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Title page

Full Title:

Assessment of microcalcifications with limited number of high precision macrobiopsies

Short Title:

Accuracy of direct & frontal macrobiopsies

RICHARD HARRIES¹, SARAH LAWSON¹, LIESBETH BRUCKERS²

1. DIANA, PRINCESS OF WALES HOSPITAL, NORTHERN LINCOLNSHIRE AND GOOLE HOSPITALS NHS TRUST, SCARTHO ROAD, GRIMSBY DN33 2BA,

2. CENTER FOR STATISTICS, HASSELT UNIVERSITY, AGORALAAN, BUILDING D, B-3590 DIEPENBEEK, BELGIUM.

Corresponding author:

Dr. Richard Harries, Diana, Princess of Wales Hospital, Northern Lincolnshire and Goole Hospitals NHS Trust, Scartho Road, Grimsby DN33 2BA, UK

email: Richard.Harries@nlg.nhs.uk tel +44 1472 875560

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Abstract

Stereotactic biopsy assessment of microcalcification clusters with direct and frontal macrobiopsies was performed in a population of 46 women screened for breast cancer. In these women the only clinical finding was microcalcification. Sensitivity of the procedure was 98% and calcifications were detected in 107 out of 148 tissue specimen (73%). This is the highest reported ratio so far. Interestingly the total number of cores inversely correlated with the success rate suggesting that the accuracy of the direct and frontal approach is high. 4 out of 46 women underwent surgery for malignancy indicating that 41 women escaped intervention with a mean follow-up of at least one year. Patient satisfaction is high, in particular regarding reported pain, fear and overall appreciation. No complications were seen. The data suggests that a lower number of macrobiopsies for microcalcifications could be acceptable with direct and frontal biopsy methods without reducing sensitivity. Lowering the number of biopsies can optimize surgical margin interpretation and reduce the number of biopsy related mastectomies.

Key words

Breast cancer, screening, microcalcification, direct and frontal macrobiopsy, biopsy

TEXT

Introduction

Clinical guidelines for microcalcification assessment propose the use of vacuum assisted biopsy (VAB) instead of tru-cut core needle biopsy under stereotactic guidance. Tru-cut biopsies are considered inappropriate because of the small tissue samples that may exclude proper histopathological analysis [1]. But even for macrobiopsies at least six biopsies are recommended in order to reach optimal sensitivity. The lateral position of the biopsy window in these needles requires a 360° biopsy to ensure that the intended cluster of microcalcifications is taken up in at least one of the samples. Some clinicians prefer to increase the number of biopsies to even more than 20, and technological improvements in the VAB devices with fast suction and cutting make this quite possible. Stereotactic guided VAB has been recommended in several guidelines for microcalcification assessment.

Increasing the number of biopsies, however, has clinical limitations: taking multiple samples from suspect lesions can result in an inability to assess free margins at the time of surgery, leading to an increase in lumpectomy volume. For small breasts this might mean mastectomy. Disruption of architecture after VAB is well-known to facilitate clip migration [2], an indicator that malignant cells might also migrate. In addition, hematoma formation may disperse cells to even larger volumes. For these reasons VAB procedures have been shown to limit breast conservative surgery in up to 30 % of the cases [3,4,5]. If multiple stereotactic macrobiopsies decrease the likelihood of breast conservation surgery, this important advantage of early detection might be lost.

Negative surgical margins of 10 mm or more remains one of the most important determinants of successful treatment [6]. Positive surgical margins at lumpectomy may be caused by disease related factors: Mammographic microcalcifications, larger tumours and multifocal tumours

are predictors for involved margins [7]. In a number of studies with a limited number of stereotactic large-core needle biopsies, however, there was a greater frequency of tumour-free margins after local excision [8], and overall, combining benign and malignant lesions, the use of VABs might reduce the need for surgical interventions [9].

To reduce safely the number of macrobiopsies required without decreasing sensitivity, direct and frontal biopsy systems have been developed with the purpose of improving targeting accuracy. In this procedure, microcalcifications are taken up at the tip of the device under stereotactic guidance and the position of the microcalcifications relative to the needle is confirmed before cutting takes place. Device navigation is under complete control of the operator. The clinical usefulness of direct and frontal biopsy (Spirotome, Coramate) has been addressed in several previous publications [10,11,12].

This paper describes a single institute's clinical results of microcalcification assessment using the Spirotome 10 Gauge.

Materials and methods

Patient population

Forty-six procedures for microcalcification, detected at mammography, were performed in 46 women between October 2007 and August 2009. The inclusion criteria were asymptomatic microcalcifications found on mammography during screening for breast cancer. The recorded data was: procedure identification number; date; starting time; end time; total time; total number of cores; number of cores with calcification; application of clip marker; histology; and further management and complications. Complications were defined as prolonged stay in hospital or the need for additional clinical measures. The number of cores taken was at the discretion of the operator, depending on the clinical situation (poor visualization of microcalcifications or area larger than 1 cm). Biopsy was performed by either RH or SL.

Instruments

Stereotactic guidance was carried out using an upright mammographic unit (Mammomat, Siemens, Germany) according to the instructions of the manufacturer. The biopsy was performed using the Spirotome 10 Gauge (MedInvents, Belgium) according to the instructions of the manufacturer. After proper skin disinfection, skin anaesthesia and deep local anaesthesia, a small (5mm) incision is made in the skin. Then the trocar with cutting cannula is advanced under the skin by twisting the trocar up to the site of microcalcifications. The trocar is removed and the receiving needle with cutting helix is inserted instead. The helix is navigated into the cluster of microcalcifications by clockwise rotation. After position verification the sample is isolated using the cutting cannula and then removed. Multiple samples can be taken during one transdermal insertion. The presence of microcalcifications is evaluated by magnification radiographs of the specimen. Tissue fixation is achieved by immersion in 5 per cent formalin. A tissue clip is inserted when radiological and/or surgical follow-up is anticipated.

Data reporting

Core biopsy diagnoses are classified according to the Non-operative Diagnosis Subgroup of the British National Health Service Breast Cancer Screening Programme (NHSBSP). B1 means unsatisfactory or normal tissue only; B2 Benign; B3 Lesion of uncertain malignant potential; B4 Suspicion of malignancy; and B5 malignant [13]. Patient acceptability based on fear and pain assessment was recorded on a scale of 1 to 5 1: no fear/pain; 2 slight; 3 equivocal; 4 moderate; and 5 severe. Processing of the specimen was performed according to the guidelines of the NHSBSP with regard to histology and immunohistochemistry.

Statistics

Statistical analysis was performed in two ways. First, a logistic regression model was used where the indicator 1 was used when all cores of a patient contained microcalcifications and 0 if at least one core did not contain microcalcifications. A Fischer Exact test was used to see if there is a difference in success percentage between the 6 groups of total number of cores.

The second type of statistical analysis is based on the Poisson regression where the number of expected cores with microcalcification is considered.

Results

Procedural time

In this population of 46 patients with cluster of microcalcification on screening the average procedural time was 48 minutes (Standard Deviation 18 min) with a minimal time of 25 and a maximal time of 100 minutes. The procedural time trend was stable during the study period.

Multiple biopsies only slightly prolonged the procedural time compared to one or two biopsies.

Number of cores with microcalcifications

The average number of cores taken was 3 (St Dev 1,28) with a minimum of 1 and maximum 6 (for larger areas of microcalcifications or difficult visualization). The distribution was 1 core in 2 patients, 2 cores in 13 patients, 3 cores in 15 patients, 4 cores in 8 patients, 5 cores in 5 patients and 6 cores in 3 patients. The number of cores with microcalcifications per total number of cores is depicted in table 1. In a total of 148 cores 107 showed the presence of microcalcifications. There is a trend for accuracy towards lesser number of total cores (Table 1). The false negative rate is 1 out of 46 patients (2%) indicating a success rate of 98%.

Logistic regression analysis

For each patient an indicator was made: 1 in case all cores from a procedure contained microcalcifications and 0 if at least one core did not contain microcalcifications. Subsequently, success chances for this indicator in view of the total number of cores are analyzed with a logistic regression model. This means that success is defined when all cores of one patient contain microcalcifications. Supposing that this chance changes linearly with the number of cores, we see that the success chance decreases with increasing number of cores ($p=0,0025$). However, this model doesn't fit well (goodness of fit $p=0,0108$). Viewing at the table, the trend is not really linear. With 4 cores the success percentage is still rather high (66%). A

Fisher Exact test was used subsequently to see if there is a difference in success percentage between the 6 groups (of total number of cores). This test is highly significant ($p < 0,0001$). But the test only indicates that there is a difference between the groups but does not identify between which groups the difference is to be seen. When we reduce the 6 groups to 2 classes: 1 to 2 cores versus 3 and more, it becomes clear that the success percentage in the first class (87%) is much higher than the second (27%) ($p = 0,0015$). Additional biopsies tend to have lower chance of containing microcalcifications.

Poisson regression analysis

In this model the number of expected cores (prediction for the total population based on the sample size of 46 patients) with microcalcification is considered. The figure depicts the total number of cores with microcalcifications to be expected (full line) with the 95 % confidence interval (dotted lines). The horizontal axis shows the total number of cores. The number of cores with microcalcifications increases with the total number of cores. But with 4 cores and more we see a decrease in the figure. The confidence intervals are relatively broad due to the small numbers of patients. Only the next groups differ: 1 core versus 6 cores ($p = 0,0870$), 2 cores versus 5 cores ($p = 0,0131$), 2 cores versus 6 cores ($p = 0,0028$), 3 cores versus 6 cores ($p = 0,0340$), 4 cores versus 5 cores ($p = 0,0347$), and 4 cores versus 6 cores ($p = 0,0073$). Based on these data and for the underlying clinical trial one can conclude that there is no use in total number of cores above 4 (Figure 1).

Histological verification and clinical follow-up

Histological analysis is depicted in table 2. In 46 patients 4 cancers have been identified. 38 patients showed no sign of malignancy. In 3 patients (B1, B1 and B3) a mammotome procedure was added. The diagnosis was confirmed in all three. In 4 patients with proven invasive cancer 3 underwent mastectomy and 1 wide local excision. One patient with DCIS had mastectomy.

Clip application

Fourteen patients had a clip placed at the site of biopsy (30%) while 31 had no clip at the end of the procedure (67%). The patient with no calcifications in 5 cores had no clip.

Patient acceptability and complication rate.

Fear and pain as well as overall impression were recorded in a 5 point score with 1 complete comfort to 5 severe discomforts. In 8 patients no score have been obtained. The distribution of the scores in 38 patients is indicated in table 3. One patient fainted during the procedure.

She had 2 cores removed while both had microcalcifications. In no patient out of 46 a complication with regard to infection, haemorrhage or excessive pain was noted. Patient acceptability seemed not related to the number of biopsies and procedural time.

Discussion

The strength of this study is in the precise selection of patients with a cluster of microcalcification on mammography, and the independence of the study towards manufacturers. ~~All equipment was owned by the institution and no financial support from the companies nor from other institutions was requested.~~ Due to the high selection criteria, the number of patients is moderate but reflects confidently the accrual in a typical reference centre.

In contrast to common belief and contemporary guidelines on classical VABs, increasing the number of macrobiopsies doesn't necessarily increase sensitivity. Even the number of cores with microcalcification per total number of cores (up to 72%) does not increase when more than 4 cores are taken. According to these figures, procedures with less than 4 biopsies using the Spirotome provides sufficient material to establish a reliable diagnosis i.e. that microcalcification are indeed in one or more samples per procedure. Sampling was guided by upright stereotactic biopsy, a widely available technique, and microcalcification was found in 45/46 patients (98% success rate with an average of 3 specimen). In comparison, ultrasound-guided VAB of microcalcification has a success-rate of 71 per cent [14] and under stereotactic guidance up to 95% with a mean of 14 samples per procedure [15,16].

Of particular interest is the high number of cores with microcalcification per procedure, indicating that the procedure can be performed with high precision as well. This is in line with the complete navigation control of the helix that localizes the biopsy site before cutting takes place. In addition, the data suggests that total manual control of the biopsy procedure improves the success rate.

The procedural time is in line with contemporary standards. Most of the time is taken up by localization of microcalcification and positioning of the patient. The biopsy step generally

takes a fraction of total procedural time and rarely exceeds 20 minutes. This is made possible through the lesser preparation time of the biopsy equipment that is available in a ready to use package.

The number of malignant specimens was 4 in a population of 46 patients. That is low compared to data from literature [15,16] where up to 30 % of the patients with microcalcification are diagnosed with malignancy. However, the number might well reflect the actual situation for a regional hospital at first referral without further selection of patients. The median follow-up time is over 1 year and no upgrading or false diagnoses were made so far. This is in line with the high number of microcalcification containing cylinders that constitute the basis of histopathology.

Three out of 4 patients with malignancy underwent mastectomy. These mastectomies were carried out according to the institutional guidelines and are not secondary to difficulties in assessing the surgical margins. More importantly, 41 out of 46 patients with breast microcalcification avoided surgery.

Tissue markers or clips are vital in the follow-up of microcalcification, in particular when surgery is indicated. In this population of patients, clip application was judged necessary in 14 patients. There was no correlation between clip placement and histopathology indicating that risk assessment based on radiological characteristics of microcalcifications is rather unreliable. This is in line with conclusions from several publications [17].

Patient acceptability was measured for fear, pain and overall acceptance. In all three areas the Spirotome showed satisfactory levels of acceptance (below 3). Because fear scored higher in the discomfort scale compared to pain and because fear is an essential determinant of pain, a substantial improvement in comfort could be obtained by proper patient information prior to the procedure. No complications were observed requiring prolonged stay or additional

intervention. This is in line with literature where low complication rates have been observed for both micro- and macrobiopsies.

The data suggests that high-precision macrobiopsies do not need excessive numbers of cores in order to provide maximum probability of breast conserving treatments. Confirmation of these data with multicentre studies is necessary before inclusion into a new standard is warranted, but the findings are encouraging that improvements in macrobiopsy technology can provide women with microcalcification a significantly higher chance of conservative management and therefore improved cosmetic outcome in the case of malignancy.

Acknowledgments

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