Utility of Adequate Core Biopsy Samples from Ultrasound Biopsies Needed for Today's Breast Pathology

Ugur Ozerdem, M.D.[1]

Abstract

Background: There is a paradigm shift in breast biopsy philosophy. In the past radiologists and clinicians used to collect as little tissue as possible for pathologists to render a diagnosis on conventional histologic H&E sections. Precision medicine has changed this philosophy in such a way that more optimal core biopsy specimens are now required to provide more data for personalizing the therapy.

Methods: A case is presented in this study to illustrate the importance of adequate ultrasound-guided breast biopsy samples. Digital mammography of left breast in a postmenopausal woman revealed a spiculated lesion, which was confirmed with ultrasonography as a 0.4 cm irregular mass. A core biopsy was performed by using an ultrasound-guided 13 gauge tetherless vacuum-assisted Mammotome Elite biopsy system. Eleven cores were submitted for paraffin embedding in four cassettes. Following microscopic examination of histologic slides, additional diagnostic and prognostic ancillary studies were performed.

Results: Microscopic examination revealed a moderately-differentiated invasive ductal carcinoma with a maximum histologically contiguous linear extent of 0.4 cm, and low to intermediate grade DCIS (DCIS grade 1-2) without calcifications. Radiological and core biopsy carcinoma dimensions of the lesion were concordant. The core biopsy sample displayed the entire invasive carcinoma which consisted of well-fixed, abundant invasive carcinoma tissue for all ancillary studies.

Conclusions: Ultrasound-guided core biopsies obtained using tetherless Mammotome Elite system provide high quality, unfragmented, adequate samples when a breast mass is targeted. Routine ancillary studies, prognostic panels, and advanced comprehensive genomic testing are performed with ease on these adequate samples.

Given the heterogeneous nature of breast carcinomas, more sufficient sampling of breast masses not only enables the pathologist to characterize the tumor adequately, but also provides better-represented, adequate tumor tissue for comprehensive genomic testing for personalized medicine. Mammotome Elite samples could easily provide optimum tumor surface area (25 mm^2) and tumor volume (2mm^3) for such genomic testing for rendering a confident diagnosis.

Author details
[1] Clinician, Department of Pathology,
Yale University School of Medicine,
Yale New Haven Hospital, 20 York Street
EP2, Room 631A
New Haven, Connecticut (06504) U.S.A.

1. INTRODUCTION:

Histopathologic examination of adequate, minimally-invasive breast core biopsy samples corresponding to an abnormal radiological finding is the standard of care prior to any therapeutic intervention or mammographic surveillance decision. Excision of breast (breast conserving surgery, mastectomy) without prior minimally-invasive core biopsy diagnosis is almost an obsolete clinical practice.

It is imperative to have a quantitatively and qualitatively adequate sample in order for a pathologist to formulate an ironclad diagnosis. Majority of patients with imaging abnormality who have undergone minimally-invasive breast core biopsy with benign diagnosis are spared further excision and excision-related complications. Many of these patients are managed with radiological surveillance only.

Quality of the individual tissue sample should be optimal to provide a confident radiological-pathological correlation. Undersampling of clinically significant lesions (invasive / in situ carcinoma, atypical ductal hyperplasia, complex radial scars, papillary neoplasms with or without atypia) and fragmented inadequate samples could easily lead to a false negative "benign breast tissue" histologic diagnosis. According to a recent article published in the Journal of Clinical Oncology, insufficient cancer tissue for biomarker testing occurred across 4 out of 5 cancer types reported on. The majority of tissue samples in which insufficient tissue was present were acquired through core biopsies (67% of all cases) or FNAs (22% of all cases).[1]

Quantity of the sample should be optimal to perform ancillary diagnostic studies (P63, calponin, CK903, E-cadherin, CK5/6, CK 7, MNF 116, S100, collagen type IV, reticulin stains etc.) or prognostic predictive markers (ER, PR, AR, Ki67, HER2, various commercial predictive-prognostic test batteries), and comprehensive genomic profiling for personalized medicine, customizing the treatment options based on tumor's genetic profile. Each immunostain would require at least a 4 micron-thick tissue section from the paraffin block to prepare a slide. Up to 600 slides could be theoretically prepared for additional studies from an adequate sample obtained with a 13 gauge equipment which provides a 2.41 mm-thick (i.e. 2410 microns) core biopsy tissue fragment. For invasive cancers more than 1mm (>1mm) linear extent of carcinoma is needed on the glass slide for diagnosis, while microinvasive carcinomas require more than 0mm but less than or equal to 1mm (>0mm-≤1mm) invasive carcinoma for diagnosis. A core biopsy fragment bearing a (2 mm x 2 mm x 2 mm) tumor mass could have about 1 million cells available for any additional tests. For example HER2-FISH testing requires at least 20 non-overlapping cancer cells. But given the tumor heterogeneity 20 cells may not adequately represent the the tumor; the more cancer cells in a sample the better the adequacy. Microarray assays detect expression patterns by hybridizing labeled mRNA isolated from tissue to microarray chips. Numerous gene products can be examined simultaneously. RT-PCR assays amplify RNA from a few specific genes and can therefore be performed on formalin-fixed tissue. Examples of commercially available assays include but not limited to Oncotype DX® Breast Cancer Assay (Genomic Health Inc, Redwood City, California) and Breast Cancer Gene Expression Ratio Assay (or H:I Ratio Test) (Quest Diagnostics, Madison, New Jersey). The Oncotype DX® test is significant because it predicts the likelihood of the patient benefiting from chemotherapy and can further forecast the likelihood of recurrence. Knowing these results can give physicians more information to determine appropriate treatment. The Oncotype DX® assay for example requires one tumor block and an H&E slide from the same block. When blocks are submitted, typically up to 65 micron thickness of the tumor tissue will be used. When the biopsy sample is inadequate performing these microarrays is challenging.

There is a paradigm shift in biopsy philosophy: In the past radiologists/clinicians used to collect as little tissue as possible for pathologists to provide a diagnosis on conventional H&E sections. Precision medicine has changed this philosophy in such a way that nowadays quantitatively and qualitatively more optimal core biopsy specimens are required to provide more data for personalizing the therapy. Pathologists have started using the core biopsy samples not only for establishing a diagnosis but also providing variety of actionable data to personalize the treatment. One such personalized precision medicine tool is FoundationOne® genomic testing, which includes testing for all classes of alterations in each of the entire coding sequence of 315 cancer-related genes plus select introns from 28 genes often rearranged or altered in cancer. These genes are known to be somatically altered in human solid cancers based on recent scientific and clinical literature. Many genomic alterations among those 315 genes, include (but not limited to) PTEN, PI3K, AKT, mTOR, EGFR, MLL2, CDKN2A/B, CCNE1, and KDM6A, AKT3, CCND1, CCND2, CCND3, CDK4, FBXW7, FGFR/FGF, and SRC in various types of breast cancer. Foundation One® genomic testing requires at least 16 unstained slides (with 5 micron thickness) from formalin fixed paraffin embedded tissue block, with an optimum 25 mm2 surface area. These assays assist oncologists with matching patients with relevant targeted therapies and immunotherapies. This could be easily achieved with larger gauge core biopsy samples.

Larger gauge core biopsy equipment provides more adequate breast tissue for evaluation. Quantity (volume) of the tissue samples is directly proportional to the length and thickness of the sample. Two core biopsies of same length (h) of tissue with 13 gauge (2r =13 gauge= 2.41 mm) equipment theoretically provides 15% more rectangular cross sectional area on the glass slide (based on flat orientation in the paraffin block) for microscopic examination than a 14 gauge tissue sample (2r =14 gauge= 2.1 mm.). **(Figure 1 A-B)**.

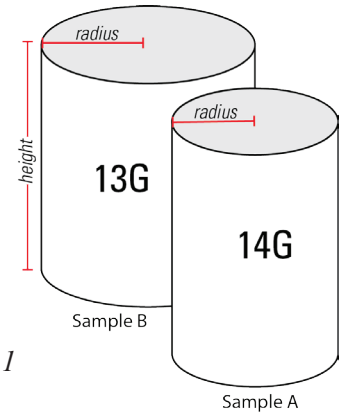


Figure 1

Figure 1. Large bore core biopsy breast samples provide more optimal (larger) cross sectional area for diagnostic evaluation and more tumor tissue for ancillary diagnostic, prognostic-predictive studies. A 13 gauge sample **(B)** would provide approximately 15% more cross sectional area for microscopic examination and 32% more tumor tissue for ancillary testing than a 14 gauge core biopsy sample **(A)**.

2. CASE STUDY

Ultrasound Case

Clinical Situation

Digital mammography of left breast in a 71 year-old female revealed a spiculated lesion, which was confirmed with ultrasonography as a 0.4 cm irregular mass with a spiculated edge. An ultrasound-guided core biopsy was recommended.

Core Biopsy Procedure

A core biopsy was performed by using Mammotome Elite 13 gauge tetherless vacuum-assisted biopsy system with ultrasound guidance.

Microscopic Findings

The specimen consisted of 11 cores which were subsequently submitted for paraffin embedding in 4 cassettes. Microscopic examination revealed moderately differentiated invasive ductal carcinoma, with a maximum histologically contiguous linear extent of 0.4 cm, involving 3 of 11 cores. P63 and calponin immunostains also delineated low grade DCIS (DCIS grade 1-2) without microcalcifications. Invasive carcinoma was ER-positive (95%, 3+), PR-negative (0%), HER (IHC) negative (1+). HER2-FISH was negative for both HER2/CEP17 ratio and HER2 copy number. Subsequent partial mastectomy, which had been entirely submitted for histologic examination, revealed biopsy site changes and residual DCIS morphologically similar to that seen in prior core biopsy. No residual invasive carcinoma was remaining in the partial mastectomy specimen.

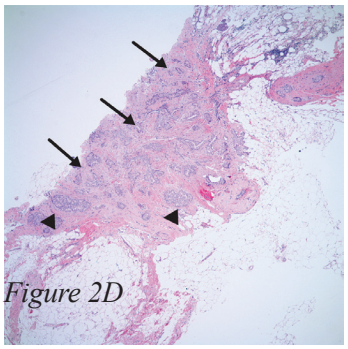
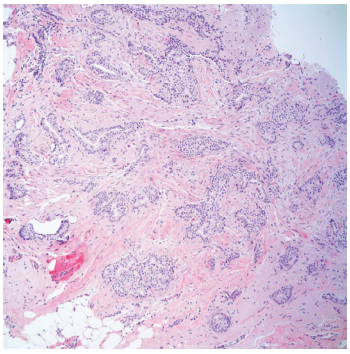


Figure 2A

Figure 2D



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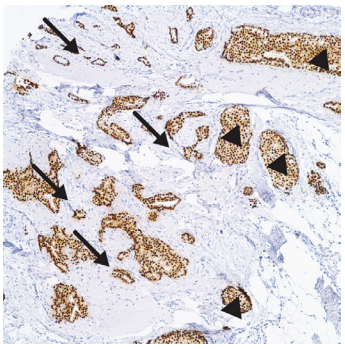

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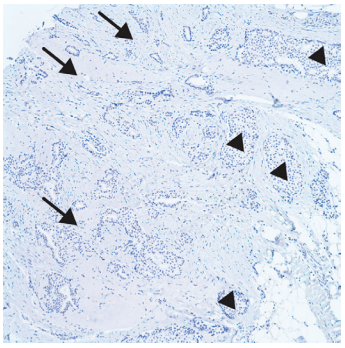

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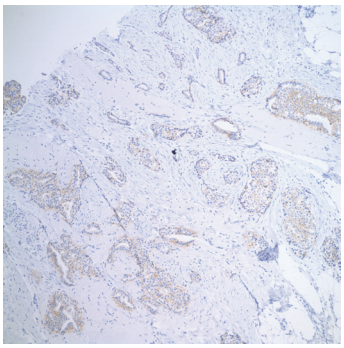

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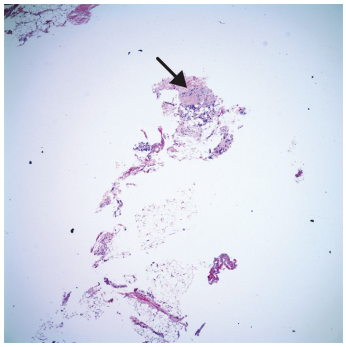

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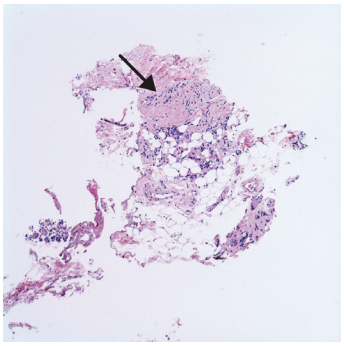

Figure 2G

Figure 2. Core biopsy of obtained with Mammotome Elite 13 gauge biopsy system revealed invasive and in situ duct carcinoma in 3 of 11 cores. The largest linear extent of invasive carcinoma was measured as 0.4 cm on a core **(A, B)**. Sample was adequate to perform ancillary diagnostic and prognostic studies. Invasive carcinoma was ER-positive (95%, 3+), PR-negative (0%), HER (IHC)-negative (1+) **(C-E)**. HER2-FISH was negative for both HER2/CEP17 ratio and HER2 copy number.

Arrows indicate invasive carcinoma, solid triangular arrowheads indicate DCIS.

For comparison a 14 gauge conventional core needle biopsy sample of a radiological architectural distortion is shown **(F-G)**. The 14 gauge core needle biopsy samples are fragmented. An infiltrating lobular carcinoma focus is identified on the core biopsy **(arrows in F-G).** Largest linear extent of invasive carcinoma is 0.6 mm (microinvasive carcinoma) in this fragmented sampling, barely sufficient for ER, PR, HER2 testing. Following this diagnosis, an excisional biopsy of the same lesion revealed a 10 mm focus of infiltrating lobular carcinoma.

Discussion

The core biopsy sample in this case consisted of the entire invasive carcinoma which consisted of well-fixed, abundant invasive tumor cells available for ancillary studies. Both radiological and core biopsy invasive carcinoma dimensions were concordant (0.4 cm). This suggests optimal sampling of the lesion. When invasive tumor size in core biopsy is larger than that seen in excision, the tumor size (T) in excision specimen may result in underclassification of the T component. Core biopsy samples of breast masses obtained using ultrasound-guided tetherless Mammotome Elite 13 gauge biopsy system are less vulnerable to crush artifact and fragmentation. Measurement of largest extent of tumor on unfragmented (contiguous) core biopsy sample could yield correct tumor size for tumor staging purposes. Pathological tumor size used for staging of this invasive carcinoma case as T1a was solely based on the largest linear extent of invasive carcinoma (0.4 cm) on the unfragmented, adequate core biopsy sample. Amount of invasive carcinoma was adequate in quality and quantity in the core biopsy sample to run all ancillary studies and prognostic panels. Since there was no residual invasive carcinoma on partial mastectomy specimen, the only tumor source for ancillary studies and tumor banking was that obtained from high quality samples obtained with Mammotome Elite tetherless biopsy system. In sharp contrast, the biopsy sample obtained by using conventional 14 gauge core biopsy needle from mammary architectural distortion in another patient (Figure 2 F-G) yielded fragmented sample, inadequately characterizing the maximum histologically contiguous extent of invasive carcinoma as 0.6 mm. Since the cellularity of the invasive lobular carcinoma is also low, a 0.6 mm extent of the tumor sample yielded only few hundred cells out of millions of tumor cells for ER, PR, and HER2 testing; further underscoring the diagnostic challenges with the fragmented, low-yield samples.

3. CONCLUSION:

Ultrasound guided core biopsies obtained using tetherless Mammotome Elite sytem provide high quality, unfragmented samples when a breast mass is targeted. If the mass in question is of cancer nature (invasive carcinoma, DCIS), routine ancillary studies (ER, PR, HER2, Ki67, AR), prognostic panels, and advanced comprehensive genetic testing are performed with ease on these adequate samples. Quantitatively and qualitatively more optimal specimens such as those obtained with Mammotome Elite provide more data for personalizing the therapy since precision medicine has changed the core biopsy philosophy from small, fragmented, inadequate samples to unfragmented, undistorted, adequate samples.

Given the heterogeneous nature of breast carcinomas, more sufficient sampling with Mammotome Elite not only enables the pathologist to characterize the tumor adequately, but also provides better-represented, adequate tumor tissue for comprehensive genomic testing for personalized medicine. Mammotome Elite samples could easily provide optimum tumor surface area (25 mm^2) and tumor volume (2mm^3) for such testing rendering a confident diagnosis.

FOOTNOTES

[1]Pieter De Richter, Jackie Ilacqua; Ipsos Healthcare, New York, NY; Ipsos Healthcare, Mahwah, NJ. "Correlation between biopsy type and insufficient tissue availability for biomarker testing in five solid cancer types." J Clin Oncol 31, 2013 (suppl; abstr e22136).

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