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PET-Guided CT Radiomics for Characterizing Multiscale Intratumoral Heterogeneity In Lung Cancer

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ABSTRACT

Purpose: To investigate whether PET-defined metabolic subregions within lung tumors exhibit distinct CT radiomic characteristics, allowing for spatially imaging-based assessment of intratumoral heterogeneity.

Methods: PET/CT scans from 27 lung cancer patients were analyzed retrospectively. Tumors were segmented into whole tumor, high-uptake (SUV ≥ 50% of SUVmax), and low-uptake (SUV ≤ 50% of SUVmax) regions. Using PyRadiomics, 1130 CT radiomic features were extracted from each scan, including original (107), wavelet (774), and Laplacian-of-Gaussian (LoG) filtered images (279). Habitat contrasts were defined as Δ = HighSUV – LowSUV. Paired Wilcoxon signed-rank tests were performed for each feature, and Benjamini-Hochberg false discovery rate (FDR) correction was applied, with tied ranks being averaged.

Results: Of the 1130 features, 213 (18.8%) differed between high- and low-uptake habitats at FDR ≤ 0.05, increasing to 511 (45.2%) at FDR ≤ 0.10. At FDR ≤ 0.05, significant contrasts were present across image types: 26/107 (24.3%) original, 119/774 (15.4%) wavelet, and 68/279 (24.4%) LoG features. Significant differences were present across feature families: first-order 52/216 (24.1%), GLCM 33/288 (11.5%), GLRLM 33/192 (17.2%), GLDM 40/168 (23.8%), GLSZM 43/192 (22.4%), and NGTDM 3/60 (5.0%). While shape features had a significance rate of 9/14 (64.3%), the low number of features available make the result vulnerable to random variability. The most robust examples (FDR q = 0.037) included LoG-sigma-3 SmallAreaEmphasis, LoG-sigma-5 LargeDependenceLowGrayLevelEmphasis, Wavelet-LHH SmallDependenceHighGrayLevelEmphasis, and original LargeDependenceLowGrayLevelEmphasis.

Conclusion: PET-defined metabolic subregions exhibit distinct CT radiomic signatures, with the strongest effects in original/LoG filtered feature sets and in first-order/texture families. PET-guided CT radiomics could, with a larger data set, provide spatially resolved, physics-informed approaches to quantifying intratumoral heterogeneity and motivate validation in larger cohorts and predictive response modeling.

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INTRODUCTION

Lung cancer remains a leading cause of cancer-related mortality worldwide, and intratumoral heterogeneity is increasingly recognized as an important determinant of treatment response and clinical outcome. Noninvasive imaging biomarkers capable of characterizing this heterogeneity may improve tumor phenotyping and support more personalized treatment strategies.

Hybrid positron emission tomography/computed tomography (PET/CT) provides complementary functional and anatomical information for tumor evaluation. ^18F-fluorodeoxyglucose (FDG) PET identifies regions of increased glucose metabolism that are often associated with more aggressive tumor biology, while CT provides detailed anatomical information. Radiomics enables quantitative characterization of CT images through the extraction of intensity, texture, and spatial features that have been associated with tumor phenotype and prognosis. However, most CT radiomics studies analyze the tumor as a single volume of interest, potentially overlooking biologically meaningful spatial heterogeneity.

Combining PET-defined metabolic habitats with CT radiomics provides an opportunity to determine whether metabolically distinct tumor subregions exhibit corresponding differences in CT imaging characteristics. Demonstrating such relationships could provide a more spatially resolved assessment of intratumoral heterogeneity and improve understanding of the structural correlates of tumor metabolism.

In this study, we investigated whether PET-defined high- and low-metabolic subregions within lung tumors exhibit distinct CT radiomic signatures. We compared radiomic features extracted from original and filtered CT images between metabolically defined habitats to evaluate whether CT radiomics can differentiate spatially distinct tumor phenotypes.

METHODS AND MATERIALS

- **Study cohort**: Pilot retrospective study of 27 lung cancer PET/CT scans.
- **Tumor segmentation**: Whole tumors segmented using the Grow from Seeds algorithm in 3D Slicer.
- **Habitat definition**: Tumors partitioned into:
  - High uptake: SUV ≥ 50% of SUVmax
  - Low uptake: SUV < 50% of SUVmax
- **Radiomics**: Extracted 1,130 CT radiomic features per subregion using SlicerRadiomics, including:
  - Original images
  - Wavelet-filtered images
  - Laplacian-of-Gaussian (LoG)-filtered images
  - First-order, shape, and texture feature families
- **Statistical analysis**: Paired Wilcoxon signed-rank test with Benjamini–Hochberg false discovery rate (FDR) correction for multiple comparisons

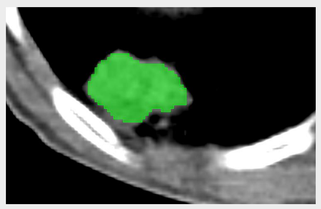


Figure 1. Full segmentation of a lung cancer tumor (CT scan)

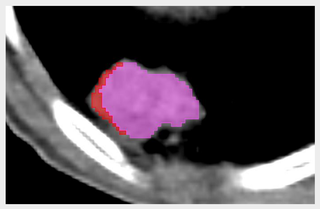


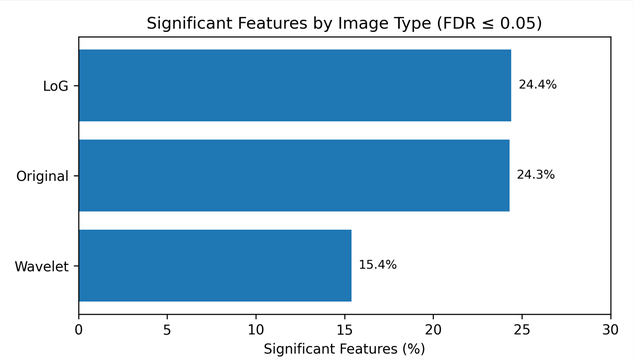
Figure 2. Segmentations of low SUV (red) and high SUV (pink) subregions

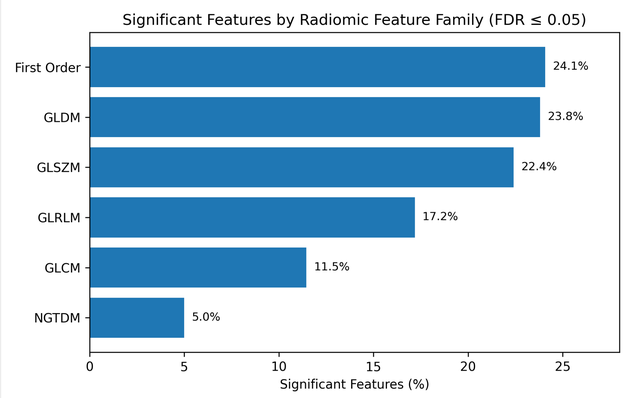
RESULTS

- Significant radiomic differences were identified between high- and low-SUV tumor subregions.
- 213/1,130 features (18.8%) were significant at FDR ≤ 0.05, increasing to 511/1,130 (45.2%) at FDR ≤ 0.10.
- By image type (FDR ≤ 0.05):
  - LoG: 24.4% significant
  - Original: 24.3%
  - Wavelet: 15.4%
- By feature family (FDR ≤ 0.05):
  - First-order: 24.1%
  - GLDM: 23.8%
  - GLSZM: 22.4%
  - GLRLM: 17.2%
  - GLCM: 11.5%
  - NGTDM: 5.0%
- Most robust features demonstrated an FDR q-value of 0.03

Percentage of Significant Features	
First order	24.07%
GLCM	11.46%
GLRLM	17.19%
GLDM	23.81%
GLSZM	22.40%
NGTDM	5.00%

Table 1. Graph representing the percent of features in each feature family that were significant at an FDR of 0.05.





DISCUSSION

- PET-defined metabolic habitats demonstrated distinct CT radiomic characteristics, indicating that metabolic heterogeneity is reflected in quantitative CT imaging features.
- The strongest differences were observed in first-order and texture features, suggesting that regional variations in CT intensity and texture are associated with differences in tumor metabolism.
- These findings support the use of habitat-based radiomics as a spatially resolved approach for characterizing intratumoral heterogeneity, beyond conventional whole-tumor analysis.
- As a pilot study with 27 patients, the results should be considered preliminary. Validation in larger, independent cohorts is needed to assess the robustness and clinical utility of these imaging biomarker

CONCLUSIONS

- CT radiomic features significantly differed between PET-defined high- and low-uptake tumor habitats.
- More than 200 radiomic features remained significant after multiple-comparison correction, demonstrating distinct quantitative imaging signatures across metabolic subregions.
- PET-guided CT radiomics shows promise as a noninvasive method for quantifying intratumoral heterogeneity.
- Future work will focus on validating these findings in larger cohorts and investigating their value for outcome prediction and personalized treatment planning.

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