ORIGINAL ARTICLE LEADERSHIP

Radiogenomics: What It Is and Why It Is Important

EC: Editor's Choice

SA-CME

Maciej A. Mazurowski, PhD

Abstract

In recent years, a new direction in cancer research has emerged that focuses on the relationship between imaging phenotypes and genomics. This direction is referred to as radiogenomics or imaging genomics. The question that subsequently arises is: What is the practical significance of elucidating this relationship in improving cancer patient outcomes. In this article, I address this question. Although I discuss some limitations of the radiogenomic approach, and describe scenarios in which radiogenomic analysis might not be the best choice, I also argue that radiogenomics will play a significant practical role in cancer research. Specifically, I argue that the significance of radiogenomics is largely related to practical limitations of currently available data that often lack complete characterization of the patients and poor integration of individual datasets. Radiogenomics offers a practical way to leverage limited and incomplete data to generate knowledge that might lead to improved decision making, and as a result, improved patient outcomes.

J Am Coll Radiol 2015;12:862-866.

INTRODUCTION TO RADIOGENOMICS

Increasingly, even casual readers of the scientific literature are encountering the terms "radiogenomics," "imaging genomics," and "radiomics." Because they have only recently been introduced, their usages and definitions are still in flux. The term "radiogenomics," in particular, has been inconsistently used to refer to a range of cancer-related endeavors and research topics.

Most often, "radiogenomics" refers to the relationship between the imaging characteristics of a disease (ie, the imaging phenotype or radiophenotype), and its gene expression patterns, gene mutations, and other genome-related characteristics [1,2]. As a simplification, I will refer to them collectively as "genomic characteristics" or simply "genomics." A particular focus of radiogenomic analysis has been on the relationship between imaging phenotypes and gene expression patterns which include expressions of individual genes as well as measures that summarize expressions of specific gene subsets (eg tumor molecular subtype, or Oncotype DX). 'Radiogenomics' also refers to a research effort aimed at finding this relationship. Another term used to refer to this kind of research is imaging genomics.

Another, also very common, use of the term 'radiogenomics' is to refer to the analysis that looks for associations between patient genetics and his/her reaction to radiation therapy [3], with a focus on radiation toxicity. As opposed to an effort to match imaging phenotype and genomic characteristics, this genre of research focused on phenotypes representing radiation toxicity [3]. In 2009, the Radiogenomics Consortium was established in the United Kingdom [4] in relation to this research area.

Finally, 'radiogenomics' has been equated with another approach called 'radiomics' [5-7]. However, rather than describing a particular relationship of interest, radiomics focuses on the methodology used in the analysis. Specifically, radiomics involves extraction of many quantitative features from images, using computer algorithms. The extracted features can be evaluated in relation to other data of interest, including patient outcomes. These features can also be related to genomic characteristics and such a pursuit could be referred to as the 'radiomics approach to radiogenomics.'

STATE OF THE ART IN BRIEF

The literature on radiogenomics is limited, but a rapidly increasing number of articles are appearing in relation to

Department of Radiology, Duke Cancer Institute, Duke Medical Physics Program, Duke University School of Medicine, Durham, North Carolina.

Corresponding author and reprints: Department of Radiology, Duke Cancer Institute, Duke Medical Physics Program, Duke University School of Medicine, Duke University, 2424 Erwin Rd, Suite 302, Durham, NC 27705; e-mail: maciej.mazurowski@duke.edu.

The author has no conflicts of interest to disclose.

1546-1440/15/$36.00 ■ http://dx.doi.org/10.1016/j.jacr.2015.04.019

brain cancer [8-11], particularly glioblastoma, breast cancer [12-16], lung cancer [17], and other cancers. Because the objective of this article is to discuss the significance of radiogenomics research, below I provide an overview of the general level of advancement, rather than an exhaustive review of specific studies in the field.

In glioblastoma (GBM), Zinn et al [8] showed that an upregulated PERIOSITIN gene is associated with a high tumor volume in FLAIR MRI exams. Jamshidi et al [9] showed that specific molecular phenotypes correlate with some imaging traits in GBM. Further evidence of the potential association between molecular phenotypes and imaging can be found in [10] and [11].

In breast cancer, Yamamoto et al [12] showed the potential for an association between imaging and genomics with a small sample of 10 patients. This was followed up by discovering a relationship between semi-automatically extracted imaging features describing MRI enhancement dynamics with Luminal A and Luminal B subtypes [13], [14] and Oncotype DX [15], [16]. Semi-automatic feature extraction involves both a human reader and a computer algorithm.

In lung cancer Gevaert et al [17] showed a correlation between molecular phenotypes and some imaging traits in lung computed tomography (CT). Radiogenomic analysis has also been applied to hepatocellular carcinoma [18] and clear cell renal cell carcinoma [19].

A typical research study in radiogenomics involves manual or semiautomatic assessment of imaging features and their correlation with individual gene expressions, combined gene expression patterns, such as previously defined genomic subtypes, and other molecular phenotypes. The currently available studies are typically characterized by smaller sample sizes (<100), which limit the conclusions that can be drawn.

LIMITATIONS AND SIGNIFICANCE

Radiogenomics attempts to establish and examine the relationship between tumor genomic characteristics and their radiologic appearance. Although there is certainly a lot to learn about these relationships, one could ask: what is the practical significance of radiogenomic discoveries? From the perspective of the patients, cancer patients in this case, it is their outcomes that are of greatest interest, such as survival, time to recurrence, or response to a particular treatment. A question appears: If imaging data and particularly specific features extracted from the images are available along with the outcome of interest, why not simply build a model that relates the imaging features to the outcomes directly? Relation between some imaging features and outcomes is already established and utilized in treatment planning. What is the benefit of including genomics in the mix?

One could argue that using genomics as an intermediate step in the analysis could damage the potential of imaging to predict patient outcomes. Specifically, current models that show associations of molecular phenotypes to outcomes and usage of different therapeutic regimens are highly imperfect. These models often show only minor differences in outcome for various molecular phenotypes (eg, for different molecular subtypes) and therefore provide limited prognostic/predictive values. Radiogenomic models relating imaging data to genomics, especially now, in their early days, are also capturing fairly weak or noisy relationships. When the tenuous imaging to genomics and genomics to outcomes relationships are combined to establish an imaging to outcomes relationship, the resulting link might be very weak or nonexistent.

Another reason for relating imaging features directly to outcomes is that imaging phenotypes potentially contain information that is not available in genomics data. For example, gene expression patterns are typically assessed based on a relatively small tumor tissue sample, or "averaged" from tissue samples from multiple tumor regions, and therefore may not reflect the usual heterogeneity of cancerous tumors [20]. Imaging on the other hand can potentially capture this heterogeneity [21]. Constructing a radiogenomic model first and then applying it to predict outcomes without incorporating the imaging-outcomes data in the model limits the information from imaging available to predict outcomes to what is already contained within tumor genomics. The imaging information that complements genomics is not used in such a scenario. To utilize such complementary information, a model directly relating imaging to outcomes is needed.

These are limitations of radiogenomics. However, this does not at all mean that radiogenomic analysis is without use. I will argue that the significance of discoveries in radiogenomics is largely related to a very practical aspect of science: availability of data and availability of knowledge.

As a result of prior and current data collection efforts, various data sets, both private and public [22,23], are available containing different combinations of imaging, genomics, and outcomes data (often just one or two components). The quality of the data components may differ dramatically among data sets.

Specifically, well organized molecular data repositories are publically available. To develop the field of radiogenomics, recent efforts have been undertaken to assemble large cancer imaging data sets (eg, The Cancer Imaging