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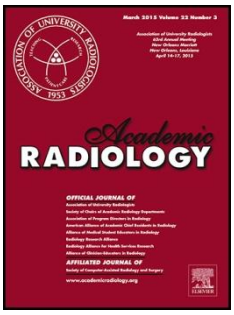

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RADIOLOGIST ENGAGEMENT AS A POTENTIAL BARRIER TO THE CLINICAL TRANSLATION OF QUANTITATIVE IMAGING FOR THE ASSESSMENT OF TUMOR HETEROGENEITY

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Abstract:

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

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

Results: Adopters of the technology comprised 5 specialists with dual accreditation in radiology and nuclear medicine supervising 2 trainees. Tumor heterogeneity information was extracted and reported in 190 of 322 (59%) eligible cases and presented at the MDT meeting in 124 of 152 (82%) patients 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 MDT 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 ($p = 0.004$ $p = 0.0057$ 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

Abbreviations:

CT: Computed Tomography

CTTA: Computed Tomography Texture Analysis

MDT: Multi-disciplinary Team

NSCLC: Non-Small Cell Lung Cancer

PACS: Picture Archiving and Communicating Systems

PET: Positron Emission Tomography

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

Introduction:

Genomic and phenotypic heterogeneity 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 co-existence of genetically distinct sub-clones within a single tumor that is a consequence of underlying genetic instability [1]. The ability of imaging to depict these sub-clones 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 sub-clones 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 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 contra-indicated or have failed [4-7]. Heterogeneity measures may also be useful in providing an indicate of tumor aggression as illustrated by the association of heterogeneity within 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 non-invasive 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 stake-holder 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, consistently made available at the point of clinical decision making (e.g. multi-disciplinary 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 RE-AIM framework [14]. RE-AIM evaluates five domains that relate to health interventions: a) the extent to

which the intervention reaches the target population, b) the effectiveness of the intervention, c) the extent to which the intervention is adopted, d) the implementation of the intervention, and e) the maintenance of the intervention over time. Using CT texture analysis (CTTA) for assessment of heterogeneity within non-small cell lung cancers (NSCLC) as a test case, this study aims to use the RE-AIM framework to identify potential barriers to the clinical implementation of quantitative imaging assessments of tumor heterogeneity.

Materials & 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 multi-disciplinary 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 & Imaging Technique*:* The quantitative imaging method for assessing tumor heterogeneity adopted in this study was CT texture analysis (CTTA) which has been shown to be related to risk of mediastinal metastasis and overall prognosis for patients with Non-Small Cell Lung Cancer (NSCLC). The reasons for this selection were: a) the high incidence of NSCLC, b) the established role of CT in the clinical management of patients with this tumour, including routine presentation of imaging findings at the MDT meeting, c) the ability to extract heterogeneity information from images currently acquired in routine clinical practice, thereby avoiding the need for additional imaging procedures, and d) 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 filtration value 4mm were reported: kurtosis and entropy. Based on a review of the literature and confirmed by local audit, the parameter thresholds above which values were considered to indicate poor prognosis were 0 and 4.57 respectively.

Clinical Workflow: The clinical workflow is summarized in figure 1. The source images for heterogeneity analysis comprised the low-dose CT component of Positron Emission

Tomography/Computed Tomography (PET/CT) examinations obtained without intravenous contrast enhancement. Following acquisition, these images were transferred to PACS. The radiologist reporting the PET/CT examination selected on PACS the CT image displaying the maximum cross-sectional area of the tumor and exported the image to dedicated software (TexRAD, Cambridge, UK) for extracting a range of parameters that reflect tumor heterogeneity. The image analysis technique used has been described in detail elsewhere [16]. The heterogeneity information was then incorporated into the PET/CT report prepared and stored using the Radiology Information System (RIS). The MDT co-ordinator retrieved the heterogeneity information from the RIS for entry into the cancer registry database and display at the MDT.

Stakeholder Engagement: The initial two stages in the figure involving the technical staff required no novel or additional input, since the necessary images were already acquired and archived as part of the standard protocol. The subsequent three stages represented additions to the routine clinical workflow for the reporting radiologists. To facilitate successful incorporation of these activities into the workflow, the radiologists received individual demonstrations of the image analysis process and an information sheet outlining the study background and aims (see appendix 1A), backed up by a summary electronic slide presentation installed onto each reporting computer terminal. Adoption of the required procedures was further encouraged by providing a fast and reliable image analysis system, a reporting template within the RIS (See Appendix 2), add access to ongoing advice and troubleshooting to solve any issues promptly. Referring clinicians were also given a short induction along with an information sheet tailored to their discipline (Appendix 1B).

Outcome Measures: The outcome measures for each RE-AIM domain are listed in table 1. The measures of Reach and Implementation were recorded every 3 months for 18 months. Trends in these measures over time provided the assessment of maintenance. Effectiveness was assessed following review of the clinical records at the end of the study period to

determine patient survival. Kaplan-Meier survival analysis was used to compare the survival of patients with CTTA parameters above and below the prescribed threshold values. Adoption was evaluated for the whole study period, supplemented by surveys of the radiologists' opinions regarding their involvement conducted by interview shortly after study commencement and twelve months later. The surveys were semi-structured comprising pre-determined areas for discussion during which radiologists' comments were evaluated qualitatively with no quantitative scoring of opinions.

Results:

Reach: Over the 18-month study period, quantitative tumor heterogeneity information was extracted and reported in 190 of 322 (59%) eligible PET/CT examinations. The reasons identified for failure to analyze or report the CTTA values comprised a) uncertainty as to whether a histological diagnosis was required for inclusion in the study, technical failure with the software preventing its application at the time of reporting, and reporting being performed by new or temporary doctors who were unaware of the study and the need to include heterogeneity information within the PET report.

Effectiveness: Survival data was available in 150 patients of whom 31 had died. Patients with tumor kurtosis values above the threshold of 0 (n=78) and/or entropy values above the threshold of 4.57 (n=99) demonstrated significantly poorer survival ($p = 0.004$ and $p = 0.0057$ respectively, figure 2).

Adoption: The radiologists extracting and reporting the tumor heterogeneity information comprised 5 specialists with dual professional accreditation in radiology and nuclear medicine, and 2 specialist trainees working under their supervision. These specialists had been targeted because the additional training in nuclear medicine was considered likely to have increased competencies in quantitative imaging principles relevant to the clinical implementation of tumor heterogeneity imaging.

The surveys conducted with the Radiology staff confirmed a high level of understanding of the aims of the project with all Radiologists expressing the view that the provision of information on tumor heterogeneity for patients was appropriate to their specialty. After 12 months of extracting and reporting tumor heterogeneity information, radiologists unanimously expressed the view that automation of the image analysis software would likely encourage adoption. The surveys also identified two factors that could impact negatively on adoption: a) lack of confidence in using the image analysis software due to insufficient training, and b) workload pressure and staff shortages.

Implementation: 152 patients for whom CTTA results had been reported were discussed at the MDT. Of these patients, the tumor heterogeneity information was presented in 124 (82%). No specific reasons for failing to present available CTTA results were identified.

Maintenance: Figure 3 displays the quarterly trends for the measures of Reach and Implementation. The measure for Reach rose progressively over the first three quarters of the study, achieving a maximum value in the third quarter when the proportion of eligible low-dose CT examinations for which heterogeneity information was extracted and reported was 80%. However, this level of Reach was not maintained over the subsequent 9 months. The low value for Reach of 59% observed in the 5th quarter coincided with a change in junior reporting radiologists. There was no other change in reporting radiologists during the study period.

The outcome measure for Implementation rose progressively to a maximum value in the fifth quarter when the proportion of patients with CTTA analysis results available for whom the data was presented at the MDT was 92%. This level of implementation was maintained in the sixth quarter.

Discussion:

Although a number of research studies have shown the potential for quantitative imaging of tumor heterogeneity to contribute to the care of patients with cancer, our study has highlighted a range of issues that may be encountered when translating these research findings into routine clinical practice. The principal constraint to effective incorporation of the heterogeneity imaging into clinical workflows in our study was inconsistent performance of image analysis and/or reporting of the CTTA results by radiologists. Despite provision of induction materials and individual training, heterogeneity data was extracted and reported for only 59% of eligible low-dose CT examinations. It seems probable that training requirements for effective use of the technology had been underestimated. The maximum value for Reach was only achieved after 9 months with heterogeneity data extracted and reported in 80% of eligible cases. However, this level of performance was not maintained in subsequent quarters. This finding implies a need to update training of radiologists at regular intervals and to repeat the induction and training for new staff, even those supervised by radiologists who have already undergone training. Higher levels of Reach and improved Maintenance might be achievable with better integration of the image analysis software into PACS and by greater automation of image analysis. It may also be helpful for the MDT coordinator to send to the reporting radiologists on the day prior to the MDT, a list of the patients for whom information on tumor heterogeneity will be required at the forthcoming meeting.

The two CTTA parameters reported in this study both demonstrated a statistically significant relationship with survival using the cut-off thresholds pre-determined by review of published literature and local audit. However, the levels of statistical significance we observed were lower than those reported previously [7,9]. Establishment of local cut-off thresholds could potentially improve the effectiveness of tumor heterogeneity imaging but would increase the complexity of implementation on account of the need to determine optimum local cut-off thresholds in a training cohort before introduction of the technology into clinical workflows.

The supervising radiologists applying the quantitative CT imaging technology in our study reported high levels of motivation at interview and all had prior experience and training in quantitative imaging. Lower rates of extraction and reporting of heterogeneity information may be anticipated if this technology were to be adopted by less specialized radiologists.

Presentation of tumor heterogeneity imaging results at the MDT is essential if the technology is to impact on clinical decision making. No significant block to presentation of quantitative imaging data was observed in our study and high levels of implementation were maintained in the latter half of the study.

We are unaware of any prior studies that have used the RE-AIM framework to assess the clinical implementation of quantitative imaging techniques. Heterogeneity imaging represents just one of a wide range of methods for quantitative tumor assessment and issues affecting implementation will to some extent be specific to each technique. CTTA entails the extraction of heterogeneity data from a region of interest constructed using an image already acquired in clinical practice and is therefore more straightforward to implement compared to other quantitative imaging methods which may require multiple analyses and/or dedicated image acquisitions. It is likely that the RE-AIM indicators for more complex imaging analysis approaches would be lower than those observed in our study.

Conclusion:

Our study suggests that particular attention to radiologist engagement will be required for effective translation of quantitative imaging assessments of tumor heterogeneity into clinical practice. The translation of quantitative imaging of tumor heterogeneity into clinical practice entails a significant departure from current radiological practice which needs to be addressed before tumor heterogeneity information can successfully contribute to clinical decision making in oncology.

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Figure Legends:

Figure 1: Summary of the clinical workflow. The text boxes indicate the equipment and staff members involved for each stage.

Figure 2: Prognostic performance of CTTA illustrated by Kaplan-Meier survival curves for patients classified by (A) kurtosis = 0 and (B) entropy = 4.57.

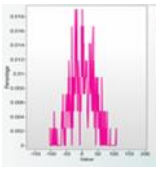
Figure 3. Trends in outcome measures for Reach and Implementation from June 2015 to November 2016.

Figure 4.

Tables: Summary of outcome measures for each RE-AIM domain. (CTTA: CT texture analysis, MDT: Multi-Disciplinary Team)

Domains	**Outcome measure**
Reach	Proportion of eligible cases for which quantitative information on tumor heterogeneity was extracted and reported.
Effectiveness	Comparison of the survival of patients with CTTA parameters above and below the prescribed threshold values.
Adoption	The number and representativeness of radiologists extracting quantitative information on tumor heterogeneity from CT
Implementation	Frequency with which available quantitative information on tumor heterogeneity is presented at the MDT meeting
Maintenance	Change in reach, adoption and implementation measures over time.

APPENDIX 1A : INFORMATION SHEET FOR RADIOLOGISTS



CT Texture analysis in NSCLC.

Information for Radiologists :

The Aim of the Study: The aim is to assess the potential clinical benefit of using CT texture analysis (CTTA) as a tool for improving the prediction of patient prognosis and treatment response in NSCLC.

Retrospective analysis of data from P.A.H. patients has so far shown good correlation with that acquired in the U.K. as regards the relationship between the texture of lung tumours and tumour histopathology.

The process :

A software package will be installed on all reporting stations used by those radiologists reporting PET/ CT scans. It will be straightforward and fast to use.

A filtration / histogram method of analysis is applied to the low-dose CT image already acquired as part of all PET / CT torso examinations for NSCLC patients.

A single CT slice that best demonstrates the tumour is selected.

- A region of a preselected size is drawn.
- The region is filtered and image features highlighted.
- A histogram of the ROI is produced with four primary definitive parameters :
    1. Mean – average pixel value
    2. Standard deviation – dispersion from the average pixel value.
    3. Skewness – asymmetry of the histogram shape.
    4. Kurtosis – sharpness of the histogram peak.

It is proposed to use kurtosis as the reported descriptor. A higher kurtosis is an indicator of a more adverse outcome.

Discussion :

The initial role of Radiology in diagnosis and staging of NSCLC patients, and its subsequent role in assessing treatment response and recurrent disease, mean that radiological reports are indispensible to those clinicians determining the most appropriate course of action.

CTTA is proving to be an accurate non-invasive biomarker that quantifies heterogeneity within a lung tumour, improving the current subjective interpretation of this parameter.

Results of studies so far performed into its significant potential applications in NSCLC include

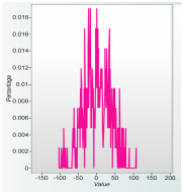
- Improved risk stratification for overall survival.
- Prediction of response to neoadjuvant and adjuvant chemotherapy.
- Identification of patients at high risk of recurrence enabling targeting of higher intensity surveillance post therapy..
- Correlation with histopathologic markers of tumour hypoxia and angiogenesis.
- Simplification of the molecular characterisation of tumour type required in the fast expanding field of individually targeted molecular therapies.

Feedback and follow-up:

The reporting radiologists will be consulted regarding their use of the CTTA software and any issues addressed.

Responses will be sought from the multi-disciplinary clinicians both personally and through the lung MDT, to assess their opinions and their use of the CTTA analysis figures.

APPENDIX 1B : INFORMATION SHEET FOR REFERRING CLINICIANS



CT Texture analysis in NSCLC

Information for Clinicians :

The Aim of the Study : The aim is to assess the potential clinical benefit of using CT texture analysis (CTTA) as a tool for improving the prediction of patient prognosis and treatment response in NSCLC.

CTTA quantifies the heterogeneity within tumours, and a retrospective analysis of data from P.A.H. patients has so far shown good correlation with that acquired in the U.K. as regards the relationship between the texture of lung tumours and tumour histopathology.

It is proposed that reporting radiologists will apply CTTA analysis to the low dose CT already acquired as part of every PET/CT examination requested for NSCLC patients, and figures derived from this will be included in the report for the referring clinicians.

No extra imaging is required over and above that for which the patient is already scheduled, no IV contrast required, and no additional radiation dose incurred.

The method :

A single CT slice that best demonstrates the tumour is selected.

A histogram of a tumour region of interest is produced with four primary definitive parameters :

1. Mean – average pixel value
2. Standard deviation – dispersion from the average value.
3. Skewness – asymmetry of the histogram shape.
4. Kurtosis – sharpness of the histogram peak.

It is proposed to use kurtosis as the reported descriptor.

A higher kurtosis is an indicator of a more adverse outcome.

Discussion:

Radiology plays an essential role in diagnosis and staging of NSCLC patients, and subsequently in assessing treatment response and recurrent disease.

CTTA is proving to be an accurate non-invasive prognostic and predictive biomarker that by quantifying heterogeneity within a lung tumour reduces the subjective interpretation of this parameter.

Results of studies so far performed into its significant potential clinical applications in NSCLC patients include :

- Improved risk stratification for overall survival.
- Prediction of response to neoadjuvant and adjuvant chemotherapy,
- Identification of patients at high risk of recurrence enabling targeting of higher intensity surveillance post therapy.
- Correlation with histopathologic markers of tumour hypoxia and angiogenesis.
- Simplification of the molecular characterisation of tumour type required in the fast expanding field of individually targeted molecular therapies.

Feedback and follow-up:

Responses will be sought from the multi-disciplinary clinicians both personally and through the lung MDT, to assess their opinion and the assistance they may gain from the CTTA analysis figures.

APPENDIX 2: QUANTITATIVE IMAGING FOR TUMOR HETEROGENEITY REPORTING TEMPLATE

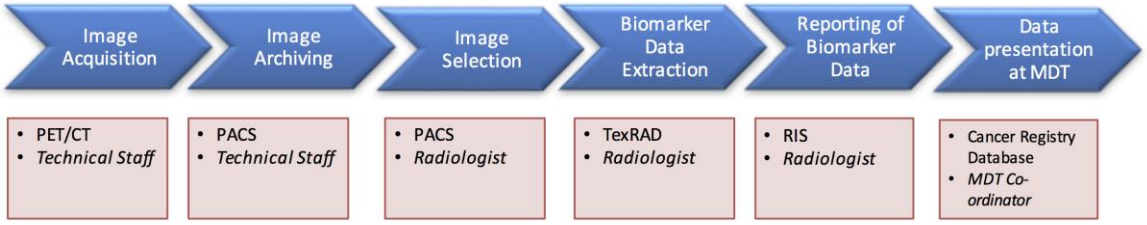
Prognostic Imaging Features from CT Texture Analysis:

(for research use, only applicable to non-small cell lung cancer, NSCLC)

Kurtosis [...]

Entropy [...]

Data from the Princess Alexandra Hospital and overseas indicate that for NSCLC, positive kurtosis and/or entropy values > 4.57 are associated with poorer survival.



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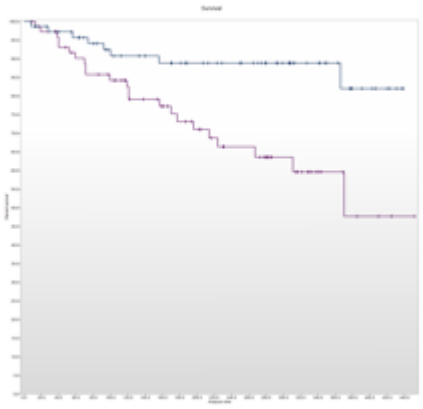

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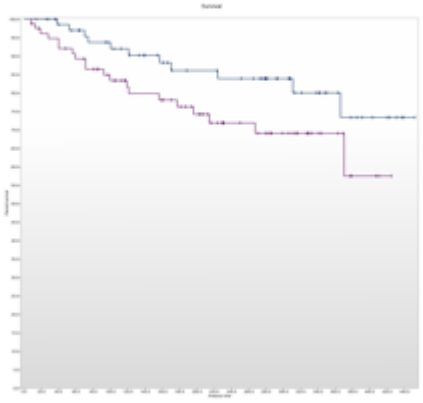

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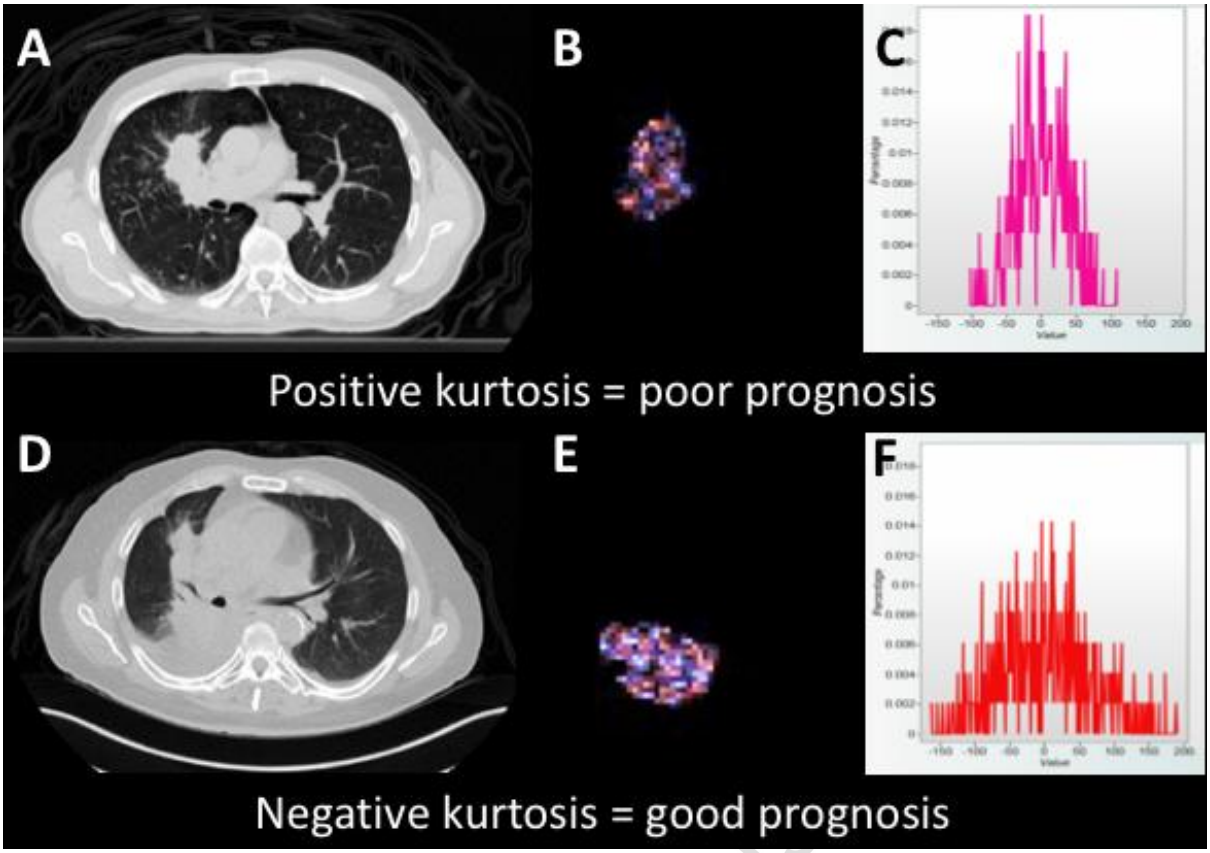

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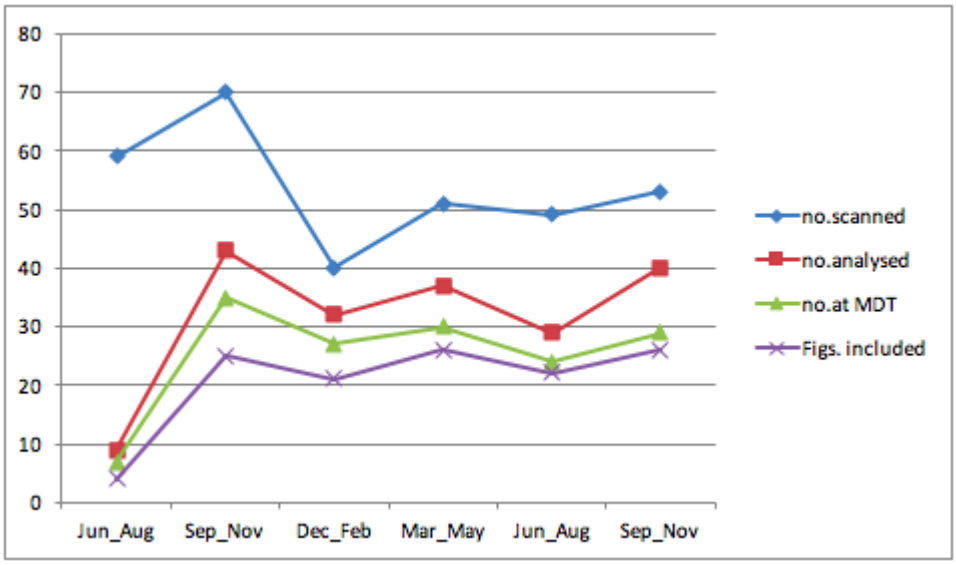

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