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Molecular and imaging biomarkers for precision therapy of breast cancer

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14. ABSTRACT

In this project, we will use surgical specimens from the TMIST Lead-In in an attempt to more completely define the underlying molecular, phenotypic and radiological features associated with cancers detected with digital breast tomosynthesis (DBT) vs. digital mammography (DM) or interval cancers, and their surrounding tissue (micro/macroenvironment). We will extract and characterize radiological features including mammographic density, parenchymal texture, lesion morphology, etc. from cancers in DBT and DM images. We will compare the molecular classifications of cancers detected by DBT vs. DM and test correlation with imaging patterns. We will process a subset of the breast cancer specimens using 3D whole-mount processing, in combination with protein marker multiplexing to study the cancer, the tumor micro-environment and the proximal "macro-environment". A protein biomarker panel reporting on: hormonal receptors, proliferative capacity, functional status of tumor infiltrating lymphocytes (TILs), macrophages and cancer-associated fibroblasts (CAFs) in the microenvironment, and mammographic density-related markers will be studied. We believe that this integrated cross-platform study will identify novel imaging signatures that could inform clinicians the biological characteristics of the cancer detected, and facilitate more appropriate, precise and efficient intervention utilizing targeted and conventional therapeutics.

15. SUBJECT TERMS

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1. Introduction

Our project aims to integrate imaging information of breast cancer to correlate to the underlying molecular alterations in order to improve characterization and prognostication of detected lesions and subsequent management of the disease. We will be studying breast cancers diagnosed from the Tomosynthesis Mammographic Imaging Screening Trial (TMIST) Lead-In component. Existing breast cancers will be retrospectively analysed. Tissue blocks will be retrieved for molecular analysis including targeted mutational sequencing and expression profiling. Mammographic images from the same cases will be studied to identify imaging patterns. In additional to studying the existing specimens, we will also prospectively recruit newly diagnosed breast cancer patients from TMIST Lead-In for whole-mount (WM) histopathological processing of their surgical specimens. Since the spatial context of tumor and surrounding stromal tissue are preserved with WM processing, we can coarsely locate the findings from our molecular examinations to imaging data to identify imaging features that could be used to predict the aggressiveness of cancer.

2. Keywords

Breast cancer, imaging, tomosynthesis, molecular, biomarker, characterization

3. Accomplishments

Our Notice of Award was received in August 2018. Since receiving the notice of award, we have been working on the submission to the Research Ethics Board (REB) at Sunnybrook Research Institute (SRI). Our project proposal involves two arms: (1) retrospectively analyzing the molecular changes of TMIST Lead-In cancers and (2) prospectively study cancers identified in TMIST Lead-In as a whole-mount processing specimens. We have worked very closely with our pathologists at Sunnybrook Health Sciences Centre to establish a protocol and an informed consent form for Arm 2. An REB application covering both Arm 1 and 2 was submitted to our REB and received approval on July 31st, 2019.

Our collaborators have also received REB approval from their institutions. Dr. John Bartlett and Dr. Lincoln Stein (both from the Ontario Institutes for Cancer Research, OICR) have received approval from the University of Toronto Office of Research Ethics for the molecular analysis of de-identified specimens/data. Dr. Melissa Troester (University of North Carolina) has received notification from the UNC's Office of Human Research Ethics determining that their involvement does not require IRB approval. All documents were forwarded to the Human Research Protection Office (HRPO). Compliance and initial approval from HRPO was received on August 7th, 2019.

Since receiving REB approval, the lab has initiated preparation and coordination with the Department of Anatomic Pathology to ensure efficient pathway for the collection and processing of tissue according to very strict conditions with respect to timing and quality. One potential study candidate was identified by the TMIST clinical research associates, and informed consent was collected. However, the lumpectomy specimen was considered ineligible for whole-mount processing by the Pathologist Assistant and Pathologist because of skin involvement. Although we could not process this case, it served to provide the team an opportunity to be readily prepared for the next potential case.

A project kick-off team with all Canadian collaborators has been scheduled for October 30th, 2019. We will initiate retrieval of existing cancer tissue blocks from our Anatomic Pathology Department with help from the study pathologist Dr. Elzbieta Slodkowska. Imaging data will also be collected and analysed using a Radiomics approach by our Physicist and Radiologists.

4. Impact

Since our work in the past year were mostly completing HRPO approval and other administrative tasks, there is no impact yet.

5. Changes/Problems

We have not encountered any changes or problems.

6. Products

Not Applicable

7. Participants and other collaborating organizations

There are no changes to collaborating organizations.

8. Special reporting requirements

   Not Applicable to this report.

9. Appendices

   Not Applicable to this report.