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Editorial

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The cassandra paradox: looking into the crystal Ball of radiomics in thoracic surgery

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INTRODUCTION

Lung cancer is the leading cause of cancer-associated death in both men and women. Research is being conducted to identify best practices for screening and diagnosing this morbid disease, and we continue to rely on computed tomography (CT) and positron emission tomography (PET)/CT scans as our modalities of choice. Historically, nodule size has been the single-most important determinant of therapeutic options as lung cancer increases exponentially with nodule size[1-6]. Radiomics is a rapidly progressing field of study that extracts quantitative variables and identifies patterns that are difficult to evaluate on the routine reading of CT or PET/CT images. Some studies have shown radiomics parameters to correlate with tumor aggressiveness[7] as well as a prognostic determinant of survival[8-11]. Given the benefits of this potential technology, clinicians hope to derive quantitative features from these images that can make more accurate diagnoses, guide patient-specific treatment options, and potentially predict tumor behavior with respect to treatment response and survival[12]. As an example, radiomics may help distinguish that the lung nodule in Figure 1 is a malignant adenocarcinoma of the lung with more metastatic potential than the larger lung nodule seen in Figure 2, which is a less aggressive typical carcinoid. Clinicians using this technology could become modern day Cassandras. Greek mythology explains that Cassandra was gifted with the knowledge of future events. Radiomics offers the ability for fortune telling through a modern crystal ball of radiology and computational informatics.

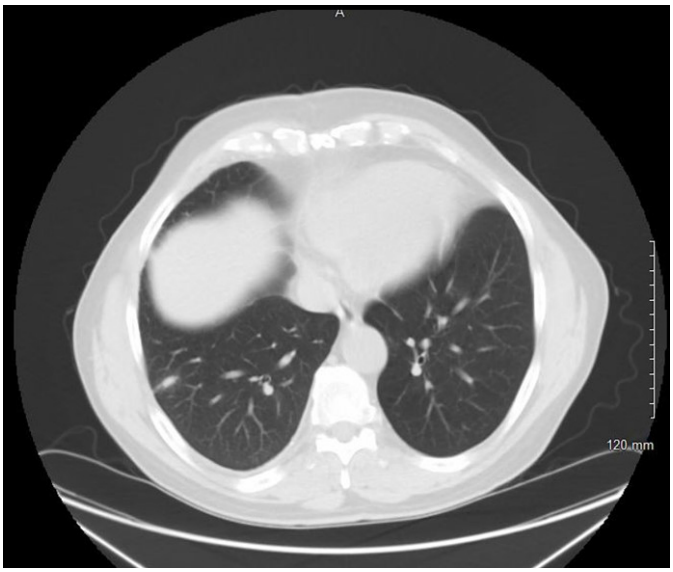

Figure 1. Adenocarcarcinoma of the lung.

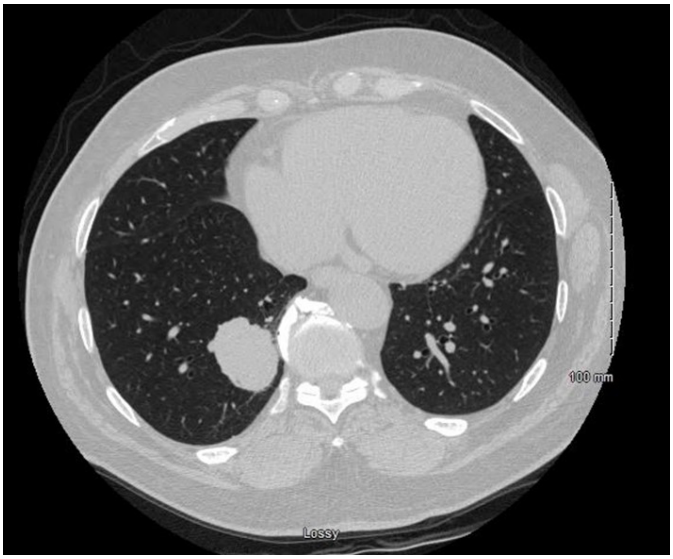

Figure 2. Carcinoid tumor of the lung.

CT images are digital images that consist of pixels when viewed in 2 dimensions and voxels when viewed in 3 dimensions. Radiomic features are derived from the pixels and can be subdivided into four distinct groups (statistical, model-based, transform-based, and shape-based)[13]. Statistical based features such as grey-level mean, max, min, variance, and percentiles are based on a single pixel, or voxel analysis. Gray-level cooccurrence matrix (GLCM), gray-level size zone matrix, gray-level run-length matrix (NGTDM), and neighborhood gray-level dependence matrix evaluate the spatial relationship of multiple voxels[7]. Fractal analysis, a model-based feature, illustrates the structural detail of a lesion with improved resolution. A transform-based feature is wavelet decomposition, which involves passing the image through multiple filters[14]. Many of these parameters describe the "texture" of the region of interest. In essence, they are describing the changes in the grayscale (neighboring pixels) within the region being evaluated. Deriving radiomic parameters is beyond the scope of our analysis, and we refer the reader to the references cited. We

aim to evaluate the feasibility, identify possible applications, and project a future for radiomics in the field of thoracic surgery.

RADIOMICS ANALYSIS

Pathologic diagnoses have previously been established with tissue biopsies. Peripheral endobronchial ultrasound with a fine needle aspiration is frequently used as a diagnostic modality for central nodules that can be identified. However, Gerlinger *et al.*[15] showed that random samples of tumor tissues acquired through this method may fail to accurately represent the breadth of biological variation within tumors. Radiomics are able to extract a substantially greater number of nodule features with much better reproducibility compared to CT and PET/CT scans[16]. Radiomics attempts to identify quantitative imaging characteristics from images in order to non-invasively predict the behavior of tumors[17,18]. This genomic heterogeneity is inadequately evaluated via CT or PET/CT because of the partial volume effect[19,20]. The heterogeneity of a tumor as a result of variations in gene expression is a common feature of malignant tumors[21-24]. Petkovska *et al.*[25] in 2006 showed that GLCM extracted from contrast-enhanced CT scans can accurately identify malignant from benign nodules more accurately than three experienced radiologists. A nodule's volume doubling time can estimate the likelihood of malignancy as indicated in the NELSON trial[26]. This method requires proper surveillance and a longer amount of time prior to official diagnosis than the use of radiomics. Hawkins *et al.*[27] identified 23 stable features that could predict nodules that would become cancerous 1 and 2 years hence with accuracies of 80% and 79%.

When Lee *et al.*[28] 2014 used texture analysis in combination with clinical and CT features; differentiating power between benign and malignant lesions increased significantly compared to clinical and CT features alone. Analysis of these nodules has the potential to identify pathognomonic features of malignant disease. Kido *et al.*[29] 2002 showed that the fractal dimensions for bronchogenic carcinomas were significantly smaller than pneumonias and tuberculomas ($P < 0.0001$). Other studies were able to identify radiomic features specific for EGFR mutant *vs.* wild type groups and K-ras mutations[30-32]. CANARY, an application designed to stratify lung adenocarcinoma into aggressive and minimally invasive, uses nine representative characteristics to identify the patient's histopathology[33]. Dong *et al.*[34] 2013 found standardized uptake value (SUV), maximum standardized uptake value (SUV MAX), GLCM-entropy, and GLCM-energy were found to be significantly correlated with T and N stage.

Predictive models that combined radiomic features significantly improved the prediction of pathologic response to therapy, according to Yang *et al.*[35] 2014. This was further supported by Cook *et al.*[36] in 2013, who found that neighborhood gray tone difference matrix (NGTDM) derived coarseness, busyness, and contrast could predict response to chemoradiotherapy better than SUVs as reported by a PET/CT scan. Additionally, Coroller *et al.*[37] in 2016 identified seven radiomic features that were predictive for pathologic gross residual disease and one for pathologic complete response. Wang *et al.*[38] identified eight features using LASSO Cox analysis to develop a radiomic signature used to predict recurrence-free survival. They found that histology ($P < 0.001$) and their radiomics signature ($P < 0.001$) were independent prognostic factors for recurrence free survival. The advantages of radiomics are clear as it would obviate the need for biopsies, which are invasive and often unsuccessful. Using radiomics to predict genomic data (radiogenomics) would allow better profiling of tumors as sampling errors would potentially be avoided as well as for the need for re-biopsy as tumors change in response to therapy over time.

RADIOMICS IN THE FUTURE

Although there is considerable promise in the field of radiomics, there are clear challenges in the burgeoning field. There is considerable variation in the conduct of radiologic examinations. Variation can

occur not only among different institutions and machines but also on the same machine on successive scans[16]. Radiologic exam variation can make interpretation of the data challenging generating too much noise to differentiate any meaningful clinical parameters. Terminology for various radiomic metrics is also incompletely standardized, leading to inconsistencies in data collection and interpretation. Many radiomic features are redundant, which can lead to both overfitting and underfitting[7]. Overfitting occurs when a model with a large dataset and a high degree of freedom remembers all data points, thus making it more difficult to differentiate disease-specific features from noise; underfitting creates an overly simplistic model. Published radiomic studies often have small sample sizes that lack a separate validation dataset to test the constructed model. Clinical relevance of radiomic models is often lacking with poor collaboration between clinicians and modelers.

As radiomics continues to evolve and become more widely accepted, additional prospective studies will be required to evaluate its feasibility. Large trials such as the National Lung Cancer Screening Trial (NLST) and lung cancer databases such as Qualitative Imaging Network (QIN), National Cancer Institute (NCI), and others could be mined to uncover possible associations between imaging characteristics and tumor histopathology. Standard acquisition parameters and image processing methods should be adopted; some studies recommend small voxels, narrow gaussian postfiltering, and point-spread function modeling[39,40]. Additionally, inter-observer variability will need to be optimized as this is a common variation within the field of radiation oncology. Pavic *et al.*[41] evaluated the impact of inter-observer variability on the accuracy and generalizability of radiomic results. They found that manual tumor delineation was variable and observer-dependent, thus leading to a reduction in the number of applicable radiologic features. Deep learning networks avoid the need to manipulate images to identify radiomic criteria personally. These neural networks are taught to identify and discriminate between objective data points within the image. Using deep learning, da Silva *et al.*[42] were able to identify small lung nodules with an accuracy of 97.6%. In combination with radiomics, features identified by a pre-trained deep learning network were 90% accurate in the prediction of survival of patients with adenocarcinoma[43]. Avanzo *et al.*[44] postulate that deep learning will "facilitate faster clinical translation of lung cancer radiomics" given the unmet clinical need for lung cancer diagnosis and surveillance.

Due to the increased surveillance of lung nodules and trials such as the NLST, the use of segmentectomy over lobectomy for early-stage non-small cell lung cancer has become more widely accepted[45-53]. Segmentectomies are notoriously difficult because of the lack of anatomic differentiation of bronchioles and vasculature. A pilot study out of the Netherlands showed the feasibility of a virtual reality-based application that uses artificial intelligence to preoperatively plan a segmentectomy[54]. Four of the ten patients evaluated in this study were found to have final pathology that was discordant with preoperative diagnosis, which could be clinically significant. One patient's final pathology was benign, while the preoperative diagnosis was suspicious for metastasis. Intraoperatively, through the use of indocyanine green, intersegmental borders can be identified, as shown by Iizuka *et al.*[55]. These platforms could change the way that patients are preoperatively evaluated and provide a more patient-specific resection.

CONCLUSION

Radiomics is a developing field that has the potential to radically change the diagnosis and management of lung nodules and lung cancer. However, the power of Cassandra comes with a potential problem. Cassandra was cursed by Apollo, who prevented others from believing her prophecy. Will clinicians and patients believe the diagnoses and treatment algorithms predicted by radiomics? Or will they still require a tissue diagnosis? Will the predictive power of radiomics lead to other unintended consequences known or unknown? Regardless, advances in imaging technology, computational power, and artificial intelligence will

hopefully drive the field forward to create a powerful clinical useful modality.

DECLARATIONS

Authors' contributions

Made major contributions to the conception, drafting, and editing of the manuscript: Decker JM
Conception and editing of the manuscript: Sesti J
Made major contributions to the editing and formating of the manuscript: Turner AL
Supervised the conception, writing, and editing of the manuscript: Paul S

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Not applicable.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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