3% and this is influenced by the nature of the lesion, the available technology, and the experience and preference of the surgeon. It was reported that the nature of the lesion was the most common cause of inadequacy of FNAC, accounting for 68% of the inadequate aspirates, followed by the experience of the aspirator that accounted for 32% of the inadequacy rate. During the procedure, patient's cooperation is valuable, and a well-informed patient with good rapport with the operator for FNAC would greatly facilitate the procedure and improve the outcome in terms of adequacy. Thus, each procedure should be patterned and restricted to clinically and radiologically appropriate scenarios (14). Some studies advocated that both aspiratorand interpreter should ideally be the same, as the number of inadequate aspirates was far lower and the accuracy of diagnosis was higher when the same person aspirated and reported on the specimens (14,15). The mean frequency of unsatisfactory aspirates by a nonpathologist was twice that when performed by a pathologist (15).

Unanimous definition of specimen adequacy in breast FNAC has not been reached so far. The National Cancer Institute (NCI) definition of adequacy was one that led to resolution of a problem presented by a lesion in a particular patient's breast. This definition was somewhat vague,being devoid of a quantifiable clause, but had the advantage of being very flexible and gave the aspirator the full mandate in deciding whether the cytologic features of the aspirate were consistent with the clinical findings and deemed adequate (16). This would be particularly useful when both the aspirator, and interpreter of the sample were the same. Most cytopathologists agree that a number of related parameters are significant determinants of the adequacy of breast FNAC, and these include clinical and imaging findings, size of the lesion, aspiration characteristics, experienceof the aspirator, and the number of the needle passes (15).

Nevertheless, many authors considered epithelial cell clusters as the most important adequacy criteria. Studies demonstrated that an appropriate number of epithelial cell clusters could be an important factor in lowering the false-negative diagnosis rate in palpable and nonpalpable breast masses (15). It was further suggested that a cut-off of six epithelial cell clusters may provide a reasonable balance between reduction of false-negative FNAC smears and an increase in the rate of inadequate smears (17).

Sensitivity and specificity

Fine needle aspiration cytology (FNAC) of the breast has two main goals. One is to confirm a radiological and clinical benign lesion and avoid unnecessary surgery and the other is to confirm a malignant diagnosis and allow definite treatment planning. FNAC of the breast is a standard diagnostic technique in diagnosis of breast benign and malignant changes as far as their further sub typing. FNAC diagnosis of the breast is reliable and accurate; it may be conveniently used in the clinical practice since it provides indications for appropriate therapeutic procedures or diagnostic surgery and avoid open biopsy. In the majority of studies evaluating FNA breast cytological accuracy, overall sensitivity was found to range from 83% to 92% and specificity between 92% and 98% according to Kocjan G (18). Therefore, FNAC is usually the first morphological diagnostic test in institutions with high volume cytology. Ghimire reports that 98%, sensitivity 100%, specificity 95,2%, and positive predictive value of 96,7% can be achieved when FANC is a part of triple test (clinical examination and imaging) (5,19). These results were confirmed in several institution where triple test, including cytology, is routinely performed (20,21). Furthermore, the technique is cost effective in stratifying breast lesions (20). FNAC is most widely used for confirmation of benign lesion, detection of recurrences, axillary lymph node analysis and intraoperative analysis of sentinel lymph node. However, it is vital to have an experienced team and high volume of breast pathology to achieve afore mentioned results as well as good quality checks and standardized steps of analysis procedure

Indications for fine needle aspiration cytology

- for patients with palpable lesions that concern the patient or her GP
- especially for young patients with lesions persistant after two menstrual cycles
- for tumor masses in patients with history of breast cancer;
- for radiologically detected, highly suspicious palpable lesions;
- for atypical lumps reported cytologically or histologically
- for lesions suspicious for local recurrence (21,22)

FNAC and Core biopsy of the breast

During the last decade there has been a shift from FNAC to CNB, partly because of a generally lack of experienced cytopathologist and also because of some limitations and controversies about FNAC.

The use of needle core biopsy has gained a wide acceptance, particularly with the advent of stereotactic guidance. Use of smaller gauge needles has avoided the complications of trauma, pain, use of anaesthetic agents and tumor implantation in a biopsy tract. With needle core samples, accurate subcategorization of carcinomas as well as study of hormone receptors and other prognostic markers is possible (23). The false-positive rate with needle biopsy is very low (0.2–0.3%); it is slightly higher for nonpalpable lesions than for palpable ones (23). However, some lesions as fibroepithelial lesions, papillary lesions, ductal carcinoma in situ and atypical hyperplasia can cause diagnostic problems. The multidisciplinary approach is necessary to amplify FNAC quality and to reduce its diagnostic limits. Only when this model of activity is not available, the role of FNAC is less effective and the addition of core biopsy (CB) to FNAC should be considered. CB as an alternative diagnostic modality should be used advisedly, in situations where it is more likely to yield diagnostic information, e.g., in the diagnosis of impalpable masses, microcalcifications or a clinically apparent malignancy where preoperative chemotherapy is planned. CB should not be used as a substitute for poor performance at FNAC. The methods are not mutually exclusive. Where there is access to skilled cytopathologists, FNAC and CB can complement each other and provide a highly accurate, rapid and cost-effective means of patient triage (24).

Both FNAB and core biopsy are valuable in the pre-operative diagnosis of impalpable breast lesions, and although FNAB is far less costly, either technique is preferable to open biopsy in terms of morbidity and cost. Both of them are recognized as accurate diagnostic methods in separating benign from malignant breast lesions with high sensitivity and specificity. Where there is access to experienced breast cytopathologists, the sequential use of the two techniques serves as a reliable and cost-effective means of triage for selecting lesions that would benefit most from

assessment by core biopsy. Core biopsy supplements FNAC and improves the rate of preoperative diagnosis of highly suspicious mammographic microcalcification (25,24).

Common limitations and interpretation errors by FNAC

The limitations of FNA can either be technical or related tothe nature of the lesion itself. Furthermore, there are limitations that are specific to FNA regardless of technique or lesion type (i.e. intrinsic limitations).

Technical limitations

False-negative diagnoses can result in diagnostic delay and provide the patient with false reassurance. They may result from incorrect localization, which can lead to nonrepresentative material. This can be overcome by using imaging guidance. False-negative diagnoses may also result from improper technique, which can yield inadequate or suboptimal material. Contamination with blood can cause difficulties in interpretation. In addition, the preparation of a thin, uniform smear is equally important for accurate interpretation. It is very important that the person conducting the FNA is well trained in the technique. Sometimes, poor technique can mislead the unwarypathologist into making a false-positive diagnosis. Excessiveapplication of force while spreading the smear canlead to crushing and nuclear distortion and dissociation (i.e. crushing artefacts), which can result in the false impression of hyperchromasia. Also, delay in fixation of the smear for Papanicolaou staining can result in cellular enlargement; comparison with air-dried Giemsa stained smears can be helpful in avoiding such false-positive diagnoses. Finally, poor quality staining can cause artefactual changes in the nature of the chromatin pattern (23).

Limitations related to the lesion itself

Apart from technical problems, sometimes the nature of the lesion itself can cause diagnostic error. Some lesions share similar features on FNA and are difficult to differentiate from each other. Cell atypia could be found in some benign breast lesions and cell specimens of in situ breast carcinomas, and well-differentiated carcinomas sometimes do not express cytomorphological features that would definitively indicate cell malignancy. A major obstacle is the lack of experienced cytopathologist in many institution (26). Certain types of lesions can lead to false-negative diagnoses. For example, it is difficult to fix the small mobile lesion by hand, and thus it may be missed. Also, it is difficult to aspirate fibrous lesions, and samples are oftenhypocellular and haemorrhagic. The smears may show only stromal fragments. Carcinomas can sometimes induce dense fibrotic stroma, and in such cases a careful search for malignant cells is necessary. The most common causes of false-positive FNAC diagnosis in breast pathology are complex sclerosing lesions, wheresmears show small uniform cells with mild or no atypia. Complex sclerosing lesions and radial scars are regularly seen in mammography cases. Complex sclerosing lesions are usually moderately to highly cellular with a pleomorphic pattern.These are radiologicaly suspicious and may be mistaken for low-grade carcinomas.In the case of complex sclerosing lesions, presence of bare nuclei may be helpful in identifying the benign nature of the lesion.However, the presence of concurrent *in situ* or invasive carcinoma can be difficult to diagnose. In a proportion of cases, further investigation with imaging modalities and core biopsies may be necessary (27). In the case of necrotic and vascular lesions, the smears may notcontain any viable cells or may be haemorrhagic.Proliferative (adenosis, fibroadenoma, complex sclerosing lesion) and borderline breast lesions, such as columnar cell lesion and intraductal and intralobular epithelial proliferation, may present findings that can be difficult to distinguish from low-grade carcinomas. Fibroadenomas are well-known causes of false positive and false-negative diagnoses. Papillary lesions may harbor a spectrum of tumors, ranging from plain benign papilloma, via cellular papillary lesions with and without cellular atypia, to papillary carcinomas (both in situ and invasive). Fat necrosis, either post-traumatic or following surgery or radiotherapy or associated with mammary duct ectasis or fibrocystic disease, is reported to be another cause of both false- positive and false-negative FNAC diagnoses (28,29). Finally, smears from lobular carcinoma can be hypocellular and cells may not show significant pleomorphism. Their resemblance to lymphocytes may result in false-negative diagnosis. Cytology of tu-

bular carcinoma can resemble many benign conditions, including adenoma, microglandular adenosis and fibroadenoma (28). There are also types of lesions that can lead to false-positive diagnoses. In epithelial hyperplasia it is sometimes difficult to differentiate between usual type hyperplasia, hyperplasia with atypia, and low-grade intraductal carcinoma. Threedimensional clusters of cells with atypia can cause diagnostic problems. Also, with respect to fibroadenomas, hyperplastic foci can mimic low-grade carcinoma. Similarly, fibroadenomas with myxoid degeneration can be mistaken for mucinous carcinoma(23). Cytologically, epithelial cells show mild nuclear pleomorphism with prominent nucleoliduring lactational changes, which can be a cause of falsepositive diagnosis. Finally, iatrogenic changes following previous FNA/biopsy can result in false-positive diagnoses. Stromal cells of granulation tissue, inflammatory cells and histiocytes can mimic carcinomas. Similarly, radiationinduced atypia in benign epithelium can be worrisome.

Intrinsic limitations

There are a number of limitations that are intrinsic to FNA cytology. First, identification of benign fibroadenoma or frankly malignant phyllodes tumour may not be difficult, but distinguishing between cellular fibroadenoma and a phyllodes tumour can cause problems. Stromal cellularity and the presence of a number of long spindle cells may be helpful in some cases (30). Second, the cytological appearances of papillary lesions, which range from benign papilloma to invasive papillary carcinoma, can be similar. In addition, benign papillomas can harbour areas of ductal carcinoma *in situ*. All papillary lesions need complete excision, and in our opinion the cytopathologist should therefore not attempt to make a definitive diagnosis on the basis of FNA findings, and often on the basis of a core biopsy as well, unless frank carcinoma is present. Third, it can sometimes be difficult to distinguish between a mucocele- like lesion and mucinous carcinoma on cytology. The presence of high cellularity, single or small three-dimensional groups of tumour cells, and cytological atypia should raise suspicion of carcinoma (31). Finally, in the absence of architectural information, the distinction between ductal carcinoma *in situ* (DCIS) and invasive carcinoma may be difficult cytologically.

Fat necrosis may be seen in most age groups and can persist for many years. Radiotherapy usually causes severe changes in both stromal cells and epithelial cells, which display hyperchromatic cell nuclei that mimic malignant cells, but are usually few in number. Clinical history of performed radiative therapy is important. Finally, lactational changes in benign lesions may be misinterpreted as malignant cells. Metastases to the breast are rare and the most frequent secondary tumor is malignant melanoma.

CONCLUSION

The use of minimally invasive and noninvasive methods in cytological diagnosis of breast cancer represents an integral component of the triple approach and is essential to the quality of the diagnostic process. An understanding of the limitations of the methods, and of their specificity and sensitivity is very important in optimizing their use in a multidisciplinary environment.

The multidisciplinary approach is necessary to amplify FNAC quality and to reduce its diagnostic limits. Only when this model of activity is not available, the role of FNAC is less effective and the addition of core biopsy (CB) to FNAC should be considered. CB as an alternative diagnostic modality should be used advisedly, in situations where it is more likely to yield diagnostic information, e.g., in the diagnosis of impalpable masses, microcalcifications or a clinically apparent malignancy where preoperative chemotherapy is planned. CB should not be used as a substitute for poor performance at FNAC. The methods are not mutually exclusive. Where there is access to skilled cytopathologists, FNAC and CB can complement each other and provide a highly accurate, rapid and cost-effective means of patient triage.

REFERENCES

1. Kelava I, Tomicić K, Kokic M, Corusic A, Planinic P, Kirac I, Murgić J, Kulis T, Znaor A. Breast and gynecological cancers in Croatia, 1988-2008. Croat Med J. 2012;53(2):100-8.
2. Hrvatski zavod za javno zdravstvo. Incidencija raka u Hrvatskoj 2012. Dostupno na: http//hzjz.hr/wp-content/uploads/2013/11/Bilten.2012_final.pdf.
3. Franzen S, Zajicek J. Aspiration biopsy in diagnosis of palpable lesions of the breast:critical review of 3479

consecutive biopsies. Acta Radiol Ther Phys Biol. 1968;7:241-262.
4. Wells CA, Ellis IO, Zakhour HD, Wilson AR. Editorial working party, cytology subgroup of the national coordinating commitee for breast cancer screening pathology. Guidelines for cytology procedures and reporting on fine needle aspirates of the breast. Cytopathology. 1994;5:316-334.
5. Ghimire B, Khan MI, Bibhusal T, Singh Y, Sayami P. Accuracy of triple test score in the diagnosis of palpable breast lump. JNMA J Nepal Med Assoc. 2008; 47:189-92.
6. Skrbnic B, Babic A, Cufer T, Us-Krasovec M. Cytological grading of breast cancer in Giemsa-stained fine needle aspiration smears. Cytopathology. 2001;12: 15-25.
7. Rekha TS, Nandini NM, Murali Dhar. Validity of different cytological grading systems of breast carcinoma - a hospital-based study in south India. Asian Pacific Cancer Prev. 2011;12:3013-16.
8. Faroog AW, Subhash B, Dinesh K, Pervez K. Cytological grading of breast cancers and comparative evaluation of two grading systems. J Cytol. 2010; 27:55-8.
9. Robinson IA, McKee G. Prognostic value of cytological grading of fine-needle aspirates from breast carcinoma. Lancet. 1994;334:947–950.
10. Rimm Dl, Stastny JF, Ayer S, Frable WJ. Comparasion of the costs of fine needle aspiration and open surgical biopsy as methodds for obtaing a pathologic diagnosis. Cancer. 1997;25; 81:51-56
11. Layfield LJ, Dodd LG. Cytologically low grade malignancies: an important interpretative pitfall responsible for false negative diagnosis in fine needle aspiration of the breast. Diagn Cytopathol. 1996. Sep; 15:250-9
12. Singh N, Ryan D, Berney D, Calaminici M, Sheaff MT, Wells CA. Inadequate rates are lower when FNAC sampels are taken by cytopathologist. Cytopathology. 2003;14:327-31
13. Boffin AM, Lydersen S, Isaksen C, Hagmar BM. Interpretation of fine needle aspiraion cytology of the breast: a comparasion of cytology, frozen section, and final histological diagnoses. Cytopathology. 2004;15: 297-304
14. Zakhour H, Wells C. Diagnostic cytopathology of the Breast, Churchill Livingstone, London, UK, 1999
15. Mendoza P, Lacambra M, Tan PH, Tse GM. Fine needle aspiration cytology of the breast: The nonmalignant categories. Pathology Research International. 2011;547580:8
16. Howell LP, Gandour-Edwards R, Folkins R, Davis R et all. Adequacy evaluation of fine- needle aspiration biopsy in the breast health clinic setting. Cancer. 2004; 102:295-301
17. Layfield LJ, Mooney E, Glasgow B et all. What constitutes an adequate smear in fine-needle aspiration cytology of the breast. Cancer. 1997; 81:16-21.
18. Kocjan G. Fine Needle Aspiration cytology. Inadequate rates compromise succes. Cytopathology. 2003; 14:307-8.
19. Ahmed I, Nazir R, Chaudhary MY, Kundi S. Triple assessment of breast lump. J Coll Physicians Surg Pak. 2007;17:535-8.
20. Morris KT, Pommier RF, Morris A, Schmidt WA, Beagle G, Alexander PW et all. Uselfulness of the Triple Test Score for Palpable Breast Masses. Arch Surg. 2001;136(9):1008-1013.
21. Mokri M, Guity M, Shariat Torbaghan S, Arab Kheradmand A, Arbabai E, Bagherzade M, Atri M. Uselfulness of Triple Test Score for Breast Lesions Iranian Journal of Cancer Prevention. 2008;1:23-25.
22. The uniform approach to breast fine needle aspiration biopsy. NIH Consensus Development Conference. Am J Surg. 1997;174:371-85.
23. Nerurkar A, Osin P. The diagnosis and management of pre-invasive breast disease. The role of new diagnostic technique. Breast Cancer Res. 2003;5:305-308.
24. Nagar S, Iaccco A, Riggs T, Kestenberg W, Keidan R. An analysis of fine needle aspiration versus core needle biopsy in clinically palpable breast lesions: a report on the predictive values and cost comparison. The American Journal of Surgery. 2012;204:193-198.
25. Kocjan G. Aspiracijska citologija u liječenju bolesti dojke:europske perspektive danas. Acta Med Croat. 2011;65:391-402.
26. Ramljak V, Sučić M, Vrdoljak DV. Expression of Ki-67 and p27Kip1 in fine-needle aspirates from breast carcinoma and benign breast diseasses. Diagnostic Cytopathology. 2011;39(5):333-40.
27. Orell SR: Radiar scar/complex sclerosing lesion: a problem in the diagnostic work-up of screen-detected breast lesions. Cytopathology. 1999;10:250-258.
28. Evans AT, Hussein KA: A microglandular adenosis-like lesion simulating tubular carcinoma of the breast. A case report with cytological and histological appearances. Cytopathology. 1990;1311-316.
29. Berner A, Sauer T. Fine-needle aspiration cytology of the breast. Ultrastruct Pathol. 2011;35(4):162-167.
30. Bhatari S, Kapila K, Verma K. Phyllodes tumour of the breast. A cytopathologic study of 80 cases. Acta cytol 2000;44:790-796.
31. Wong NL, Wan SK. Comparative cytology of mucocelelike lesion and mucinous carcinoma of the breast in fine needle aspiration. Acta Cytol. 2000;44:765-770.

Author's address:Vesna Ramljak, Department for Cytology, University Hospital for Tumors, University Hospital Center Sestre milosrdnice, Ilica 197, 10000 Zagreb, Croatia; e-mail: vesna.ramljak@kbcsm.hr