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Coordinated and interdepartmental processing of image-guided core needle biopsies improves recovery of diagnostic material for molecular testing

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ABSTRACT

Core needle biopsies (CNBs) are the current standard by which tissue is procured by minimally invasive means for diagnostic purposes. However, their diminutive nature often creates an imbalance between the amount of tissue available for morphologic examination and the growing number of tests being requested to be performed from them. An under-recognized by-product of this procedure may alleviate some of these supply issues, but requires a cooperative effort from personnel in interventional radiology and pathology to bring to fruition. We describe the theory, practice, and results of how to maximize the amount of diagnostic material that is available and coming from CNB's for these growing number of tests. This coordinated approach will maintain the value of the CNB in the growing and competitive arena of minimally invasive assay development.

Keywords: Core needle biopsy, DNA, Molecular, Pathology

INTRODUCTION

The dramatic shift in the amount of available tissue procured by image-guided core needles versus an open excisional biopsy has contributed to an unresolved problem between supply and demand.[1] The smaller amounts of tissue sent to laboratories have hampered the ability of pathologists to distribute material for biomarker testing and enrollment into clinical trials.[2] Appropriate tissue management and regulatory considerations are underlying factors that contribute to the inability, in a certain percentage of cases, to provide sufficient material for molecular testing.[2-4] Identifying a solution to this problem would maximize the value of tissue biopsies, which still remains the gold standard for establishing a clinical diagnosis. Although a number of authors have discussed the emerging role of molecular analysis as part of the modern pathology service, practical and applicable solutions have not been proposed as they relate to the issues of supply and demand with respect to the core needle biopsy. Herein, we describe our approach to this problem, which is surprisingly simple and facile, but does require a coordinated effort between personnel in the departments of radiology and pathology. Understanding the logic behind our suggested approach should make integration readily palpable and adoption widespread, maintaining the value of this vital diagnostic approach in an era of competing technologies such as the liquid biopsy.[5]

MATERIAL AND METHODS

The modification in the processing of the specimen we employed occurs immediately after procurement of the tissue specimen. It involves no contact or harm to the patient and is an effort to improve on current practice. Nevertheless, Institutional Review Board approval was obtained. The modification involves the immersion of the needle tip into a non-formalin containing phosphate buffered saline solution immediately after acquisition [Figure 1]. This is in contrast to the practice of depositing the tissue core into a container by another needle or scalpel blade, or on to a saline soaked gauze pad. The reasoning behind immersing the needle tip into a buffered solution is simple. During the biopsy procedure, cells are dislodged from the tissue but are normally lost because they cannot be seen by the naked human eye, and either remain on the needle tip or the gauze pad. Placing them in a buffer solution allows the laboratory to manually recover the tissue core, and recover as well the dislodged cells from the supernatant by centrifugation.[6] These dislodged cells can be variable in amount, but if recovered, can be extremely valuable for clinical use. This approach enables the creation of two specimens from what was initially intended to be one: the tissue core (the intended target) which can be visually identified, and the dislodged cells (the procedural by-product) which cannot be individually, visually identified. We have previously determined that recovery of these dislodged cells is dependent upon whether normal or tumor tissue has been sampled, with the number of passes performed also playing a role.[7] In a recent study, we integrated the biopsy procedure directly into the laboratory processing workflow. As a coordinated effort, the biopsy specimen was immersed in buffer in the interventional radiology suite immediately after procurement from the patient, and the specimen then brought to the pathology laboratory. For the first three specimens collected in this study, the tissue from the first pass was performed by the interventional radiologist as previously, routinely done. For these first few samples, the final pass was performed in the modified approach that involved immersion of the needle tip in a solution of phosphate buffered saline. For the final two cases, the buffer into which the needle with the tissue was swirled around in was autoclaved/sterilized before the procedure. This allowed the interventional radiologist to deposit all the tissue and dislodged cells from every pass into the buffer solution. At the laboratory, the specimen was filtered through a strainer (MACS SmartStrainer 100 µm, Miltenyi Biotec, San Jose, CA, USA), the parent tissue core identified and transferred to a cassette followed by placement in formalin and routine processing to create a paraffin embedded tissue block. The filtered buffer was then spun down and the supernatant discarded, followed by the addition of 500 µL of the molecular preservative DNA/RNA Shield (Zymo Research, Irvine, CA, USA). Time points as to when the tissue was procured

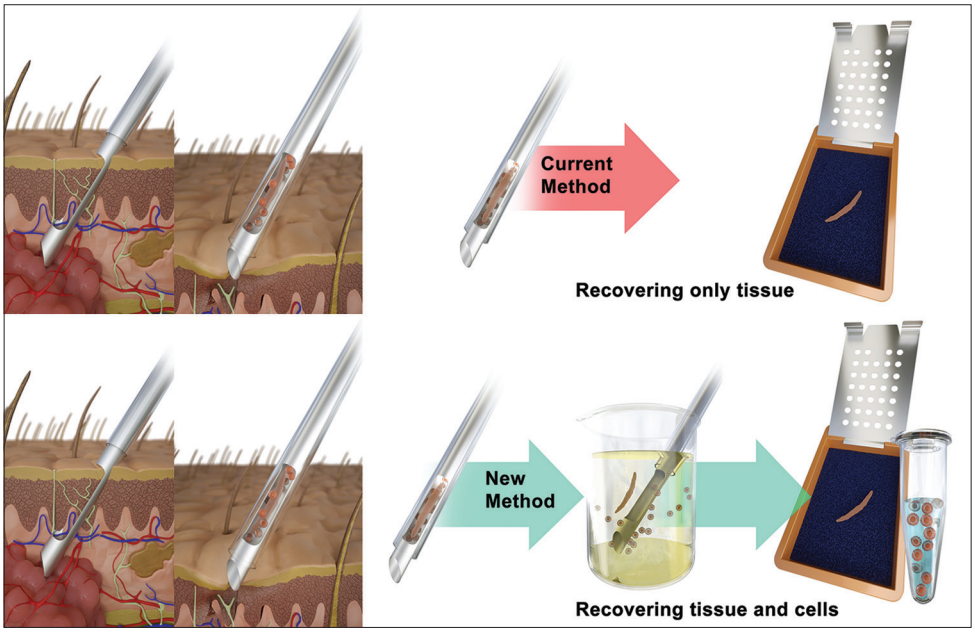

Figure 1: Top half the image shows placement of tissue either scraped off the needle or placed on a gauze pad. On arrival and processing, only the tissue can be identified and placed in a cassette. Bottom half image shows placement of the tissue and dislodged cells in a buffered solution. At the laboratory, the tissue can be recovered and placed in a cassette while the dislodged cells can be recovered from the supernatant. This simple approach is based on awareness of what can be recovered from the procedure and manipulating laboratory processing to take advantage of that knowledge.

in the interventional radiology suite and when the molecular preservative was added to the specimen with dislodged cells, were recorded to assess time commitments from laboratory personnel. The tube with the dislodged cells in the Zymo molecular preservative was then kept in a −20°C freezer until five cases had been collected. DNA was extracted from each specimen using the GenFind V3 Blood, Cell and Serum Genomic DNA Isolation Kit (Beckman Coulter Life Sciences, Brea, CA, USA). Quantification and qualitative assessment of the DNA was performed on a 5200 Fragment Analyzer (Agilent Technologies, Santa Clara, CA, USA) and software designed for data analysis.

RESULTS

Tissue from five separate procedures was collected using the washing protocol to create daughter aliquots and was performed on some or all of the passes done by the interventional radiologist [Table 1]. Our initial approach was to have the interventional radiologist perform the number of cores he had decided to do, with the last core being subjected to the "washing" in buffer. This was done for the first three cases because the buffer was not sterilized and so we did not want him to "wash" the specimen in a non-sterilized buffer with the initial core tissues and reintroduce the needle back into the patient for any subsequent passes; hence, only the last core was "washed." However, because there was a significant amount of time between the collection of specimens 3 and 4, we were able to locate an autoclave and adjust our approach. For the last two cases, we were able to provide the interventional radiologist a sterilized container with buffer from which he could wash off the tissue and cells from each pass, not just the last one. The time commitment for laboratory personnel to receive, transport, and process the specimen, was under 20 min for every case except for one instance where receipt of the specimen was delayed due to laboratory personnel issues. This parameter is significant in that it demonstrates a minimization of the introduction of pre-analytic variables and the amount of time required for dedicated time from pathology department personnel.[8,9] The amount of DNA recovered from every daughter wash aliquot was >100 ng. This amount was sufficient to fulfill the input needs (>10 ng) for most next-generation sequencing platforms and some recently introduced instruments like the Idylla™ Platform (Biocartis, Jersey City, NY, USA) and MassARRAY® System (Agena Bioscience, San Diego, CA, USA).[10] It should be mentioned that the quality of the DNA, as assessed on the fragment analyzer, was favorable for library preparation in all five cases. The Genomic Quality Number (GQN), a quality metric designed to assess extracted nucleic acids on the Agilent Fragment Analyzer for genomic sourced material and calibrated on a scale from 0 to 10, with the former the worst possible and the latter the best value, yielded optimally recovered material [Table 1].[11] These results show the consistent recovery of high quality DNA. When compared to DNA from formalin-fixed, paraffin embedded tissue blocks, and the current standard type of clinical specimen from which nucleic acids are extracted from, the quality of DNA can be highly variable, with the GQN ranging between 2.5 and 7.1.[11]

DISCUSSION

Advancements in technology have impacted the practice of medicine and how physicians need to approach patient care. New challenges may be accompanied by innovative methods and improved insights in specific arenas of patient management not previously recognized.[12] A more holistic understanding of the role each physician plays and how it translates into the domain of other specialists should be embraced, with expiation of the past history of departmental siloed thinking.[13] As such, we have described a modification in the processing of the critically important small biopsy specimens designed to maximize their utility in diagnostic applications. One observation we found is that the daughter aliquots with the lower amount of recovered DNA came from cases where normal liver tissue was taken (case #2), and areas of cirrhosis (case #5). The indication for these two cases was the presence of suspected nodules not confirmed by the corresponding parent tissue specimen. Another observation is that in the tissues with malignant tissue, the amount of DNA recovered was greater when the

Table 1: Types of tumor tissue obtained by the core needle biopsy and technical metrics related to time, quantity and quality of the DNA from cells recovered by the wash procedure.

Case #	Diagnosis	Pre-analytic time (minutes)	Number of cores taken	Number of cores "washed"	Amount of recovered DNA (ng)	DNA quality number
1	Metastatic small cell carcinoma	15	3	1	1,600	10
2	Normal liver	14	3	1	151	10
3	Metastatic prostatic adenocarcinoma	16	4	1	395	9.9
4	Pancreatobiliary carcinoma	55	3	3	2,605	9.9
5	Cirrhotic liver	15	5	5	102	9.9

For specimen #2, the indication was a nodule in a woman with a recent history of starting oral contraceptives. In specimen 5, the indication was to rule out hepatocellular carcinoma in a patient with extensive use of alcohol.

dislodged cells from more than one pass was collected and processed (Case 4 vs. Case 3). However, other factors based on the tissue characteristics (e.g., cellularity) do contribute to this observed variability (e.g., Cases 1 and 4, based on examination of the tissue histology – data not shown). In regards to quality assessment, immediate processing using the molecular preservative kept the extracted DNA in optimal condition for subsequent sequencing library preparation irrespective of time spent in cold storage (e.g., Cases 1 and 2 vs. Case 5). Other notable observations include the DNA that came from tumor material metastatic to bone (Case 3) was similar in quality to all the other specimens which did not come from bone. This important point demonstrates the value of this processing approach on specimens coming from bone, namely, the ability to recover diagnostic material for downstream analysis unencumbered by the use of a decalcification reagent and its untoward effects on nucleic acid integrity normally needed for the processing of the parent tissue specimen.

One of the limitations of this study is the small number of cases examined. The reason for the small number of cases was based on the limited time-frame we had to perform this study, and the number of cases performed by the interventional radiologist during that time. This study was performed at a small community hospital, where the number of cases biopsied per year does not exceed single digits. While the small sample size may not uncover problems that may be identified by studying a larger cohort, it did prove that this approach was feasible in a low-resource community hospital setting and simple enough to perform without the need for specially trained personnel. We felt it responsible to inform others of this approach of its efficacy as it may prove to be similarly advantageous to the management of small tissue specimens and patient welfare at other institutions. Larger studies in larger centers with multiple operators in varied clinical environments are needed to validate our findings.

Although the improved results and observations discussed in this report are predominantly pathology and molecular-analysis related metrics, it should be understood that they are achievable only because of the cooperation with interventional radiology occurred at the first step of processing in this proposed modified specimen handling method. Interventional radiologists play a crucial role in Precision Medicine as the first health-care providers encountering the tissue specimen where it needs to be properly optimized before continuing along its processing journey.

CONCLUSION

Inclusion of a biopsy wash step at the point of procurement allows for the recovery of valuable, diagnostic cellular material that otherwise is lost. In the current era of reduced tissue size but increasing testing demands, this simple approach represents one means of providing sufficient amounts of material to meet the demand for molecular testing.

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Declaration of patient consent

Patient's consent not required as patient's identity is not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

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