Novel Idea

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Stereotaxic Core-Needle Biopsy in Assessing Intraductal Pathologic Findings at Ductography

G.A. Belonenko[1], N.A. Sukhina[1], A.A. Aksyonov[2], E.G. Aksyonova[3]

[1]Donetsk National Medical University, Donetsk, Ukraine
[2]National Cancer Institute, Kyiv, Ukraine
[3]T. Shevchenko National University, Kyiv, Ukraine

ABSTRACT

Objective: The purpose of this study was to analyze the capabilities of ductography (DG) to navigate stereotactic core-needle biopsy (sCNB) for localizing and differentiating intraductal benign and malignant proliferations of the breast in patients with pathological nipple discharge (PND).

Materials and Methods: Patients underwent physical, radiological, ultrasound, endoscopic and histopathological examinations.

Results: The study included 183 patients. In 51, traditional DG was performed and in eight patients DG was performed using endoscopic mammoductoscopy (EMDS). A routine ductectomy labeled with methylene blue or propylene thread was performed in 81 patients. In 77 cases, a ductectomy was performed after double wire marking of intraductal proliferations (IDP) through the nipple and through the skin. In 26 patients, a preoperative sCNB under guidance of DG was performed. After sCNB 23/26 patients had benign IDP and three (11.5%) had invasive cancer. Breast surgery confirmed histology to be the gold standard in all patients, with the exception of 7 (26.9%) under the age of 45 years with benign IDP. These patients had watchful waiting and after 35 months of follow-up no signs of malignant growth were detected.

DG was characterized by high (87.9%) sensitivity and low (33.3%) specificity. False positive rate was 25.9% and the cause was peripheral location of IDP (>3 cm from the nipple) in 57.1% and inadequate excision with leaving them outside the resection.

Conclusion: This initial study on sCNB under the guidance of traditional or selective DG reports promising findings. Further studies are needed to determine whether preoperative histological assessment of pathologic intraductal lesions at DG would reduce the number of open surgeries with benign histology at sCNB.

Keywords: Breast; intraductal proliferations; ductography; stereotactic core-needle biopsy

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Key Points

- DG is characterized by frequent false results and low (33.3%) specificity
- 57.1% cause of the false-positive results of DG is the unsuccessful excision of peripherally located IDN
- To maximize the elimination of false results and increase the diagnostic efficiency of DG, we proposed selective contrasting of the ducts under the control of EMDS, as well as the use of images obtained as a result of traditional and / or selective DG for navigating sCNB.

Introduction

Ductography (DG) is a method of X-ray visualization of intraductal proliferations (IDP) of the breast after contrasting the milk ducts with pathological nipple discharge (PND) which was first described in the 1930s (1). Today, DG has been described as a technically incomplete, non-standardized procedure, which is accompanied by additional radiation exposure and is less specific than magnetic resonance imaging (MRI) and/or high-resolution ultrasonography (US) (2, 3).

In contrast, some authors consider DG to be the gold standard and are confident that its high (up to 95.0%) sensitivity allows identification of IDP and providing supporting evidence for surgical intervention (4, 5). According to the criteria of the American College of Radiology (ACR),

Corresponding Author:
Gennady Belonenko: belonenko49@mail.ru

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DG is not a mandatory procedure, but DG may be used by surgeons who need additional information about the topography of IDP (6). However, the simple detection of IDP and routine ductectomy no longer corresponds to the current level of oncomammology, since with IDP the cancer frequency reaches 20.0%–23.0% with a tendency to decrease to 5.0%–6.0% when there are negative results on MG and/or US (7, 8).

In order to avoid unnecessary surgery in benign conditions, and in cases of cancer, to establish its invasive and molecular-genetic characteristics, histopathological verification and a reliable histological characterization of IDP is recommended, which may be "benign", "lesions of undetermined oncological potential", "high risk lesions" and/or "malignant lesions". This approach allows the personalization of therapies including neoadjuvant, targeted, and/or immune therapies, perform breast-conserving and/or oncoplastic surgery, and the use of alternative ablation procedures (9-11). At the same time, the utility of minimally invasive, visually controlled biopsies for histopathological verification are limited; 38.0%–85.0% of IDP cannot be identified by MG, 35.0%–71.0% is not visualized by US and 16.3%–22.7% is not detected by endoscopic mammoductoscopy (EMDS) (7, 12).

Navigation of a biopsy under the control of MRI requires complex, expensive equipment, is not technically developed and has not yet become widespread (13). Therefore, currently, routine ductectomy retains its utility, although the detection of cancer by means of a traumatic open biopsy is not clinically effective nor cost-effective, given that about 20.0% of IDP confirmed with the help of DG or EMDS are not detected by histopathology after surgery (14).

Some reports have shown that a more successful excision of IDP is possible after wire marking under the control of the DG. However, the evidence is poor as these studies are single, contain few observations and do not consider alternatives to routine ductectomy (15, 16).

To the best of our knowledge, there are no reports concerning the performance of a minimally invasive stereotactic core needle biopsy (sCNB) under the control of DG for preoperative histopathological assessment of IDP.

The purpose of this study was to analyze the capabilities of DG for orientation navigating sCNB when there is radiological evidence of possible IDP after standard or selective contrast of milk ducts and to compare the results with alternative approaches that did not use preoperative sCNB.

Materials and Methods

This study was approved by the Commission on Bioethics at the National Cancer Institute of the Ministry of Health of Ukraine and complies with the principles of the Helsinki Declaration (protocol no: 77, date: 12/09/2015). All patients received verbal informed consent.

The criteria for inclusion in this study were: female gender; adulthood; and the presence of PND. According to the recommendations of ACR, the main clinical signs of PND were considered to be bloody, amber-colored or watery discharge, which was unilateral and spontaneous and , persistent (6). Exclusion criteria were: bilateral lactorrhea, not associated with childbirth; severe somatic or mental conditions; acute galactophoritis; and allergy to iodinated contrast agents.

In 183 patients, physical, radiological, ultrasound, endoscopic, and histopathological studies were performed. For X-ray studies, digital mammography systems, the "Mammomat 3000 Nova" (Germany) and Hologic M-4 (Fort Myers, Florida, USA) were used, equipped with stereotactic puncture attachments. Standard DG (n = 51) was performed under aseptic conditions under local application anesthesia with EMLA® (Recipharm Karlskoga AB, Sweden). A SteryLab® device (Italy) with a tip diameter of 30G and the contrast agent Ultravist® (Bayer Pharma AG, Germany) were used. Selective DG (n = 8) under the control of EMDS was performed according to our own method (Ukrainian patent 106064). For this, if it is impossible to introduce a ductoscope into the secreting milk duct of second, third and fourth order of magnitude, it was intubated with a flexible microcapillary tube and a contrast agent was introduced through it (17). Ductograms were evaluated as technically inadequate (insufficient filling of the duct, extravasation, air bubbles); with normal duct structure; with ductectasia (>0.2 cm); with filling defects; with lines of "amputation"; or with the presence of filling defects and "amputation" lines simultaneously (18).

US was performed using high-frequency transducers on modern scanners, which were the EnVisor (Netherlands), Prosound-6, and Aplio SSA-780A (Japan) in the B-mode gray scale. Additional examination techniques were used, including the rolled-nipple, peripheral compression, and two-handed compression (19). Both MG and US results were assessed according to the assessment categories of ACR® Breast Imaging Reporting and Data System (BI-RADS) (20).

For EMDS, a rigid two-channel ductoscope from Karl Storz (Germany) with a tube length of 12.0 cm and an outer diameter of 0.13 cm (16G) was used. The results were evaluated in accordance with the recommendations of the Japanese Association of Mammary Ductoscopy and four types of lesions were distinguished: solitary; multiple; superficial; and mixed, as described (21).

After a comprehensive diagnostic process, 81 patients underwent a routine ductectomy with a marking of the secreting duct with indigo carmine or propylene thread. In 77 patients, a ductectomy was performed according to our own method after double wire marking of IDP through the nipple under the control of EMDS and through the skin under the control of US (Ukrainian patent 116603) (22).

In 26 patients, sCNB under the guidance of DG, was performed as described in detail by Ukrainian patent 119847. To do this, traditional or selective contrasting of the secreting milk duct was carried out, characteristic radiological signs of IDP (filling defect/amputation line) were identified and sCNB was performed. When there was a filling defect, the biopsy needle (G14) was introduced directly to the center of the filling defect. In the presence of an amputation line, the biopsy needle was aimed at the adjacent target next to the amputation line, but not further than 0.1 cm in the direction from the nipple (23).

Examination by light microscopy of 5 μm preparations stained with hematoxylin and eosin was chosen as the reference method. If necessary, immunohistochemical staining was used. Biological markers that were investigated included human epithelial growth factor receptor 2 (HER-2 neu), estrogen and progesterone receptors, and the marker of cellular proliferation, Ki-67).

Statistical Analysis

Data were analyzed by Microsoft Office Excel 2007 for Windows (Microsoft Corporation, Redmond, Washington, USA). Statistical indicators of sensitivity, specificity, positive and negative predictive values were calculated according to standard formulas, based on the

number of true and false positives, and true and false negative results of diagnostic tests. Histopathological findings confirming the presence/absence of benign or malignant IDP were used as the gold standard for all imaging tests.

Results

The performance indicators of the diagnostic tests are presented in Table 1. Paradoxically, DG, as a selective test intended exclusively for the diagnosis of IDP with high (87.9%) sensitivity is characterized by low (33.3%) specificity.

We found that IDP, diagnosed pre-operatively by DG and EMDS after ductectomy and using localization with indigo carmine or propylene thread, were histopathologically proven in only 31 (38.3%) cases. Thus, removal was unsuccessful in the remaining 50 (61.7%) cases. In contrast, after double marking with wire, all IDPs were adequately excised (Table 2).

In a detailed analysis of the causes of the 14 false-positive DG results, it was found that in 8 (57.1%) cases, IDP was located at a distance of at least 3 cm from the nipple and could remain outside the resection tissue and was thus not removed. Thorough histopathological analysis revealed that the remaining six (42.9%) false-positive DG results were due X-ray artefacts simulating IDP (Figure 1), which were described histopathologically as pseudopapillary intraductal structures with proliferation, apocrinization and desquamation of the ductal epithelium in the presence of chronic inflammation (Figure 2).

These results show that the low (33.3%) specificity of DG is associated with frequent (25.9%) false-positive results due to unsuccessful excision of peripherally located IDP, as well as the formation of pseudopapillary intraductal structures against the background of chronic inflammation.

To increase the diagnostic efficiency of DG, selective contrasting of secreting milk ducts of the second, third and fourth orders, under endoscopic control is proposed. The possible use of selective DG, under the control of EMDS, is illustrated in Figures 3 and 4. It is also proposed to use ductographic images obtained as a result of traditional and/or selective contrasting to navigate sCNB, which was done in 26 patients, the main clinical and pathological characteristics of which are given in Table 3. sCNB orientation and navigation using a ductographic image was carried out as follows. In a patient with PND and negative MG, conventional or endoscopically controlled DG was performed, a characteristic radiological sign of an IDP, such as a filling

Table 1. The effectiveness of diagnostic tests

Tests Parameters	MG (n = 64)	US (n = 82)	DG (n = 54)	EMDS (n = 158)
Results (amt., %)				
True positive	9 (14.0)	16 (19.5)	29 (53.7)	98 (62.1)
True negative	14 (21.9)	20 (24.4)	7 (13.0)	16 (10.1)
False positive	3 (4.7)	10 (12.2)	14 (25.9)	34 (21.5)
False negative	38 (59.4)	36 (43.9)	4 (7.4)	10 (6.3)
Indicators (%)				
Sensitivity	19.1	30.8	87.9	90.7
Specificity	82.4	66.7	33.3	32.0
PPV	75.0	61.5	67.4	74.2
NPV	26.9	35.7	63.6	61.5

MG: mammography; US: ultrasound; DG: ductography; EMDS: endoscopic mammoductoscopy; PPV: positive predictive value; NPV: negative predictive value, Amt: amount

Table 2. The results of histopathological studies after ductectomy

Histopathological diagnosis	Marking	
	Indigo carmine or propylene thread (n = 81)	Dual (n = 77)
Multiple papillomas	12 (14.8%)	40 (51.9%)
Solitary papillomas	11 (13.6%)	30 (39.0%)
Atypical ductal hyperplasia	2 (2.5%)	5 (6.5%)
Invasive carcinoma	6 (7.4%)	2 (2.6%)
Fibroadenomatosis	40 (49.4%)	-
Inflammation	7 (8.6%)	-
Ductectasia	3 (3.7%)	-

defect (Figure 5), was revealed, which was used to guide the biopsy needle (Figure 6).

After sCNB and histopathological analysis, benign processes were detected in 23 (88.5%) cases and invasive carcinomas in three (11.5%) cases. In 16 patients aged 45 years and older with benign sCNB results, ductectomies were performed and these showed complete concordance with the histopathological diagnosis, both before and after the operation. In seven patients under the age of 45 years with benign IDP, monitoring was carried out for up to 35 months. Signs of malignant growth were not found in them. In three women, aged 48, 59, and 60 years, poorly-differentiated (G3) invasive carcinomas of the luminal B subtype were detected: Her-2/neu positive in one, and pronounced positive reaction to estrogen receptors in the other two with high proliferative activity in all patients. Comprehensive treatment was given to all three women, in accordance with modern protocols. There was no relapse of the disease at follow up in 1.5, 2.5 and 3 years.

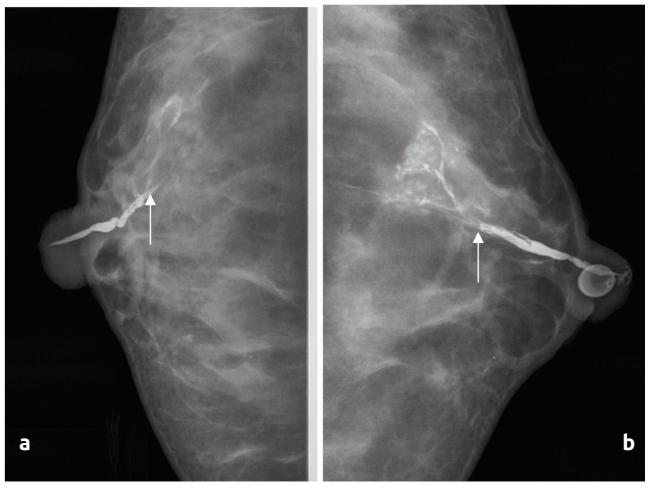

Figure 1. Traditional DG in a 55-year-old patient: a) craniocaudal and b) mediolateral projections; defective filling indicated by arrow

DG: ductography

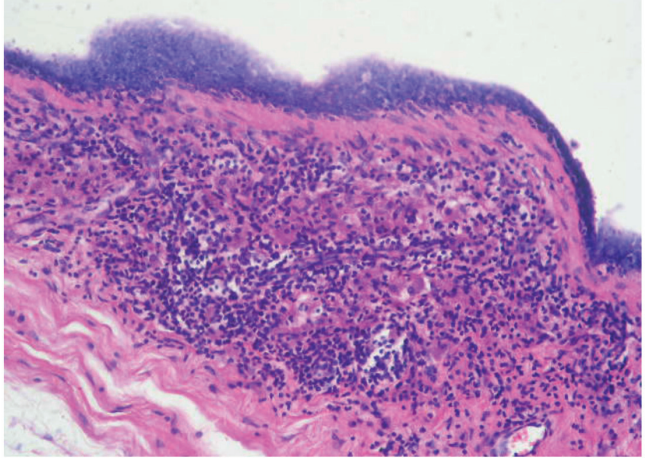

Figure 2. Histopathological examination in the same patient as in Figure 1. The formation of a pseudopapillary intraductal structure against a background of chronic inflammation. H&E x200

H&E: hematoxylin and eosin stain

Discussion and Conclusion

Current trends in oncological surgery of breast IDP are to favor the avoidance of unnecessary surgery in benign processes and to personalize therapy for invasive carcinomas. This approach requires confident preoperative histopathological verification with accurate assessment of the degree of invasiveness and molecular-genetic subtyping of the tumor.

Minimally invasive, visually guided biopsy has clear advantages over open biopsy, in the form of routine ductectomy with labeling of the secretory ducts of the first order with indigo carmine or propylene thread. However, as our studies have shown, without ductography, only 15.4% and 30.8% of the IDP are visible on mammography (MG) or US, respectively.

The highest sensitivity was demonstrated by EMDS (90.7%) and DG (87.9%), but intraductal biopsy does not yet have sufficient technical support and has not yet become widespread (24), and the usefulness of DG for orientation and navigation during biopsy are virtually unstudied. Paradoxically DG, as a focused procedure designed

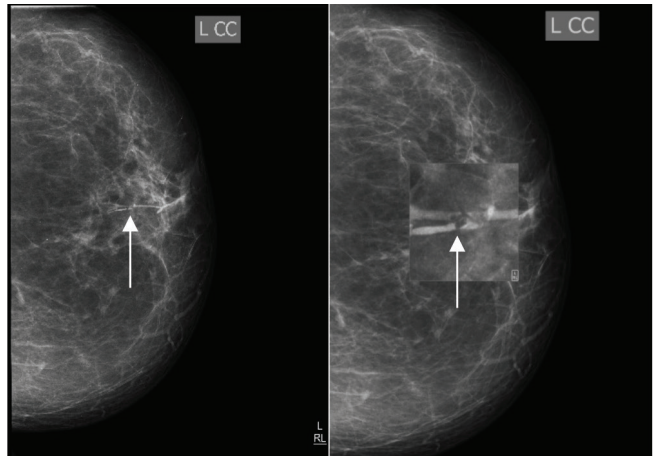

Figure 3. The ductogram after selective contrasting of the duct of the second order under the control of endoscopy (filling defect is indicated by an arrow)

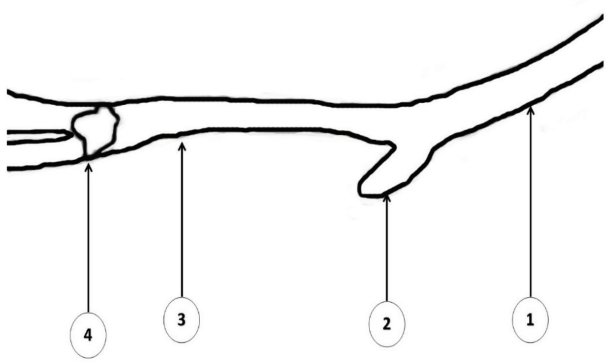

Figure 4. The scheme of ductogram after selective contrasting of the duct of the second order under the control of endoscopy: 1) duct of the second order; 2) lower branch of a duct of the third order; 3) upper branch of a duct of the third order; 4) filling defect due to intraductal proliferation

exclusively for the diagnosis of IDP, is characterized by frequent false results and low (33.3%) specificity.

Jiang et al. (25) reported the development of a system for assessing and classifying DG, taking into account some X-ray signs of IDP, which showed improvement in the differentiation of benign and malignant processes. However, there is insufficient evidence to support this use routinely and the final differentiation continues to rely on histopathological verification.

We found that the leading (57.1%) cause of false-positive results after DG was the unsuccessful excision of peripherally located IDP, in accordance with the findings of Istomin et al. (14). To eliminate false positives as far as possible and increase the diagnostic efficiency of DG, we proposed selective contrasting of the ducts under the control of EMDS, as well as the use of images obtained as a result of traditional and/or selective DG for orientation and navigation during sCNB.

The first experience of using the proposed methods showed their full technical reproducibility and safety. The combined use of well-known

Table 3. The main characteristics of patients undergoing sCNB under the control of DG (n = 26)

Indicator	Amt. (%)
Laterality: right/left	9 (34.6%)/17 (65.4%)
The nature of the discharge	
Bloody;	16 (61.5%)
Transparent;	6 (23.1%)
Amber colored	4 (15.4%)
MG results (BI-RADS®-2–4 categories)	4 (15.4%)
US results (BI-RADS®-2–4 categories)	8 (30.8%)
DG results	
Lines of "amputation";	10 (38.5%)
Filling defects;	9 (34.6%)
A combination of these symptoms;	7 (26.)
Distance from the nipple (less than 3 cm/3 cm or more);	8 (30.%)/18 (69.2%)
IDP dimensions in cm (min/max/mean)	0.2/6.0/0.9

MG: mammography; US: ultrasonography; BI-RADS: Breast Imaging Reporting and Data System; min: minimum; max: maximum; n: number, Amt: amount

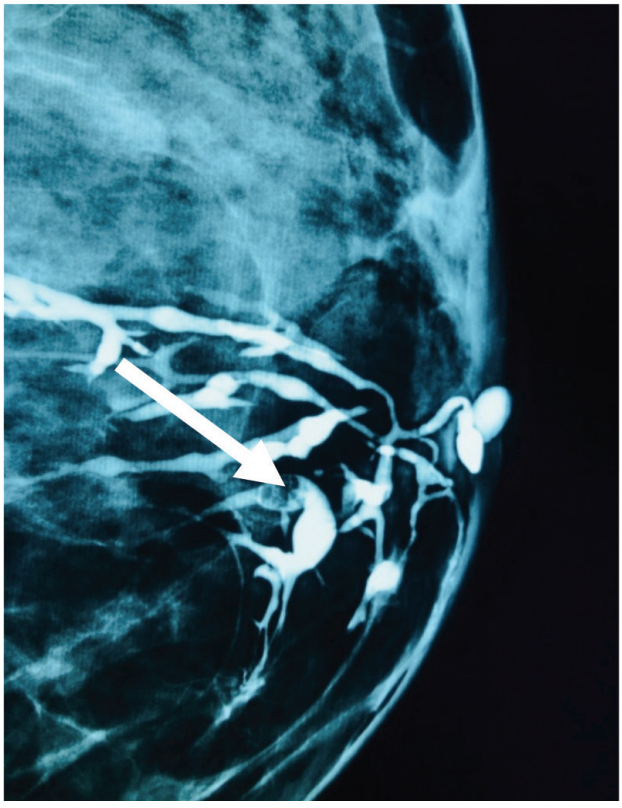

Figure 5. Ductogram after the traditional introduction of a contrast medium (filling defect is indicated by an arrow)

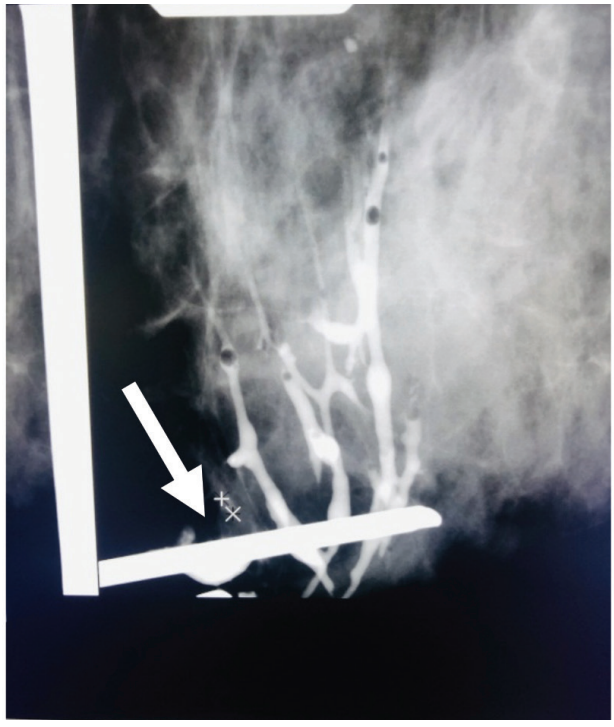

Figure 6. sCNB under the control of traditional DG. The position of the puncture needle after taking the material (filling defect is indicated by the arrow). Note: Multiple round filling defects due to air bubbles are also visible

DG: ductography; sCNB: stereotactic core-needle biopsy

techniques, DG and sCNB, means that there are no learning curves to deal with and there should be no new complications, except for the well-known and already described for DG and sCNB.

Selective contrasting of the second, third and fourth order ducts under the control of EMDS provided additional visualization and created the conditions for the navigation of sCNB when the IDP is peripherally located, and undetectable on X-ray and US, when endoscopic revision is impossible.

The advantages of sCNB under the control of traditional or selective DG are that it is less traumatic to obtain a complete biopsy for a reliable histopathological analysis, which opens up the possibility of planning further treatment tactics, including surgery, depending on the benign or malignant nature of IDP. An additional advantage of sCNB under the control of DG is the presence of a puncture channel and hemorrhage around it, which can be used as a kind of marker before routine ductectomy, and which is economically beneficial for medical institutions with a limited budget (26). The possibilities of sCNB under the control of DG are limited by well-known circumstances. The combined technique is technically not feasible in patients with flat breasts (thickness <2.5–2.7 cm after compression on a mammograph) and is potentially dangerous if the critical location of the IDP is near the ribs, pleura, large blood vessels and nerves (27). Furthermore, the feasibility of performing sCNB under the control of DG in cases of large, X-ray positive and echopositive IDP is debatable, but, in our opinion, the contrasting of the secreting duct allows precise selection of the area of the tumor that most closely matches the nature of the lesion.

This study has some limitations. These include a small number of observations and a lack of randomization which do not allow for a complete statistical analysis and, therefore, to safely draw robust conclusions from the findings.

In conclusion, further study of the possibilities of sCNB under the control of traditional or selective DG is promising in terms of minimizing the number of open biopsies (routine ductectomy) for preoperative verification of the benign or malignant nature of IDP of the breast.

Ethics Committee Approval: Ethics committee approval was received for this study from the Commission on Bioethics at the National Cancer Institute of the Ministry of Health of Ukraine (protocol no. 77 dated 12/09/2015).

Informed Consent: Verbal informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: G.A.B., N.A.S., A.A.A., E.G.A.; Design: G.A.B., N.A.S., A.A.A., E.G.A.; Data Collection and/or Processing: G.A.B., N.A.S., A.A.A., E.G.A.; Analysis and/or Interpretation: G.A.B., N.A.S., A.A.A., E.G.A.; Literature Search: G.A.B., N.A.S., A.A.A., E.G.A.; Writing: G.A.B., N.A.S., A.A.A., E.G.A.; Critical Review: G.A.B., N.A.S., A.A.A., E.G.A.

Conflict of Interest: The authors have no conflicts of interest to declare.

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