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Underestimation of cancer in case of diagnosis of atypical ductal hyperplasia (ADH) by vacuum assisted core needle biopsy

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ABSTRACT

Background: With the introduction of mammography screening, we are more often dealing with the diagnosis of precancerous and preinvasive breast lesions. An increasing number of patients are observed to show a premalignant change of ADH (atypical ductal hyperplasia). It also involves a wider use of the vacuum assisted core biopsy as a tool for verifying nonpalpable changes identified by mammography.

Aim: This paper describes our experience of 134 cases of ADH diagnosed at Mammotome® vacuum core needle biopsy.

Material and methods: Of 4326 mammotomic biopsies performed at our institution in 2000–2006, ADH was diagnosed in 134 patients (3.1%). Patients underwent surgery to remove the suspected lesion. All histopathological blocks were again reviewed by one pathologist. Clinical, radiological and pathological data were collected for statistical evaluation.

Results: Underestimation of invasive changes occurred in 12 patients (9%). The only clinicopathologic feature of statistical significance radiologically and pathologically was the presence of radial scar in the mammography.

Conclusions: More frequent diagnosis of precancerous changes in the mammotomic breast biopsy forces us to establish a clear clinical practice. The problem is the underestimation of invasive changes. The occurrence of radial scar on mammography for diagnosis of the presence of ADH increases the risk of invasive changes.

1. Background

Atypical ductal hyperplasia (ADH) is a premalignant change in the breast. This change is detected when at least two lines or areas connected with the ducts are present by atypical cell changes, or if the area occupied by atypical cells is less than two millimeters. Otherwise, we speak of DCIS (ductal carcinoma in situ). It follows that the difference between ADH and DCIS is minor, especially in the case of excision by core

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biopsy when we cannot visualize the entire area of a suspicious change. This implies a great difficulty in putting the final diagnosis. Atypical ductal hyperplasia (ADH) of the breast was first described by Page in 1985 as an amendment to the border between the ductal hyperplasia and ductal cancer in situ (DCIS).[1] Therefore, more and more suspicious nonpalpable changes of the breast discovered mammographically, increased the frequency of mammotomic biopsies performed. It has revolutionized the detection of early forms of breast cancer. Thus, screening mammography and mammotomic biopsy has contributed to the increased frequency of detection of ADH. Nevertheless, mammotomic biopsy has its drawbacks associated with the underestimation of invasive change in the final histological diagnosis.

In the case of diagnosis of ADH by core biopsy, it is necessary to widen the resection of the change to the final pathologic examination. Known issue of underestimation of lesions in the case of primary invasive diagnosis of ADH applies up to 88% of cases when using 14G needles and is reduced to a few percent if vacuum core needle biopsy is used.[2–8] With ADH diagnosed, the risk of breast cancer increases 4–5 times. This risk is doubled if we are dealing with a positive family history of breast cancer.[9] Collins et al. investigated a group of women undergoing core biopsy in the Nurses' Health Study, with atypical hyperplasia as the most advanced change.[10] The women with atypia (ADH and ALH (atypical lobular hyperplasia)) were older, less frequently premenopausal and nulliparous, compared with the control group. Women with ADH drank slightly more alcohol, were more likely to have undergone bilateral resection of the ovaries and a greater proportion of applied hormone replacement therapy for longer than 5 years. In the Mayo Cohort Study, women with atypia (ADH and ALH) showed a very high risk of developing breast cancer (risk >50% over 20 years) in the event of multiple foci of histologically found atypia and the presence of microcalcifications.[11] In this group of patients, family history of breast cancer had no effect on increasing breast cancer risk.

In the model of cancer cell lines from normal glandular breast to invasive cancer have several stages until the preinvasive and invasive cancer.[12] In the case of growth of normal cells, we are talking about usual ductal hyperplasia (UDH). In the case of accumulation of irregularities within the cell nucleus, we can talk about the acquisition and the characteristics of atypical histology that can be observed in flat epithelial atypia (FEA). A continued proliferation of this change is the next stage of ADH. Then we have to deal with cancer, only that it is separated from the basal membrane of normal cells and thus qualified as DCIS. In the case of tumor cell invasion through the basement membrane of DCIS initially taking with microinvasive and then to invasive breast cancer.

2. Aim

The aim is to evaluate the underestimation of the preinvasive and invasive changes after an initial diagnosis of ADH using mammotomic vacuum core needle biopsy.

3. Materials and methods

We analyzed retrospectively 134 patients with a primary diagnosis of ADH on the basis of Mammotome 11 G vacuum assisted core needle biopsy.

A biopsy was performed in the outpatient mammotomic unit at the Department of Surgical Oncology and General Surgery I, Greater Poland Cancer Centre. For six and a half years, 4326 biopsies have been performed. Biopsies were done in patients with nonpalpable breast changes seen in mammography. Patients who had undergone ultrasound guided biopsy were excluded from this study. Mammotomic biopsy was performed on the table, where patients were turned to face downwards (Fisher Imaging, Denver, CO, USA) using an 11 G directional vacuum assisted biopsy system (Mammotome; Biopsy/Ethicon Endo-Surgery, Cinncinatti, Ohio). We obtained an average of 12 cores (from 7 to 30). In case of ADH, all patients were admitted for surgical resection of the breast area where ADH was found. For all cases, images and descriptions of mammography, or ultrasound data were collected for review. The medical histories were re-examined and verified in terms of clinical data such as age, data on the patient's oncological history, family burden, mammographic presentation, concomitant benign lesions of the breast, type of operation. The size of the breast change was not identified. All pathological slides were again reviewed by one pathologist (PK).

Collected clinical parameters, as well as radiological and pathological findings were statistically analyzed to determine differences in study groups or the relationship between the measured traits.

All tests were analyzed at the significance level $\alpha = 0.05$. For statistical analysis statistical package Statistica 8.0 (StatSoft Inc.) was used.

4. Results

Underestimation of invasive changes occurred in 12 patients (9%). Age of patients diagnosed with ADH without cancer in final pathology was 55.6 and for patients with underestimation of cancer 60.7. When dividing patients into 2 groups (less or equal to 60 years and more than 60 years), no significant difference in ADH proportions was observed. But analyzing groups with and without underestimation, a significance was observed $p = 0.0349$. Patients with underestimation were on average older than those without underestimation.

There was a significant difference in the frequency of different diagnoses, mammography, depending on final changes to non-invasive diagnosis and under-invasive changes ($p = 0.0001$).

Radial scar is more common in the evolution of invasive breast screening and other diagnoses (microcalcifications, macrocalcifications, mass and density) are more characteristic for non-invasive change (Table 1).

Among patients diagnosed with ADH on the basis of Mammotome biopsy, there were no statistically significant differences in the incidence of various histopathological factors in breast glands, depending on the invasiveness of the change. We analyzed such changes as the CCC (columnare

Table 1 – Underestimation of cancer in comparison with mammographical manifestation of the ADH during biopsy.

Mammographical picture	Noninvasive change, $n = 122$	Underestimation of invasive cancer, $n = 12$
Microcalcifications	93 (76.9%)	4 (33.3%)
Macrocalcifications	0	1 (8.3%)
Tumor mass	17 (14.1%)	1 (8.3%)
Radial scar	6 (5%)	5 (41.7%)
Density	5 (4.1%)	1 (8.3%)

Statistical importance proved by Fisher–Freeman–Halton test: $p = 0.0001$.

cell changes), CCH (columnare cell hyperplasia), UDH (usual ductal hyperplasia), adenosis simplex, adenosis sclerosans, microcalcifications, mastopathy (Table 2).

Additionally, no statistical significance was observed according to breast side, and accurate position in the breast using quadrants. Analyzing numbers of foci in both groups in ADH only the mean number of foci was 2.53 and in the underestimated one 3.55. No statistical significance was observed.

5. Conclusions

Mammotome biopsy of mammographically suspicious nonpalpable breast changes is associated with less morbidity and shorter hospital stay, lower cost compared with open surgical biopsy, which used to be a standard practice in the past. The frequency of detection of ADH by core needle biopsy is, according to different authors, from 2 to 11%.[13,14] In our study, ADH was diagnosed in 134 patients, representing 3.1% of the diagnoses made on the basis of Mammotome® biopsy. In the early studies of underestimation of the changes after the initial biopsy, 14 G AGCB (automated gun core biopsy) was used. Unfortunately, this resulted in underestimation of invasive change in the limits of 17–88%, on average 44%.[2–8] In the case of 14G VACB (vacuum assisted core biopsy) average underestimation of the tumor decreased to 24%.[15] Currently, the 11G VACB is performed. With this device, the underestimation of invasive changes was reduced to the value from 0 to 38%, average 19%.[5,16] In our study, it amounted to 9%. The desirability of a subsequent operation in all cases is being discussed. Researchers are looking for predictors of co-occurrence in ADH of DCIS or invasive changes. According to Liberman et al., the most common image of ADH in the mammogram are clustered microcalcifications.[17] They could not, however, identify the characteristics associated with the interaction of invasive changes. According to Ely et al., the factor associated with an increased incidence of DCIS or IDC is the presence of ≥4 foci of ADH, or cases with the presence of micropapillary ADH only.[15] With ≤2 foci of ADH and a complete removal of suspicious mammographic changes, there appeared to be no need for surgical resection. Gombos et al. propose using immunohistochemistry for the evaluation of core biopsy ADH.[18] Lack of CK 34 beta E12 was associated with the presence of atypia in hyperplasia inside the duct. Liberman et al. stresses the importance of total excision biopsy of the lesions rather than just sampling for pathological examination.[7] Thanks to this procedure the underestimation of the incidence of invasive changes is reduced. In this study, the complete removal of the lesions with the VACB resulted in the underestimation was 18.8%. When the specimens were only partially collected from the lesions, the underestimation was 31.3%. The review paper by Jacobs et al. proposed, in the case of micro-histological diagnosis of ADH, a limited extent of total lesion resection during core biopsy when there are no indications for surgical removal.[19]

In the study by Forgeard et al. a group of 300 patients with a diagnosis of ADH in 11 G Mammotome biopsy was divided into a subgroup of patients undergoing surgical resection (116 patients – 39%) and oncological observation (184 patients – 61%).[20] Patients were divided according to the risk of cancer presence into 3 groups. First, without an underestimation of the tumor in case of change of diameter <6 mm complete the removal by the Mammotome biopsy. The second group of low underestimation of concomitant tumor (4%) in the presence of ≤2 foci of ADH in the area of microcalcifications with concurrent changes in diameter <6 mm and the incomplete removal or ≥6 mm and <21 mm. The third group of patients at high risk of concomitant cancer – 36–38% of the tumor in the presence of >2 foci of ADH in microcalcifications and diameter change <6 mm with incomplete resection of microcalcifications, or ≥6 mm and <21 mm with complete and incomplete removal of microcalcifications, or the size of changes ≥21 mm. The average number of cores was 16, with 11.5 in other studies,

Table 2 – Underestimation of invasive cancer in comparison with concomitant benign changes diagnosed together with ADH during biopsy.

Concomitant changes diagnosed with ADH on biopsy	Noninvasive change, $n = 122$	Underestimation of invasive cancer, $n = 12$	p value
CCH	11 (9%)	1 (8.3%)	0.94
CCC	6 (4.9%)	0	0.43
UDH	43 (35.3%)	5 (50%)	0.58
Adenosis simplex	11 (9%)	0	0.28
Mastopatia	74 (60.6%)	5 (41.7%)	0.2
Mikrozwapnienia	98 (80.3%)	8 (66.7%)	0.27
Adenosis sclerosans	69 (56.6%)	7 (58.3%)	0.9
Lipomatosis	18 (14.8%)	0	0.15
Fibroadenoma	8 (6.56%)	0	0.36

also the rate of change was 2 times higher than in comparable publications.

The study group in Plantade et al. diagnosed with ADH was divided into those requiring surgical resection and those subjected to intensive follow-up.[21] The indication for surgery was breast cancer (or family history), lesion size >10 mm, the presence of ADH in the last deleted core tissue and concomitant LN (lobular neoplasia). Ely et al. study of 46 patients demonstrated relation between the underestimation of tumor and extent of ADH.[15] When this change concerned a 2 or fewer foci of ADH no other concomitant change was observed, whereas in the presence of 3 or 4 foci of ADH, the underestimation of DCIS/invasive cancer reached 50 and 87%. The authors did not recommend surgical resection in the presence of 2 and fewer foci of ADH. Sneige et al. give 3 or less ADH lesions after total resection of the ADH lesions as a value where no further concomitant preinvasive or invasive changes were seen.[22]

Currently, stereotactic core needle biopsy under mammographical guidance is a standard diagnostic tool in examination of non-palpable breast lesions. We presented our experience in the group of clinico-pathological challenges in case of diagnosis by core needle biopsy of a premalignant or preinvasive change in previous papers.[23–26] Selected clinical factors, radiological and pathological, can be used to assess the risk of invasive changes coexistence. The occurrence of radial scar on mammography for diagnosis of the presence of ADH increases the risk of invasive changes. Additionally we should also think about better information for patients as well as support especially in case of increased risk of breast cancer in the future.[27,28]

Conflict of interest

None declared.

REFERENCES

1. Page D, Dupont WD, Rogers LW, Rados MS. Atypical hyperplastic lesions of the female breast: a long term follow-up study. *Cancer* 1985;**55**:2698–708.
2. Brem RF, Behrndt VS, Sanow L, et al. Atypical ductal hyperplasia: histologic underestimation of carcinoma in tissue harvested from impalpable breast lesions using 11-gauge stereotactically guided directional vacuum assisted biopsy. *AJR* 1999;**172**:1405–7.
3. Brown TA, Wall JW, Christensen ED, et al. Atypical hyperplasia in the era of stereotactic core needle biopsy. *J Surg Oncol* 1998;**67**:168–73.
4. Dahlstrom JE, Sutton S, Jain S, et al. Histological precision of stereotactic core biopsy in diagnosis of malignant and premalignant breast lesions. *Histopathology* 1996;**28**: 537–41.
5. Doren E, Hulvat M, Norton J, Rajan P, Sarker S, Aranha G, Yao K. Predicting cancer on excision of atypical ductal hyperplasia. *Am J Surg* 2008;**195**:358–62.
6. Jackman RJ, Nowels KW, Shepard MJ, et al. Stereotaxic large-core needle biopsy of 450 nonpalpable breast lesions with surgical correlation in lesions with cancer or atypical hyperplasia. *Radiology* 1994;**193**:91–5.
7. Liberman L, Cohen MA, Dershaw DD, et al. Atypical ductal hyperplasia diagnosed at stereotaxic core biopsy of breast lesions: an indication for surgical biopsy. *AJR* 1995;**164**: 1111–3.
8. Moore MM, Hargett CW, Hanks JB, et al. Association of breast cancer with the finding of atypical ductal hyperplasia. *Am J Surg* 1997;**225**:726–33.
9. Dupont WD, Page DL. Risk factors for breast cancer in woman with proliferative breast disease. *N Engl J Med* 1985;**312**:146–51.
10. Collins LC, Baer HJ, Tamimi RM, Connolly JL, Colditz GA, Schnitt SJ. Magnitude and laterality of breast cancer risk according to histologic type of atypical hyperplasia: results from the Nurses' Health Study. *Cancer* 2007;**109**(2):180–7.
11. Degnim AC, Visscher DW, Berman HK, et al. Statification of breast cancer risk in woman with atypia: a Mayo cohort study. *J Clin Oncol* 2007;**25**:2671–7.
12. Yeh IT, Dimitrov D, Otto P, Miller AR, Kahlenberg MS, Cruz A. Pathologic review of atypical hyperplasia identified by image guided breast needle core biopsy. *Arch Pathol Lab Med* 2003;**127**:49–54.
13. Harvey JM, Sterret F, Frost FA. Atypical ductal hyperplasia and atypia of uncertain significance in core biopsies from mammographically detected lesions: correlation with excision diagnosis. *Pathology* 2002;**34**(5):410–6.
14. Jackman RJ, Birdwell RL, Ikeda DM, et al. Atypical ductal hyperplasia: can some lesions be defined as probably benign after stereotactic 11 gauge vacuum-assisted biopsy, eliminating the recommendation for surgical excision. *Radiology* 2002;**224**:548–54.
15. Ely KA, Carter BA, Jensen RA, et al. Core biopsy of the breast with atypical ductal hyperplasia: a probabilistic approach to reporting. *Am J Surg Pathol* 2001;**25**:1017–21.
16. Jackman RJ, Burbank F, Parker SH, et al. Stereotactic breast biopsy of nonpalpable lesions: determinants of ductal carcinoma in situ underestimation rates. *Radiology* 2001;**218**:497–502.
17. Liberman L, Smolkin JH, Dershaw DD, et al. Calcification retrieval at stereotactic 11 gauge, directional, vacuum assisted breast biopsy. *Radiology* 1998;**208**:251–60.
18. Gombos EC, Poppiti Jr RJ. Percutaneous core needle biopsy of radial scars of the breast. *Am J Roentgenol* 2003;**181**(31):275.
19. Jacobs TW, Connolly JL, Schnitt SJ. Nonmalignant lesions in breast core needle biopsies: to excise or not to excise. *Am J Surg Pathol* 2002;**26**:1095–110.
20. Forgeard C, Benchaib M, Guerin N, et al. *Am J Surg* 2008;**196**:339–45.
21. Plantade R, Hammou JC, Fighiera M, et al. Underestimation of breast carcinoma with 11 gauge stereotactically guided directional vacuum-assisted biopsy. *J Radiol* 2004;**85**: 391–401.
22. Sneige N, Lim SC, Whitman GJ, et al. Atypical ductal hyperplasia diagnosis by directional vacuum-assisted stereotactic biopsy of breast microcalcification. Consideration for surgical excision. *Am J Surg Pathol* 2003;**119**:248–53.
23. Polom K, Murawa D, Pawelska A, Murawa P. Atypical lobular hyperplasia (ALH) and lobular carcinoma in situ (LCIS) without other high-risk lesions diagnosed on vacuum-assisted core needle biopsy. The problem of excisional biopsy. *Tumori* 2009;**95**(1):32–5.
24. Polom K, Murawa D, Wasiewicz J, Nowakowski W, Murawa P. The role of sentinel node biopsy in ductal carcinoma in situ of the breast. *Eur J Surg Oncol* 2009;**35**:43–7.
25. Polom K, Murawa D, Murawa P. Flat epithelial atypia diagnosed on core needle biopsy-clinical challenge. *Rep Pract*

Oncol Radiother 2012, http://dx.doi.org/10.1016/j.rpor.2011.12.001.
26. Połom K, Murawa D, Nowaczyk P, Adamczyk B, Giles E, Fertsch S, Michalak M, Murawa P. Vacuum-assisted core-needle biopsy as a diagnostic and therapeutic method in lesions radiologically suspicious of breast fibroadenoma. *Rep Pract Oncol Radiother* 2011;**16**:32–5.
27. Bernad D, Zysnarska M, Adamek R. Social support to oncological patients—selected problems. *Rep Pract Oncol Radiother* 2010;**15**(2):47–50.
28. Kacprowska A, Jassem J. Partial breast irradiation techniques in early breast cancer. *Rep Pract Oncol Radiother* 2011;**16**(6):213–20.