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An exploratory radiomics analysis on digital breast tomosynthesis in women with mammographically negative dense breasts

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ABSTRACT

Purpose: To compare Digital Breast Tomosynthesis (DBT) for cancers and normal screens in women with dense breasts and negative mammography using a Radiomics approach.
Materials and Methods: A substudy (N = 40) of the 'Adjunct Screening With Tomosynthesis or Ultrasound in Women With Mammography-Negative Dense Breasts (ASTOUND)' trial was done based on 20 women who had DBT-detected, histology-proven, breast cancer and 20 controls matched for age and density. Using a Radiomics approach normal and pathological breast parenchyma were evaluated, and correlations among Radiomics features and clinical and prognostic parameters were investigated.
Results: The median age of the patients was 50 years (range 39–70 years). After Radiomics feature number reduction, 3 of 6 (50%) selected features differed between controls and cancers (Skewness (0.002); Entropy (p.004); 90percentile (p.006)). Three Radiomics features (Energy, Entropy and Dissimilarity) significantly correlated to tumor size (r = −0.15,r = 0.49,r = 0.51), but not with prognostic factors. Entropy correlated with Estrogen Receptor status (r = −0,46; p.004).
Conclusion: Radiomics features in patients with dense breasts and negative mammography appear to differ between cancerous and normal breast tissue, with evidence of correlation with tumor size and estrogen receptors. This new information warrants further evaluation in larger studies and could contribute to improved understanding of breast cancer through imaging, and may support tailored screening and treatments.

1. Introduction

Radiomics is an advanced quantitative image features analysis methodology defined as the conversion of clinical images to higher dimensional data and the subsequent mining of these data for improved decision support [1]. Radiomics can be performed with the majority of clinically available medical images such as tomographic images from CT, MR imaging, and PET studies, ultrasound, mammography or digital breast tomosynthesis (DBT) and 18F FDG PET/CT [1–3].

In Radiomics mathematical algorithms are applied to examine features within imaging, indeed, images are considered more that pictures, but as data sources [1]. Using Radiomics, hundreds of quantitative image features from clinical images can be extracted

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using automatic or semi-automatic software. Radiomics is based on the assumption that extracted imaging data are the product of mechanisms occurring at a genetic and molecular level linked to the genotypic and phenotypic characteristics of the tissue [4–6].

In the past, texture analysis, an approach much more simple than radiomics has been used with DBT. Mammographic texture analysis was used to assess breast density to predict breast cancer risk [7], to differentiate women who are carriers of BRCA1/2 from those at low risk for breast cancer [8–11] and to improve the estimation of breast cancer risk [12]. It has been recently shown by Ray et al. [13] that measures of breast texture could suggest false-positive recalls from screening with digital mammography therefore having the potential to influence supplemental screening. Radiomics evaluations are more probing than texture analysis and should be more informative in characterizing breast parenchyma and ultimately could result in more accurate measures to estimate breast cancer risk and to evaluate breast tissue. The presence of dense breast tissue reduces the sensitivity of mammography and mammography screening is associated with a higher risk of an interval breast cancer [14] therefore supplemental screening with tomosynthesis or ultrasound can be performed [15]. Indeed, in many American States laws require that women are informed that in case of dense (heterogeneously dense or extremely dense) breasts, a negative mammogram does not reliably exclude the presence of cancer. For supplemental screening the increased reading time to read tomosynthesis, especially with double reading [16,17] could represent a barrier to its wide usage. In this setting Radiomics could be investigated to assess if some features in tomosynthesis images in women with mammographically negative dense breasts can differentiate patients with and without cancer; such information could ultimately help radiologists in supplemental screening. Given the results obtained in the past with texture analysis, the relevance of adjunct screening for dense breasts with tomosynthesis and the lack of data regarding Radiomics data especially in women with dense breasts our hypothesis was that a Radiomics analysis of breast parenchyma on DBT could differentiate normal breast tissue from cancerous breast tissue. In addition we correlated Radiomics feature with standard clinical and prognostic parameters.

2. Material and methods

This is an exploratory (post-hoc) sub-study of the ASTOUND trial, an Italian prospective multi-centre study which has reported interim detection data [15]. The ASTOUND trial compared ultrasound and tomosynthesis in women with dense breasts and negative digital mammography. The study received institutional review board approval (514REG2014), and written informed consent was obtained from participants. ASTOUND is a registered study (NCT02066142) sponsored by the University of Genova, which was responsible for governance and coordination.

Ongoing prospective recruitment of patients into the ASTOUND trial, as per protocol, used tomosynthesis acquisitions performed in COMBO-mode (dual-acquisitions) progressively also implemented with reconstructed synthesized 2D images (S-2D). Tomosynthesis acquisitions were acquired using commercially available equipment (Hologic, Selenia Dimensions, Bedford, MA, USA).

2.1. Patients and controls

Images of consecutive participants evaluated with DBT (inclusive of S-2D images) acquired during the trial period (December 2016–September 2017) recruited from six different centres were used to create a data set of breast cancer patients and matched controls. The patients' data set included 20 mammography-negative cancer cases consecutively enrolled in the trial in which the cancer was detected at tomosynthesis and confirmed at histopathology after surgery. The control data set included 20 cases with negative mammography and no cancer detected with either tomosynthesis or ultrasound matched for age and density groups. We did not include cancer cases that were detected only with US since we were evaluating radiomics of DBT.

2.2. Radiomic analysis

Radiomic analysis was performed on all DBT images within manually selected regions of interest (ROIs) including all the dense part of the breast and excluding the fatty part of the breast. ROI tracing was made on a single slice on the central digital breast tomosynthesis projection images similarly to breast density estimation [18]. ROIs were placed by two researchers (A.T. and F.V.) expert in quantitative image analysis (8 and 4 years of experience). Theoretically, breast cancers are more likely to be present in the dense part of the breast, indeed, in ASTOUND all cancers were in the dense part of the breast. From DBT images, we extracted 104 image features using an open-source software platform for medical image informatics, image processing, and three-dimensional visualization (3D Slicer 4.7; www.slicer.org) built over two decades through support from the National Institutes of Health and a worldwide developer community [19]. 3D-Slicer can be employed for quantitative image feature extraction and image data mining research in large patient cohorts [20]. Radiomics feature descriptors of skewness, energy, entropy, kurtosis, 90percentile and dissimilarity were computed. These descriptors have been selected after initial screening of 104 Radiomic features to reduce the risk of over-fitting and according to features previously used to associate breast parenchymal patterns with cancer risk [2,21]. Although many of the 104 Radiomics feature do not have a clear biological correspondence, skewness reflects the asymmetry of the gray-level pixel value distribution and has been previously used to assess parenchymal density [21]. Energy, entropy, 90percentile and kurtosis are first-order statistical features describing the gray level distribution of the image; the sharpness of the histogram is described by the kurtosis. Dissimilarity is a gray level co-occurrence matrix based features. Details of the mathematical notations and the computation of these texture features have been previously published [10,11]. After ROIs placement on DBT, the six Radiomics features were computed from each of the tomographic sections and the average value was used for each feature as previously done in the literature [20].

3. Statistical analysis

A) Comparison of Radiomics features of normal and pathological breast parenchyma on DBT was done with non-parametric tests (Mann-Whitney U test for unpaired data with 1000 bootstraps samples to compare patients and controls) considering a p value of 0.05 as statistically significant.

B) Accuracy was measured using receiver operating characteristic (ROC) analyses to estimate the area under the curve (AUC) and by estimating thresholds for sensitivity and specificity for the Radiomics features that significantly differed between patients and controls, considering the mean value. Ninety-five percent confidence intervals (95%CIs) were calculated. A threshold value of the mean value of the six Radiomics features was computed to differentiate between patients with cancer and patients without cancer. Using statistical software, p values below 0.05 were considered statistically significant.

C) Correlation analysis and univariate linear regression were performed to determine the association between the individual