Original Investigation

Radiologist Engagement as a Potential Barrier to the Clinical Translation of Quantitative Imaging for the Assessment of Tumor Heterogeneity

Kenneth Alan Miles, MBBS, MSc, MD, Julia Squires, DSR(D), Michelle Murphy, MBBS

Abbreviations and Acronyms

CT
computed tomography

CTTA
computed tomography texture analysis

MDT
multidisciplinary team

NSCLC
non–small cell lung cancer

PACS
picture archiving and communicating systems

PET
positron emission tomography

RE-AIM
Reach, Effectiveness, Adoption, Implementation, and Maintenance

Rationale and Objective: This study aims to identify potential barriers to the clinical implementation of quantitative imaging for the assessment of tumor heterogeneity.

Materials and Methods: An 18-month prospective observational study was undertaken in which the clinical implementation of computed tomography texture analysis (CTTA) as a technique for quantifying tumor heterogeneity in patients with non–small cell lung cancer was assessed using the Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) framework.

Results: Adopters of the technology comprised five specialists with dual accreditation in radiology and nuclear medicine supervising two trainees. Tumor heterogeneity information was extracted and reported in 190 of 322 eligible cases (59%) and presented at the multidisciplinary team meeting in 124 of 152 patients (82%) for whom CTTA had been performed. The maximum proportion of eligible cases in which heterogeneity information had been extracted and reported in any quarter was 80%, but fell in the latter half of the study. The maximum frequency with which available CTTA results were presented at the multidisciplinary team meeting in any quarter was 92% and was maintained in the latter part of the study. Significant differences in survival were observed for patients categorized using the two reported CTTA values ($P = 0.004$ and $P = 0.0057$, respectively).

Conclusions: Radiologist engagement is a potential barrier to the effective translation of quantitative imaging assessments of tumor heterogeneity into clinical practice and will need to be addressed before tumor heterogeneity information can successfully contribute to clinical decision making in oncology.

Key Words: Quantitative imaging; tumor heterogeneity; translational research; oncology.

INTRODUCTION

Genomic and phenotypic heterogeneities are recognized features of malignancy that have prognostic significance and potential impact on treatment response (1). It is increasingly acknowledged that this biological heterogeneity is also represented within images produced by a range of routine diagnostic tests (2–4). A key aspect of tumor heterogeneity is the coexistence of genetically distinct subclones within a single tumor that is a consequence of underlying genetic instability (1). The ability of imaging to depict these subclones is reinforced by the cumulative identification of imaging correlates for a range of genomic aberrations in different tumor types (5), and by data from biopsy studies confirming the spatial separation of subclones to be sufficiently large for detection by imaging (1). Nevertheless, information reflecting tumor heterogeneity is rarely included in clinical reports from diagnostic imaging tests in oncology and, if included, is typically

Acad Radiol 2017; ■:■■–■■

From the Department of diagnostic imaging, Princess Alexandra Hospital, Brisbane, Australia (K.A.M., J.S.); Institute of Nuclear Medicine, University College London, London, UK (K.A.M.); Department of thoracic medicine, Princess Alexandra Hospital, Brisbane, Australia (M.M.). Received July 14, 2017; revised November 3, 2017; accepted November 24, 2017. Funding: This work was supported by a grant from Feedback Plc, United Kingdom. **Address correspondence to:** K.M. e-mail: kenneth.miles@ucl.ac.uk

https://doi.org/10.1016/j.acra.2017.11.019

expressed in subjective descriptive terms rather than quantitative measures.

There is considerable potential for quantitative imaging of tumor heterogeneity to contribute to the clinical care of patients with cancer. Possible applications include the characterization of lesions as benign or malignant, for instance, in the evaluation of pulmonary nodules (4). For lesions known to be malignant, imaging measures of heterogeneity can potentially provide correlates for biological features such as gene mutations when tissue-based assays are contraindicated or have failed (4–7). Heterogeneity measures may also be useful in providing an indication of tumor aggression as illustrated by the association of heterogeneity within computed tomography (CT) images of primary lung cancers with the likelihood of mediastinal metastases (8) and overall prognosis (6,7,9–11). Heterogeneity imaging can also potentially provide an indication of likely response to treatment. The application of quantifiable imaging characteristics as indices for disease status has a number of advantages over tissue-based assays. Imaging has an established role in cancer management, and tumor heterogeneity measurements can frequently be obtained as part of routine diagnosis. Imaging is noninvasive and can therefore be repeated at different stages during the evolution of the disease or treatment. Being closely related to the tumor phenotype, imaging assessments of tumor heterogeneity can provide information that is complementary to gene-based assays (12).

Although there has been much research interest in the use of a range of imaging techniques for the assessment of tumor heterogeneity, there are significant translational gaps that must be crossed before these techniques can be routinely used to guide clinical decisions for patients of cancer. A synopsis of the adoption pathway for imaging technologies after manufacturer development has recently been published in a white paper produced by the Radiology Research Alliance Task Force on Translating New Imaging Technologies into Clinical Practice (13). This document highlights the importance of considering not only workflow and training requirements but also stakeholder engagement in both the early adoption and broad adoption phases. The integration of tumor heterogeneity imaging into clinical workflows also faces a number of technical challenges, including the development of user-friendly software for image analysis and data extraction, ease of incorporation of results into clinical reports, and seamless integration with picture archiving and communicating systems (PACS). Unless tumor heterogeneity information can be extracted and reported efficiently, and consistently made available at the point of clinical decision making (eg, multidisciplinary meetings), and interpretable by decision makers, it is unlikely that the measurements will be adopted into routine clinical practice. It is therefore essential that such practical issues around the incorporation of tumor heterogeneity imaging into routine workflows are addressed.

Methods for evaluating the ability of quantitative imaging techniques to meet the practical requirements for incorporation into clinical workflows are underdeveloped. However, approaches that have been proposed for the assessment of other forms of clinical informatics interventions are likely to be equally suited to the translation of the imaging informatics interventions encompassed by the image processing, data extraction, and reporting aspects of quantitative imaging for tumor heterogeneity. One such approach is the Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) framework (14). RE-AIM evaluates five domains that relate to health interventions: (1) the extent to which the intervention reaches the target population, (2) the effectiveness of the intervention, (3) the extent to which the intervention is adopted, (4) the implementation of the intervention, and (5) the maintenance of the intervention over time. Using computed tomography texture analysis (CTTA) for the assessment of heterogeneity within non–small cell lung cancers (NSCLCs) as a test case, the present study aimed to use the RE-AIM framework to identify potential barriers to the clinical implementation of quantitative imaging assessments of tumor heterogeneity.

MATERIALS AND METHODS

Study Design and Setting

This health implementation research project comprised a prospective observational study undertaken in the diagnostic imaging and respiratory medicine departments of a tertiary oncology center. The evaluation focused on the incorporation of quantitative assessments of tumor heterogeneity into clinical workflows and the subsequent delivery of heterogeneity information to the multidisciplinary team (MDT) meeting at which clinical decisions were made. However, it was not intended that imaging assessments of tumor heterogeneity should contribute to clinical decision making during the evaluation. The institutional ethics committee had therefore waived the need for individual patient consent as the study entailed no change in treatment or other medical intervention.

Patient Population and Imaging Technique

The quantitative imaging method for assessing tumor heterogeneity adopted in the present study was CTTA, which has been shown to be related to the risk of mediastinal metastasis and overall prognosis for patients with NSCLC. The reasons for this selection were (1) the high incidence of NSCLC; (2) the established role of CT in the clinical management of patients with this tumor, including routine presentation of imaging findings at the MDT meeting; (3) the ability to extract heterogeneity information from images currently acquired in routine clinical practice, thereby avoiding the need for additional imaging procedures; and (4) increasing research evidence for the prognostic value of CTTA in this patient population (6–11). CTTA parameters were derived using TexRAD software (Feedback, Cambridge, UK), which implements the filtration-histogram method (15). Two CTTA parameters for a filtration value of 4 mm were reported: kurtosis and entropy. Based on a review of the literature and confirmed by local