★月刊インナービジョン 2018 年 7 月号（Vol.33, No.7） 13-17p 掲載英文テキスト★

# Advances in the development of Breast CADx with AI

Maryellen L. Giger, Ph.D.
A. N. Pritzker Professor of Raiology / Medical Physics
Department of Radiology
The University of Chicago

**Acknowledgements**
Funded n parts by NIH U01CA195564, U01 CA189240, and R01CA166945.

M.L.G. is a stockholder in R2/Hologic, co-founder and equity holder in Quantitative Insights, shareholder in QView, and receives royalties from Hologic, GE Medical Systems, MEDIAN Technologies, Riverain Medical, Mitsubishi, and Toshiba. It is the University of Chicago Conflict of Interest Policy that investigators disclose publicly actual or potential significant financial interest that would reasonably appear to be directly and significantly affected by the research activities.

## Abstract

AI in breast cancer detection and diagnosis has been advancing over the past 30 years. These advances have led to developments in various breast imaging interpretation tasks, such as risk assessment, detection, diagnosis, prognosis, and therapy response, as well as in multi-omics disease discovery. Translation to FDA-cleared clinical care has occurred for aiding in detection (CADe) and diagnosis (CADx). The expansion of the computer-extraction of features and machine learning, typically found within CAD systems, is now referred to as radiomics. Radiomics aim to provide quantitative features for association & discovery studies with clinical data, histopathology data, and other "-omics" data, such as genomics, proteomics, etc. Studies of radiomics also aim to develop predictive models utilizing the image-based features for precision medicine. Deep learning methods are also rapidly advancing and being applied to image interpretation tasks. These various AI methods are expected to augment radiologists' interpretation, thus, making clinical decision making more effective and efficient.

## Introduction

Within the field of artificial intelligence (AI) there is the subfield of machine learning, which includes deep learning. Artificial intelligence in breast cancer detection and diagnosis has been advancing over the past 30 years (Refs. 1-3). These advances have led to developments in various breast imaging interpretation tasks, such as risk assessment, detection, diagnosis, prognosis, and therapy response, as well as in multi-omics disease discovery. Image interpretation by humans is hindered by the presence of structure noise (camouflaging normal anatomical background), incomplete visual search patterns, fatigue, distractions, the assessment of subtle and/or complex disease states, vast amounts of image data, and physical image quality. The expansion of the computer-extraction of features and machine learning, typically found within CAD systems, is now referred to as radiomics. Radiomics aim to provide quantitative features for association & discovery studies with clinical data, histopathology data, and other "-omics" data, such as genomics, proteomics, etc. Studies of radiomics also aim to develop predictive models utilizing the image-based features for precision medicine. Deep learning methods are also rapidly advancing and being applied to image interpretation tasks. These various AI methods are expected to augment radiologists' interpretation, thus, making clinical decision making more effective and efficient. This paper gives a brief overview of the areas of CAD and recent progress.

## CADe

Breast CADe involves a localization task to be performed by the computer serving as a second opinion to radiologists in screening mammography programs, leaving the patient management decisions to the radiologist. Over the past three decades, computer-aided detection in screening mammography has been developed, with it receiving FDA approval in 1996 and subsequent clinical use (Refs. 4, 5). Breast CADe systems have progressed in various ways including the use of symbols of varying intensity in order to indicate how likely the computer algorithm estimates that a computer detection is an actual cancer. Other CADe systems have been investigated with radiologists' prompts to potential lesions, with the computer then giving an estimate of the likelihood that the region is actually suspect of being cancer. More recently deep learning methods have been investigated in which the input is the mammographic image with an output of an estimate of the probability that the image contains a suspect breast cancer. These methods have also advanced through challenges, such as the Dream Challenge (Ref. 6).

Many deep learning methods utilize computational neural networks (CNNs). CNNs can be used for classification, filtering, segmentation, and feature extraction. The earliest journal paper of CNNs in medical imaging was published in 1994, in which CNNs were used in the computerized detection of microcalcifications for screening mammography (Ref. 7). The CNN served as a filter to enhance the signal of microcalcifications in the processed mammograms so that subsequent computer vision methods could be used to extract potential microcalcifications (Ref. 7). Others also used CNNs on mammograms, such as in the task of distinguishing between biopsy-proven masses and normal tissue on mammograms (Ref. 8). CNNs continue to be investigated for CADe (Ref. 22).

## CADx

Once a suspect lesion is found, by either a radiologist or computer, the computer can further process the image in order to estimate the likelihood that the lesion is actually cancerous or not. Here the task is one of classification, and not localization. With computer-aided diagnosis (CADx), the computer characterizes the lesion in question, leaving the decision on patient management to the radiologist.

Within CADx systems, the computer might be programed to segment the suspect lesion from the breast parenchymal background. The segmented lesion then undergoes feature extraction in which characteristics such as lesion size, shape, margin morphology, texture, and kinetics are automated extracted (Refs. 9-12, 39). [Figure 1] These features, i.e., radiomics, are then merged using some classifier into a lesion signature, whose value is related to a likelihood of malignancy. More recent systems are being focused on distinguishing between benign lesions and specific cancer subtypes, such as the Luminal A subtype (Ref.13).

Various commercial systems have been developed over the past ten years to analyze breast magnetic resonance images (MRIs) and characterize specific aspects of the suspect lesion, such as the kinetics on dynamic contrast enhancement MRI (DCE-MRI). (Ref. 14). Kinetic characterizations of the lesion are extracted in order to indicate the uptake and washout of the contrast agent in the blood stream.

In 2017, the first CADx system was cleared by the FDA as a machine learning system to assist radiologists in breast cancer diagnosis (Ref. 15). This system includes various computer-extracted characterizations of the lesion, which are subsequently merged into a tumor signature score that is related to a likelihood of malignancy for use by radiologists, who then make the final decision on patient managment.

Rapid advances in deep learning have also been applicable to breast cancer diagnosis. (Refs. 16-23). Since databases are still limited, transfer learning has been used in CADx using pretrained CNNs with and without "fine tuning". Basically, CNN features are extracted, i.e., transferred, from pretrained CNNs (i.e., pre-trained), where the information in the CNN layers serve as features. For example, a CNN trained on natural scenes (dogs, cars, houses), could be used from which to extract features when breast images are fed through the trained CNN. (Refs. 20, 21). Another form of transfer learning is fine tuning, which involves freezing early layers of a pretrained CNN, and then training the latter layers specifically for a new task.

Recently, transfer learning was conducted for the diagnosis of breast tumors on mammography, ultrasound, and breast MRI (Refs. 20, 21). Investigators compared a CADx system with conventional computer-extracted features, a CADx system with CNN-extracted features, and a fusion classifier trained on both types of features. The complimentary aspects of both conventional and deep-learned tumor features in breast cancer classification were demonstrated with the fusion classifier yielding the performance level. [Figure 2]

Given the limited number of cases for training a CNN, it is beneficial, at times, to input preprocessed images to enhance the network. For example, investigators compared the CNN performance in CADx when using post-contrast MRIs, post-contrast subtraction MRIs, and maximum intensity projection images (MIP) as input to CNNs in an attempt to incorporate both the spatial and temporal aspects of DCE-MRI (Ref. 23). In the study, it was found that MIPs yielded statistically significant performance results [Figure 3].

**Beyond CADx: Radiomics and Imaging-Genomics (radiogenomics)**

While AI of lesion and normal background features has successfully been used for CADe and CADx, they also have a growing role in prognosis and assessing response to therapy, as well as in datamining for discovery (Refs. 12, 38). Radiomics, an expansion of computer-aided diagnosis, involves the conversion of images to minable data (Refs 3, 24-26). Basically, a computer method in which images are input and numbers are output that characterize the tumor, i.e., image-based phenotypes.

Datamining of the radiomics features without and with other "omics", such as clinical data, histopathology, and genomics, can then be conducted, i.e., imaging-genomics/radiogenomics (Ref. 36). For example, in a multi-institutional National Cancer Institute (NCI) collaboration of invasive breast carcinomas involving The Cancer Genome Atlas (TCGA) and The Cancer Imaging Archive (TCIA) (Refs. 27, 28), investigated associations between breast MRI radiomic features and various clinical, molecular, and genomics markers of prognosis and risk of recurrence, including gene expression profiles were investigated (Refs. 12, 28-31, 35).

Given the heterogeneity of cancer, both genomics and radiomic studies are being conducted to elucidate this characteristic. (Refs. 12, 29, 30). With breast DCE-MRI, texture of the dynamic contrast uptake can yield phenotypes that characterize the heterogeneous aspect of contrast uptake within the breast tumor. (Ref. 10) For example, a high value of the texture entropy could signify a more heterogeneous uptake pattern within the tumor, thus indicating the heterogeneous nature of angiogenesis & treatment susceptibility.

An example of radiomics in predicting a patient's outcome used the functional tumor volume from breast MRI as a predictor of recurrence-free survival on breast cancer patients receiving neoadjuvant therapy (Ref. 32, 37).

These image-based phenotypes can be viewed as providing a location-specific "virtual biopsy", which covers the entire tumor, is repeatable, and could be non-invasive. Virtual biopsies have the potential to provide information when an actual biopsy is not practical, such as in screening or for serial "biopsies" with multiple imaging exams during cancer treatment to assess response.

The application of AI in medical imaging requires the use of images from routine clinical imaging exams, and thus the requirement for harmonization of the imaging exam and/or the image analysis methods and features. Various groups are addressing these aspects of robustness and harmonization, such as the Quantitative Imaging Network (QIN) of the NCI (Ref. 33) and the Quantitative Imaging Biomarker Alliance (QIBA) of the RSNA (Ref. 34).

**Discussion and Summary**

More investigations are needed, as imaging datasets become larger and better annotated, and as AI algorithms advance in complexity, especially for distinguishing subtle disease states and abnormal/normal patterns. The field is advancing quickly.

In addition, users need to understand that a CNN is not a "black box" as there are methods to assess the learned components to understand what in an input image is being enhanced, detected, etc.

AI in CAD and radiology is expected to have a profound clinical impact, alleviating some routine tasks from radiologists while simultaneously forcing them to incorporate AI findings into the clinical workflow and interpretation for the betterment of patient care.

●References

1）Lodwick GS. Computer-aided diagnosis in radiology : A research plan. Invest Radiol 1: 72-80, 1966.

2）Giger ML, Chan H-P, Boone J. Anniversary Paper: History and status of CAD and quantitative image analysis: The role of Medical Physics and AAPM. Medical Physics 35:5799-5820, 2008.

3）Giger ML, Karssemeijer N, Schnabel J. Breast image analysis for risk assessment, detection, diagnosis, and treatment of cancer. Annual Review of Biomedical Engineering (invited) 15:327-357, 2013.

4）Freer TW, Ulissey MJ. Screening mammography with computer-aided detection: Prospective study of 12,860 patients in a community breast center. Radiology 220:781-786, 2001.

5）Rao VM, Levin DC, Parker L, Cavanaugh B, Frangos AJ, Sunshine JH. How widely is computer-aided detection used in screening and diagnostic mammography? J Am Coll Radiol 7: 802-805, 2010.

6）https://www.synapse.org/#!Synapse:syn4224222/wiki/401744

7）Zhang W, Doi K, Giger ML, Wu Y, Nishikawa RM, Schmidt RA. Computerized detection of clustered microcalcifications in digital mammograms using a shift-invariant artificial neural network. Medical Physics 21: 517-524, 1994.

8）Sahiner B, et al. Classification of mass and normal breast tissue: A convolution neural network classifier with spatial domain and texture images. IEEE Trans Med Imag 15(5): 598-610, 1996.

9）Chen W, Giger ML, Bick U, Newstead G. Automatic identification and classification of characteristic kinetic curves of breast lesions on DCE-MRI. Medical Physics 33:2878-2887, 2006.

10）Chen W, Giger ML, Li H, Bick U, Newstead G. Volumetric texture analysis of breast lesions on contrast-enhanced magnetic resonance images. Magnetic Resonance in Medicine 58:562-571, 2007.

11）Chen W, Giger ML, Newstead GM, Bick U, Sanaz SA, Li H, Lan L. Computerized assessment of breast lesion malignancy using DCE-MRI: Robustness study on two independent clinical datasets from two manufacturers. Academic Radiology 17: 822-829, 2010.

12）Li H, Zhu Y, Burnside ES, Perou CM, Ji Y, Giger ML, et al. Quantitative MRI radiomics in the prediction of molecular classifications of breast cancer subtypes in the TCGA/TCIA Dataset. NPI Breast Cancer 2, Epub 2016 May 11.

13）Whitney H, Taylor NS, Drukker K, Edwards A, Papaioannou J, Schacht D, Giger ML. Additive benefit of radiomics over size alone in the distinction between benign lesions and luminal A cancers on a large clinical breast MRI dataset. Academic Radiology, in press, 2018.

14）Pan J, Dogan BE, Carkaci S, et al. Comparing performance of the CADstream and the DynaCAD breast MRI CAD systems. J Digit Imaging 26:971-976, 2013.

15）https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/denovo.cfm?ID=DEN170022

16）Krizhevsky A, Sutskever I, Hinton GE. Imagenet classification with deep convolutional neural networks, in Advances in Neural Information Processing Systems, F. Pereira et al., Eds., Vol. 25, pp. 1097–1105, Curran Associates, Inc. 2012.

17）Simonyan K, Zisserman A. Very Deep Convolutional Networks for Large-Scale Image Recognition. arXiv:1409.1556, 2014.

18）Szegedy C, et al. Going Deeper with Convolutions. arXiv : 1409. 4842, 2014.

19） Giger ML. Machine Learning in Medical Imaging. J Am Coll Radiol 15 (3 Pt B):512-520, 2018.

20） Huynh B, Li H, Giger ML. Digital mammographic tumor classification using transfer learning from deep convolutional neural networks. J Medical Imaging 3(3), 034501, 2016.

21）Antropova N, Huynh BQ, Giger ML. A deep fusion methodology for breast cancer diagnosis demonstrated on three imaging modality datasets. Medical Physics, 44(10):5162-5171, 2017.

22）Samala R, Chan H-P, Hadjiiski L, Helvie MA, Wei J, Cha K. Mass detection in digital breast tomosynthesis: Deep convolutional neural network with transfer learning from mammography. Medical Physics 43: 6654-6666, 2016.

23）Antropova N, Abe H, Giger ML. Use of clinical MRI maximum intensity projections for improved breast lesion classification with deep convolutional neural networks. J Med Imaging (Bellingham) 5(1):014503, 2018.
24）Limkin EJ, Sun R, Dercle L, et al. Promises and challenges for the implementation of computational medical imaging (radiomics) in oncology. Ann Oncol 28(6):1191-206, 2018.
25）Gillies RJ, Kinahan PE, Hricak H. Radiomics: Image are more than pictures, they are data. Radiology 278: 563-577,2016.
26）Avanzo M, Stancanello J, El Naqa I. Beyond imaging: The promise of radiomics. Physica Medica 38:122-39, 2017.
27）Cancer Genome Atlas Network, Comprehensive molecular portraits of human breast tumours. Nature 490: 61, 2012.
28）Clark K, et al. The Cancer Imaging Archive (TCIA): Maintaining and operating a public information repository. J Digit Imaging 26:1045, 2013.
29） Li H, Zhu Y, Burnside ES, Perou CM, Ji Y, Giger ML, et al. MR Imaging Radiomics Signatures for Predicting the Risk of Breast Cancer Recurrence as Given by Research Versions of MammaPrint, Oncotype DX, and PAM50 Gene Assays. Radiology 281(2):382-391, 2016.
30）Zhu Y, Li H, Giger ML, Ji Y, et al. Deciphering genomic underpinnings of quantitative MRI-based radiomic phenotypes of invasive breast carcinoma. Sci Rep 5:17787, 2015.
31）Guo W, Li H, Zhu Y, Giger ML, Ji Y, et al. Prediction of clinical phenotypes in invasive breast carcinomas from the integration of radiomics and genomics data. J Medical Imaging 2(4): 041007, 2015.
32）Drukker K, Li H, Antropova N, Edwards A, Papaioannou J, Giger ML. Most-enhancing tumor volume by MRI radiomics predicts recurrence-free survival “early on” in neoadjuvant treatment of breast cancer. Cancer Imaging 18:12, 2018.
https://doi.org/10.1186/s40644-018-0145-9, 2018
33）https://imaging.cancer.gov/programs_resources/specialized_initiatives/qin.htm
34） https://www.rsna.org/qiba/
35）Burnside E, Drukker K, Li H, Morris E, Giger ML, et al. Using computer-extracted image phenotypes from tumors on breast magnetic resonance imaging to predict breast cancer pathologic stage. Cancer 122(5):748-757, 2016.
36） Aerts HJ, Velazquez ER, Leijenaar RT, et al. Decoding tumour phenotype by noninvasive imaging using a quantitative radiomics approach. Nat Commun 5:4006, 2014.
37） Hylton NM, Gatsonis CA, Rosen MA, Lehman CD, et al. Neoadjuvant Chemotherapy for Breast Cancer: Functional Tumor Volume by MR Imaging Predicts Recurrence-free Survival-Results from the ACRIN 6657/CALGB 150007 I-SPY 1 TRIAL. Radiology 279: 44-55, 2016.
38） Bhooshan N, Giger ML, Jansen S, Li H, Lan L, Newstead G. Cancerous breast lesions on dynamic contrast-enhanced MR images: Computerized characterization for image-based prognostic markers. Radiology 254:680-690, 2010.
39） Chen W, Giger ML, Lan L, Bick U. Computerized interpretation of breast MRI: Investigation of enhancement-variance dynamics. Medical Physics 31:1076-1082, 2004.