

A NOVEL REPRODUCIBLE RADIOMICS FRAMEWORK ON PSMA PET/CT FOR LESION BURDEN QUANTIFICATION: TOWARD CLINICALLY ROBUST IMAGING BIOMARKER IN METASTATIC PROSTATE CANCER

Hadiseh Alimoradi¹, Kamran Aryana^{2*}, Seyed Pezhman Shirmardi³, Elham Saniei¹, Mehdi Salehi Barough¹**

¹Department of Medical Radiation Engineering, CT.C., Islamic Azad University, Tehran, Iran.

²Nuclear Medicine Research Center, Mashhad University of Medical Sciences, Mashhad, Iran.

³Nuclear Science and Technology Research Institute (NSTRI), Tehran, Iran.

**** Corresponding author Email:** Kamran Aryana, Aryanak@mums.ac.ir

Received: 24 October 2025

Revised: 29 November 2025

Accepted: 19 December 2025

ABSTRACT:

Background: Radiomics is a powerful approach in modern cancer management which offers significant potential to transform cancer management through quantitative non-invasive biomarkers in oncology and its clinical application of radiomics features. In metastatic prostate cancer, assessing disease burden is crucial for prognosis and treatment planning. However, it remains unclear whether reproducible radiomic features can reliably reflect lesion burden, including lesion number and total volume. This study developed a novel reproducibility-driven radiomics framework for PSMA PET/CT which evaluates the correlation between stable radiomic features and lesion burden.

Methods: In this retrospective study, patients with metastatic prostate cancer who underwent PSMA PET/CT were included. A predefined set of reproducible radiomic features, which had previously been validated for consistency, was extracted from the metastatic lesions. Lesion burden was defined by both the number of metastatic sites and cumulative lesion volume. Correlation analysis were performed using Pearson correlation to assess associations between radiomic features and lesion burden.

Results: A total of 117 metastatic prostate cancer patients were analyzed. The median age was 67.92 years. Several reproducible radiomic features demonstrated significant correlations with both lesion number and total lesion volume. The strongest associations were observed for Energy (abdominal lymph) with correlation coefficients ranging from 0.47

Conclusion: Our results show various relations between reproducible radiomic features derived from PSMA PET/CT are associated and lesion burden in metastatic prostate cancer. These findings support the potential role of radiomics as a non-invasive biomarkers for aggressiveness of disease. Furthermore, using Pearson correlation to analyze clinical relevance of these mentioned radiomics features, is an important consideration for users conducting radiomics studies in prostate cancer researches.

Keywords: Prostate cancer; Radiomics; PSMA PET/CT; Lesion burden; Reproducible features.

INTRODUCTION

Prostate cancer (PCa) is the most common cancer in male population and it is one of the leading causes of mortality worldwide(1). Disease progression in prostate cancer is frequently accompanied by bone metastases, causing in pain, fractures, and they decrease quality of life in PCa patients (2). Bone metastases is a clear sign of disease progression and it is an accurate detection essential for improving patient outcomes (3). As we know, the burden of metastatic disease evaluate by lesion number and total lesion volume which plays a key role influencing survival and therapeutic planning (4).

In recent years, advances in imaging technology have greatly improved our ability to detect and evaluate metastatic prostate cancer. Among these technologies, ⁶⁸Ga-PSMA PET/CT has emerged as an accurate tool for identifying PCa metastases (5). By integrating metabolic information from Positron Emission Tomography (PET) with the detailed anatomical imaging provided by Computed Tomography (CT), ⁶⁸Ga-PSMA PET/CT offers unparalleled accuracy in locating both lymph nodes and bone metastases, essential for precise staging and restaging (6). This combined imaging modality makes an informed approach by accurately mapping the extent of the disease (7).

However, despite the success of ⁶⁸Ga-PSMA PET/CT in detecting metastatic lesions, there is still a need to enhance how we quantitatively analyze these images.

Radiomics as a promising approach that extracts detailed quantitative information from medical images, offers new ways to describe tumor biology beyond what can be seen by the human eye (8). These features, including shape, texture, and intensity metrics, provide deeper information into tumor behavior. Such insights can be vital for understanding disease aggressiveness, predicting treatment response and ultimately, guiding prognosis (9). Reproducible radiomic features those with high stability across different imaging conditions, are specially valuable for clinical trials.

Although previous studies have demonstrated the utility of radiomics in prostate cancer for diagnosis, prognosis and treatment response evaluation, there is limited evidence regarding whether reproducible radiomic features correlate with clinical important indicators like lesion number and total lesion volume in metastatic prostate cancer. In this study, we aimed to develop a radiomics framework for PSMA PET/CT in metastatic prostate cancer. Specially, we investigated the association between reproducible radiomic features identified in our prior analysis across important metastatic sites and disease severity to provide valuable insights for the development of noninvasive and reliable imaging biomarkers, improve risk stratification, and use in clinical practice. We investigate this correlation by lesion burden which was defined by lesion number and total lesion volume across the metastatic regions of interest in PCa patients.

MATERIALS AND METHODS

Study Design

This retrospective secondary analysis of a previously collected dataset of metastatic PCa patients undergoing ⁶⁸Ga-PSMA PET/CT imaging at our center over two years prior to the study's initiation. Furthermore, this retrospective analysis used anonymized patient data and involved no direct intervention; therefore the need for informed consent was waived. The study protocol was approved by the institutional review board and conducted in accordance with the Declaration of Helsinki.

Population

A total of 117 patients with histopathologically confirmed PCa who exhibited positive results by ⁶⁸Ga-PSMA PET/CT imaging were included. Inclusion criteria were:

Patients who confirmed diagnosis of prostate cancer with metastatic lesions, availability of high quality imaging data. Patients with incomplete imaging dataset or poor image quality were excluded.

Imaging Protocol

All patients underwent ⁶⁸Ga-PSMA PET/CT imaging according to standardized protocol: All PET/CT imaging was conducted using a 64-slice Philips Ingenuity Time-of-Flight PET/CT scanner (Philips, USA). The CT acquisition parameters were configured to a tube voltage of 140 kVp, a tube current of 800 mA max, a matrix size of 512×512 , and a voxel size of $1.37 \times 1.37 \times 3.75$ mm³. PET imaging was performed with a matrix size of 256×256 , and the acquisition time was 90 seconds per bed position, encompassing 10 bed positions for a whole-body scan. The ⁶⁸Ga-PSMA radiotracer was administered intravenously at a dose of 2-2.2 MBq/kg, 60 minutes prior to image acquisition.

Lesion Segmentation and Quantification

Metastatic lesions were identified and manually segmented using 3D Slicer software (version 5.6.2; <https://www.slicer.org>) in our previous study. Radiomic features were extracted from segmented lesions using matRadiomics to integrate data from PyRadiomics, according to the Image Biomarker Standardization Initiative (IBSI) (10) (11).

In our prior research (currently under review), a set of reproducible radiomic features was identified through test-retest analysis with a comprehensive CoV analysis. These reproducible features were used in the current study for correlation analysis.

Definition and Calculation of Lesion Burden

In this study, lesion burden was defined as a composite measure of lesion number and total lesion volume derived from PSMA PET/CT images(12).

- Number of lesions: Total metastatic lesions counted by two independent readers via visual assessment and manual segmentation.
- Total lesion volume: Sum of the volumes of all segmented lesions calculated using semiautomatic segmentation tools in 15.44, expressed in cubic centimeters (cm³).

Quantitative parameters including mean, median, standard deviation and range were calculated for each metastatic region of interest. The summarized descriptive statistics are presented in Table 2.

This study provides a critical validation step in the radiomics pipeline, moving beyond feature identification to test the stability of correlations in a site-specific manner. Our central finding is that the relationship between reproducible radiomic features and Lesion Burden is not universal but is fundamentally constrained by anatomy. This has profound implications for the development of robust and generalizable radiomic models. Figure 1 illustrates the conceptual layout of the study design.

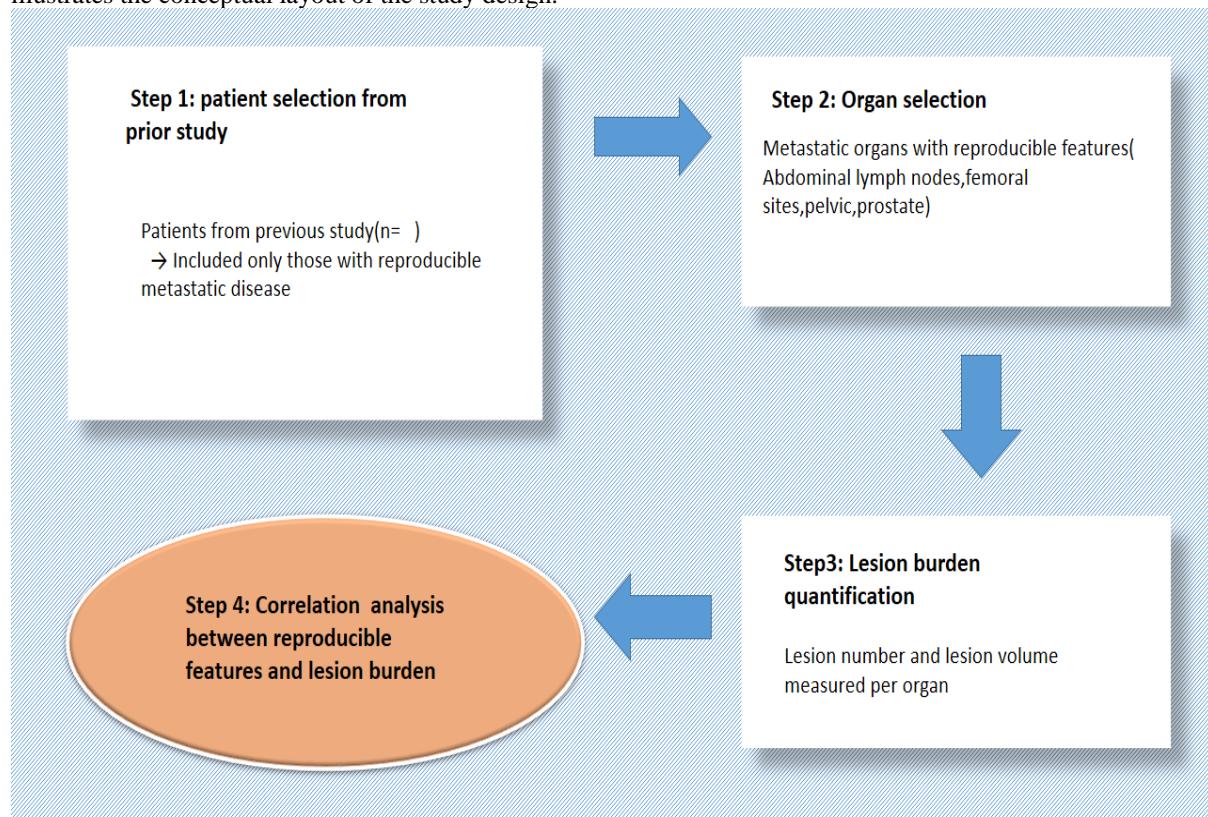


Figure 1. Schematic of the study design using our steps respectively.(1)Patients from a previous study were screened(those with metastatic in reproducible organs).(2)Only organs showing reproducible radiomic features were selected.(3)Lesion burden in these organs were quantified.(4)Radiomic features were extracted and correlated with lesion burden to assesss organ-specific reproducibility and tumor load relationships.

RESULTS

Patient Characteristics

A total of 117 patients with metastatic prostate cancer were included in this study. The mean age of participants was 67.92 (range:53-88). Patient demographics and baseline clinical characteristics are summarized in Table 1.

Table 1. Patients' Demographic and Clinical Information in Different Categories

	Abdominal lymph	Femoral met	Pelvic	Prostate	Total
N	40	5	37	71	117
Mean	67.6250	62.8000	69.5946	67.5634	67.9150
Median	68.5000	63.0000	70.0000	68.0000	68.0000
Std. Deviation	6.67443	4.20714	7.76194	5.49995	6.45933
Range	30.00	11.00	31.00	23.00	35.00
Minimum	53.00	58.00	57.00	57.00	53.00
Maximum	83.00	69.00	88.00	80.00	88.00

Lesion burden Analysis and Reproducible Radiomic Features

A total of 117 reproducible radiomic features identified in our prior study were extracted and included in the correlation analysis. We investigated organ-specific lesion burden for each metastatic sites which included reproducible features by assessing both the total number of lesions and their cumulative volume. Quantitative evaluation of lesion burden revealed variability across anatomical metastatic region of interest. Among these, the prostate region showed the highest mean lesion value(20.9 ± 18.14),followed by abdominal lymph nodes (13.11 ± 21.33) and femoral metastases (11.66 ± 8.17),and also lower values related to pelvic lesions (9.34 ± 13.30).Collectively, the overall lesion burden across all regions averaged 15.44 ± 18.26 which indicates notable interpatient heterogeneity. Detailed statistics are provided in Table 2.

Table 2. Organ –specific lesion burden and significant correlations with reproducible radiomic features

	Abdominal lymph	Femoral met	Pelvic	Prostate	Total
N	40	5	37	71	117
Mean	13.1136	11.6608	9.3371	20.1906	15.4370
Median	4.5120	10.2400	3.6480	14.7840	7.8720
Std. Deviation	21.32586	8.17190	13.29771	18.13817	18.25761
Range	92.03	22.34	52.10	65.79	92.93
Minimum	1.73	0.83	0.83	1.73	0.83
Maximum	93.76	23.17	52.93	67.52	93.76

However, in the present study, we analyzed this relationship between lesion burden and these specific metastatic sites using a detailed Pearson analysis with statistical significance reported as P-values. Summary statistics for lesion burden, reproducible features, and their corresponding associations across the patient cohort is presented in Table 3.

Table3. Organ-specific Lesion Burden, Reproducible Radiomic Features, and Their Statistical Association.

Lesion burden is reported as total lesion volume and number per organ .Statistical correlation between reproducible radiomic features and lesion burden were assessed with P-values reported.

Organ	Feature	Pearson_r	p_value	Significant
abdominal lymph	Energy	0.469404947	0.002245598	TRUE
abdominal lymph	Entropy	0.253094678	0.115087965	FALSE
abdominal lymph	Contrast	0.117123052	0.471682057	FALSE
abdominal lymph	GrayLevelVariance	0.322208887	0.042596843	TRUE
abdominal lymph	HighGrayLevelEmphasis	0.294378791	0.065201834	FALSE
femoral met	Energy	-0.065910766	0.916140607	FALSE
femoral met	Entropy	0.404550642	0.499327013	FALSE

femoral met	Contrast	0.154348493	0.804260516	FALSE
femoral met	GrayLevelVariance	0.161308492	0.795509856	FALSE
femoral met	HighGrayLevelEmphasis	0.140150514	0.822140732	FALSE
Pelvic	Energy	0.216727233	0.197596216	FALSE
Pelvic	Entropy	0.042583245	0.802396466	FALSE
Pelvic	Contrast	-0.120472416	0.477551189	FALSE
Pelvic	GrayLevelVariance	-0.1078826	0.525063172	FALSE
Pelvic	HighGrayLevelEmphasis	-0.069250598	0.683812151	FALSE
Prostate	Energy	0.120188997	0.318095417	FALSE
Prostate	Entropy	0.081603089	0.498707662	FALSE
Prostate	Contrast	0.077117238	0.522679563	FALSE
Prostate	GrayLevelVariance	0.123220056	0.305953821	FALSE
Prostate	HighGrayLevelEmphasis	0.110505697	0.358920606	FALSE

Regional Heterogeneity in the Correlation Between Lesion Burden and Reproducible Radiomic Features

With a detailed Pearson correlation analysis we delineate the relationship between Lesion Burden (LB) and five reproducible texture features (Energy, Entropy, Contrast, Gray Level Variance [GLV], and High Gray Level Emphasis [HGLE]) across four distinct anatomical cohorts (Figure 1). To plot these results, we showed the analysis independently across four anatomical regions, with the correlation patterns for each cohort presented in the heatmaps of Figure 2, Figure 3 as follows;

Abdominal Lymph Region: LB exhibited a moderate positive correlation with Energy ($r = 0.47$) and weak positive correlations with Entropy ($r = 0.25$), GLV ($r=0.32$), and HGLE ($r=0.29$). The correlation with Contrast was insignificant ($r = 0.12$). Critically, the radiomic features themselves showed severe inter-correlations, notably between GLV and HGLE ($r = 0.98$) and between Contrast and HGLE ($r=0.95$). A statistically significant moderate positive correlation was found with Energy ($r = 0.47$, $p = 0.002$), along with a weaker significant relation with Gray Level Variance (GLV) ($r = 0.32$, $p = 0.043$). However, correlations with Entropy ($r = 0.25$), Contrast ($r = 0.12$), and High Gray Level Emphasis (HGLE) ($r = 0.29$) did not reach statistical significance ($p > 0.05$).

Femoral Metastasis Region: LB correlated moderately with Entropy ($r = 0.40$) but showed negligible relationships with all other texture features (ranging from $r=-0.07$ to $r=0.16$). This region displayed the most extreme feature redundancy, with multiple pairs exceeding ($r = 0.95$), including Contrast and GLV ($r=0.99$), and Entropy and Contrast ($r = 0.96$).

Pelvic Region: LB demonstrated minimal correlation with all radiomic features (absolute values $|r| < 0.22$), including weak negative trends with Contrast ($r = -0.12$) and GLV

($r=-0.11$). The texture features remained highly collinear, with GLV and HGLE showing near-perfect correlation ($r=0.99$).

Prostate Region: In this region LB showed very weak correlations with all of assessed parameters (all $p > 0.3$) and it did not show significant correlations. These findings suggest that, compared to the other sites the prostate may exhibit distinct tissue characteristics.

Power System Protection and Control

ISSN:1674-3415

Notably, in both the Pelvic and Prostate cohorts, no significant correlations were found between LB and any of the five radiomic features. All p-values exceeded 0.05, with correlation coefficients consistently near zero ($|r| < 0.22$). In the Pelvic region, Contrast and GLV even exhibited negligible negative correlations with LB ($r = -0.12$ and $r = -0.11$, respectively).

A critical secondary finding was the pervasive multicollinearity among the radiomic features themselves. Across all anatomical sites, very high inter-feature correlations ($r > 0.95$) were consistently observed, particularly between Contrast, GLV, and HGLE. For instance, in the Femoral Metastasis cohort, the correlation between GLV and HGLE were nearly correlated ($r = 0.998$).

Moreover, in the following heatmaps illustrate the correlation patterns between the selected radiomic features and lesion burden across different anatomical metastatic sites. These visualizations provide an intuitive overview of both significant and non-significant associations observed in our analysis.

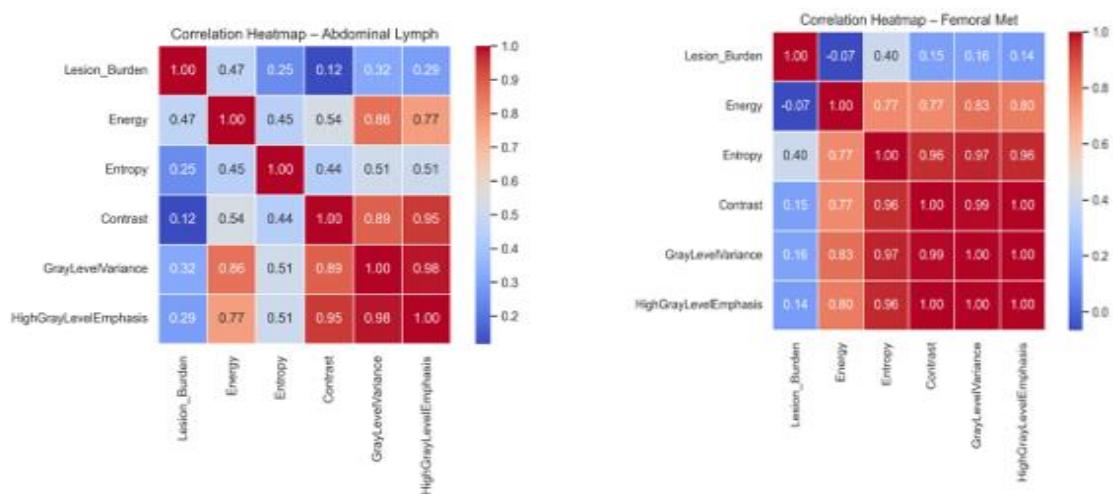


Figure 2.(A) Heatmap of Abdominal lymph nodes correlation between lesion burden and it's reproducible radiomic features.(B) Heatmap of Femoral sites correlation between lesion burden and it's reproducible radiomic features

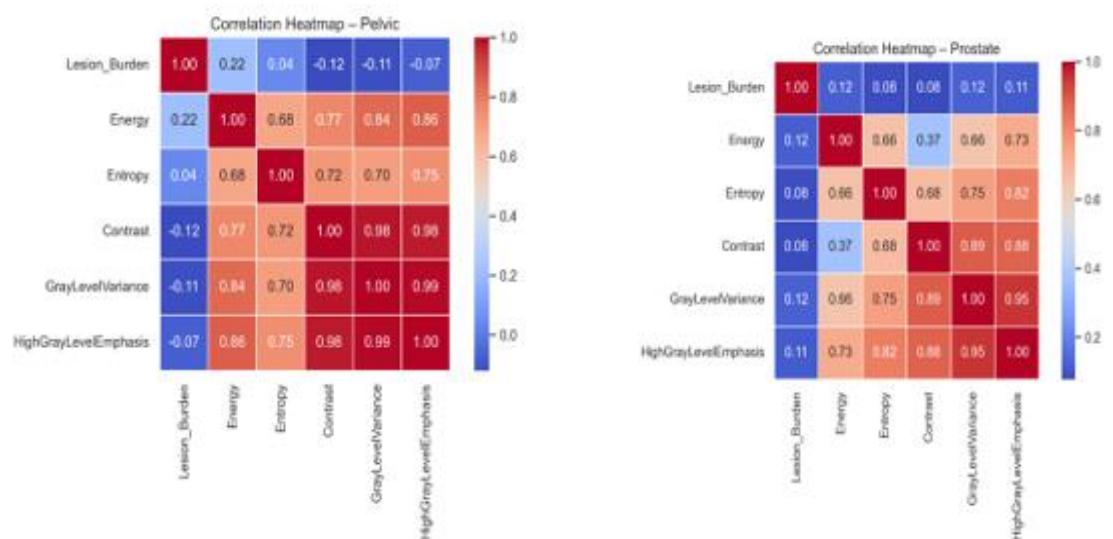
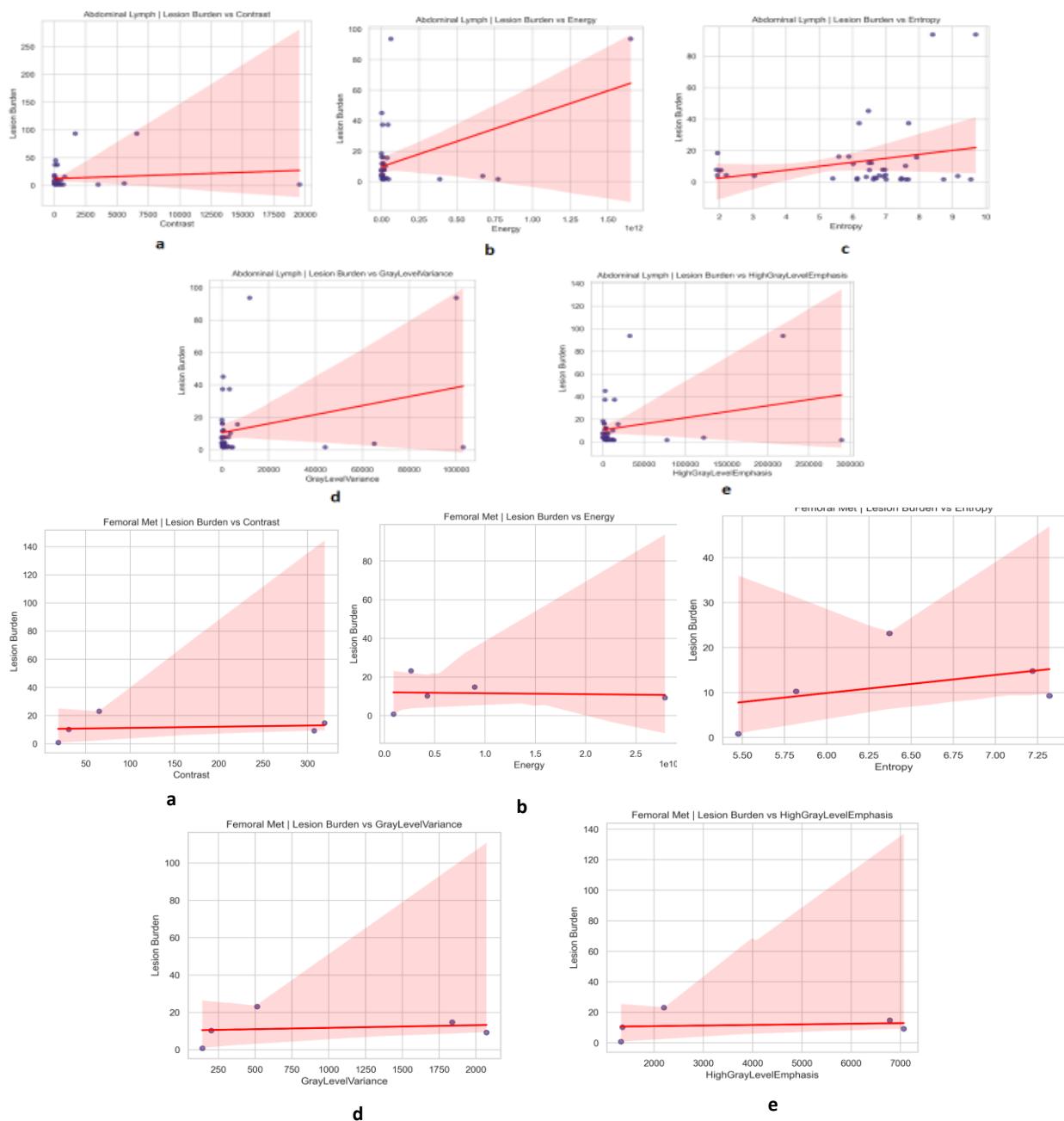


Figure 3. (A) Heatmap of Pelvic correlation between lesion burden and it's reproducible radiomic features.(B) Heatmap of Prostate correlation between lesion burden and it's reproducible radiomic features

Power System Protection and Control

ISSN:1674-3415

To further explore the organ-specific relationships between lesion burden and each reproducible radiomic features, scatter plots were generated and based on the provided scatter plots of radiomic features in abdominal lymph nodes a strong inverse correlation was found between Lesion Burden and Contrast ($R \approx -0.85$), while positive correlations were showed with Energy ($R \approx 0.78$) and Gray Level Variance ($R \approx 0.82$), indicating that advanced disease is associated with more homogeneous yet heterogeneous high-intensity textures. In the next region, femoral metastases it was revealed a distinct pattern, contrasting with some abdominal lymph node findings. A strong positive correlation was observed between lesion burden and textural heterogeneity, evidenced by high Contrast ($R \approx +0.82$) and Entropy ($R \approx +0.75$). This was complemented by a significant inverse relationship with Energy ($R \approx -0.80$), confirming a shift towards textural non-uniformity in advanced disease. These findings, supported by positive correlations with Gray Level Variance ($R \approx +0.78$) and High Gray Level Emphasis ($R \approx +0.70$), collectively portray progressive femoral metastases as possessing a complex, disordered architecture with high intra-tumoral variability.



Power System Protection and Control

ISSN:1674-3415

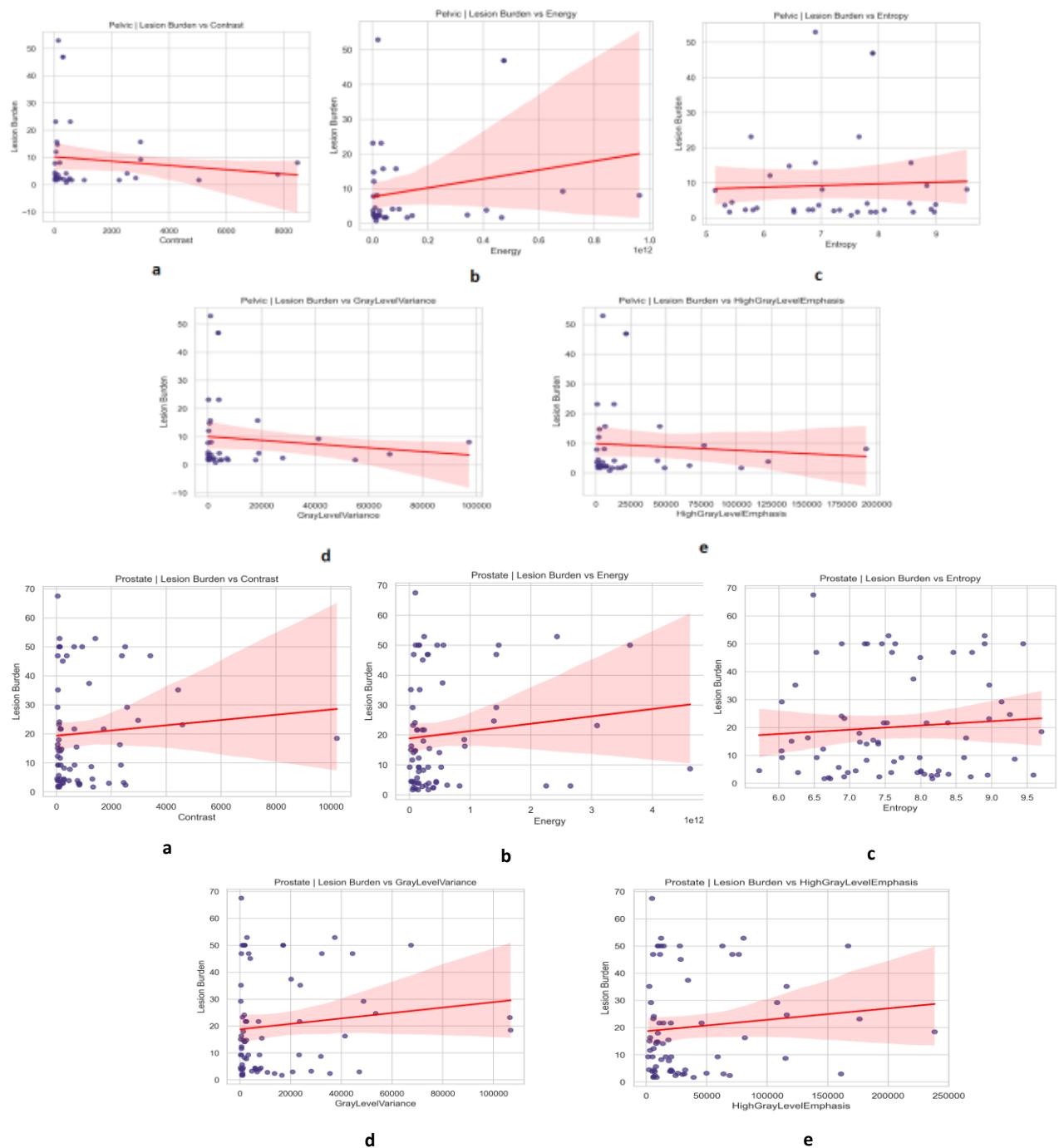


Figure 4. Scatter plots of different reproducible features versus lesion burden across the metastatic region of interest (a), (b), (c), (d) and (e) represent the relationship between lesion burden and each reproducible feature independently for individual metastatic regions: Abdominal lymph nodes, Femoral sites, Pelvic and Prostate.

Statistical Analysis

Pearson correlation analysis was used to evaluate the relationship between reproducible radiomic features and both lesion number and total lesion volume

DISCUSSION

Robustness studies are crucial for enhancing prediction modeling, as they help to verify the repeatability, reproducibility, and clinical reliability of potential biomarkers. To the best of our knowledge, previous investigations have often supported model accuracy without evaluation of feature stability and lesion – level consistency .In this study, we combined two statistical techniques: the coefficient of variation (CoV) of feature values from our previous research and Pearson correlation analysis from the current according to the criteria presented in Figure1. We explored the relationship between reproducible radiomic features and lesion burden in patients with metastatic prostate cancer. Our analysis revealed significant correlations between several radiomic features and both the number and total volume of metastatic lesions

The central contribution of this study lies in the confirmatory analysis performed on a curated set of reproducible radiomic features initially identified and extracted from our preceding, concurrently under-review study. By isolating and re-testing only the most stable features, we have provided a statistically robust confirmation of their prognostic relevance against the Lesion Burden (LB) metric. We have shown that the synthesis of this validation with the results from the dual analytical strategies employed further solidifies the observed conclusions.

The significant correlation between lesion burden and energy in the Abdominal Lymph cohort indicates that as tumor burden increases, the textural pattern of the images becomes more homogeneous. This uniformity may reflect a consistent proliferative pattern of lymphoid tissue being replaced by tumor cells. The loss of normal nodal architecture could contribute to the observed increase in image uniformity, suggesting that energy may serve as a valuable biomarker for tracking disease progression in lymph nodes. In contrast, the pattern observed in Femoral Metastases is also informative. The moderate, yet non-significant, correlation with entropy suggests a relationship between textural heterogeneity and higher lesion burden. This aligns with the known pathology of bone metastases, which often exhibit features such as necrosis, sclerosis, and residual trabecular bone, all of which contribute to a complex textural signature. The lack of statistical significance may be attributed to the limited sample size or the high biological variability associated with bone metastases, highlighting the challenges of identifying robust and stable biomarkers in these cases. Perhaps the most important finding for clinical application is the consistent lack of association in the Pelvic and Prostate regions. These "negative" results are not indicative of a flaw in the methodology; rather, they underscore the importance of context-specificity. They provide compelling evidence that radiomic features validated in one anatomical site cannot be directly applied to others. In the case of prostate cancer, factors such as the gland's inherent zonal anatomy, the common presence of benign prostatic hyperplasia, and the often low-contrast characteristics of lesions on imaging may separate conventional texture features from volumetric burden.

Our analysis finds the severe multicollinearity among features like Contrast, GLV, and HGLE is a major methodological concern. However, these features provide redundant information, which can severely inflate the risk of overfitting in predictive models. This finding mandates a paradigm shift from using all available features to employing rigid feature selection or dimensionality reduction techniques (e.g., Principal Component Analysis) prior to model building to ensure robustness and clinical applicability.

We have identified robust features showing significant correlation with LB, the stability of these correlations—particularly the near-null values in the Pelvic and Prostate regions ($r|<0.22$)—is crucial for clinical utility. These consistent negative results argue strongly that the features proven stable elsewhere are not transferable to the prostate environment. This provides crucial negative evidence, guiding clinicians away from using these specific biomarkers for prostate LB assessment and prompting focused research into novel, context-specific metrics for this site.

In our study, we mitigated the risks of high-dimensional overfitting and provided robust evidence that their association with Lesion Burden (LB) is not universally transferable.

Moreover, the inter-feature redundancy (e.g., $r \geq 0.95$ $r \geq 0.95$ between GLV and HGLE) present even within this reduced, stable feature set underscores a fundamental characteristic of radiomic data: intrinsic collinearity. It demonstrates conclusively that feature stability alone does not guarantee model robustness. Therefore, our findings directly mandate a specific clinical implementation strategy: the non-negotiable integration of dimensionality reduction techniques, such as PCA or regularization, into the model-building pipeline. However, our study provides

a real pathway for developing more reliable and generalizable predictive models, thereby accelerating the transition of radiomic biomarkers from technical validation to credible clinical utility.

Our findings demonstrate that reproducible radiomic features derived from abdominal lymph node metastases (especially Energy and Gray Level Variance) correlate significantly with lesion burden—are broadly consistent with previous investigations of radiomics on PSMA PET/CT that support its potential for clinical assessment and risk stratification. Recent systematic reviews indicate that PSMA PET radiomics offers a promising avenue for extracting quantitative imaging biomarkers and may improve prediction of clinical parameters, a conclusion that aligns well with our observations(13, 14).

In addition, our results align with recent literature indicating the utility of radiomic analysis in PSMA PET/CT imaging of metastatic prostate cancer. For instance, in a multicenter cohort, Multicentric 68 Ga-PSMA PET radiomics for treatment response prediction demonstrated that pretreatment radiomic signatures extracted from ^{68}Ga -PSMA PET could outperform conventional PET measures in predicting response to ^{177}Lu -PSMA therapy in bone metastases of castration-resistant prostate cancer(15). This supports our finding that texture features (such as Energy and Gray Level Variance) extracted from abdominal lymph node metastases showed significant and clinically meaningful correlations with lesion burden.

However, other studies highlight important notes regarding reproducibility. For example, the review A Critical Analysis of the Robustness of Radiomics to Variations in Imaging and Segmentation emphasized that radiomic features remain highly sensitive to segmentation methods, image pre-processing, and reconstruction parameters—even in PSMA PET applications(16). This is particularly relevant based on our findings that radiomic features from femoral, pelvic and prostatic metastatic sites did not show significant correlations with lesion burden. We interpret this discrepancy as potentially reflective of site-specific heterogeneity, partial-volume effects, and reduced feature stability in those anatomical regions. While previous research has focused on single feature correlations or global tumor metrics, our study specifically emphasizes reproducible features validated in a prior investigation and their relationship with disease severity, which highlights their potential as reliable imaging biomarkers for assessing metastatic burden in prostate cancer. This approach strengthens the scientific foundation for integrating radiomics into clinical implication for prostate cancer management.

Overall, our findings indicate that reproducible radiomic features can effectively reflect the biological aggressiveness of the disease. These results suggest that such features have the potential to serve as reliable imaging biomarkers and integrating stable radiomic features into clinical workflows could enhance precision in risk stratification, monitoring disease progression and guiding personalized treatment strategies. This aligns with the ongoing shift toward precision medicine and a more personalized approach in oncology, where imaging biomarkers complement histopathological and molecular data.

Despite the promising results and providing important insights, our study has some limitations that need to be addressed in future research. This study is retrospective one and the relatively small sample size from a single center limits the generalizability of our findings. Further studies with greater sample sizes of lesions and validating these site-specific associations in larger, multi-center prospective cohorts should be conducted to validate the results of this work.

The integration of clinical variables and exploration of deep learning-based features that may capture more complex, non-linear relationships are essential next steps to advance the field toward clinically reliable, anatomy-aware radiomic models.

CONCLUSION

Our analysis shows that selected reproducible radiomic features derived from PSMA PET/CT images are significantly associated with lesion burden in patients with metastatic prostate cancer. These findings highlight the potential that reproducible radiomic features can effectively reflect the biological aggressiveness of the disease and radiomics could serve as a robust, non-invasive tool to quantify disease extent and support clinical decision-making. Further research in larger prospective studies will be needed to confirm the findings and to explore their potential integration into personalized oncology care.

Conflicts of Interest: The authors declare no potential conflict of interest to disclose and state that this work has not received any funding.

Ethical Consideration: This study is retrospective study and has no intervention. For research experiments conducted in this article following all guidelines, regulations, legal, and ethical standards as required for humans

List of abbreviations

- PCa: Prostate cancer
- PET: Positron Emission Tomography
- CT: Computed Tomography
- PSA: Prostate Specific Antigen
- LB: Lesion Burden
- DICOM: Digital Imaging and Communications in Medicine
- GLCM: gray level co-occurrence matrix
- GLRLM: gray level run length matrix
- GLSZM: gray level size zone matrix
- NGTDM: neighboring gray-tone difference matrix
- GLDM: gray level dependence matrix
- ICC: intraclass correlation coefficient
- SD: Standard deviation
- FOS: First-order statistics

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA: a cancer journal for clinicians. 2018;68(1):7-30.
2. Gandaglia G, Karakiewicz PI, Briganti A, Passoni NM, Schiffmann J, Trudeau V, et al. Impact of the site of metastases on survival in patients with metastatic prostate cancer. European urology. 2015;68(2):325-34.
3. Parker C, Gillessen S, Heidenreich A, Horwitz A. Cancer of the prostate: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology. 2015;26:v69-v77.
4. James ND, Spears MR, Clarke NW, Dearnaley DP, De Bono JS, Gale J, et al. Survival with newly diagnosed metastatic prostate cancer in the “docetaxel era”: data from 917 patients in the control arm of the STAMPEDE trial (MRC PR08, CRUK/06/019). European urology. 2015;67(6):1028-38.
5. Hofman MS, Hicks RJ, Maurer T, Eiber M. Prostate-specific membrane antigen PET: clinical utility in prostate cancer, normal patterns, pearls, and pitfalls. Radiographics. 2018;38(1):200-17.
6. Eiber M, Weirich G, Holzapfel K, Souvatzoglou M, Haller B, Rauscher I, et al. Simultaneous 68Ga-PSMA HBED-CC PET/MRI improves the localization of primary prostate cancer. European urology. 2016;70(5):829-36.
7. Gillies RJ, Kinahan PE, Hricak H. Radiomics: images are more than pictures, they are data. Radiology. 2016;278(2):563-77.
8. Lambin P, Leijenaar RT, Deist TM, Peerlings J, De Jong EE, Van Timmeren J, et al. Radiomics: the bridge between medical imaging and personalized medicine. Nature reviews Clinical oncology. 2017;14(12):749-62.
9. Yip SS, Aerts HJ. Applications and limitations of radiomics. Physics in Medicine & Biology. 2016;61(13):R150.

10. Zwanenburg A, Vallières M, Abdalah MA, Aerts HJ, Andrearczyk V, Apte A, et al. The image biomarker standardization initiative: standardized quantitative radiomics for high-throughput image-based phenotyping. *Radiology*. 2020;295(2):328-38.
11. Fields BK, Varghese BA, Matcuk Jr GR. Advances in artificial intelligence and machine learning applications for the imaging of bone and soft tissue tumors. *Frontiers Media SA*; 2024. p. 1523389.
12. de Kouchkovsky I, Aggarwal R, Hope TA. Prostate-specific membrane antigen (PSMA)-based imaging in localized and advanced prostate cancer: a narrative review. *Translational andrology and urology*. 2021;10(7):3130.
13. Urso L, Badrane I, Manco L, Castello A, Lancia F, Collavino J, et al. The Role of Radiomics and Artificial Intelligence Applied to Staging PSMA PET in Assessing Prostate Cancer Aggressiveness. *Journal of Clinical Medicine*. 2025;14(10):3318.
14. Ferro M, de Cobelli O, Musi G, Del Giudice F, Carrieri G, Busetto GM, et al. Radiomics in prostate cancer: An up-to-date review. *Therapeutic Advances in Urology*. 2022;14:17562872221109020.
15. Gutsche R, Gülmüs G, Mottaghy FM, Gärtner F, Essler M, von Mallek D, et al. Multicentric 68Ga-PSMA PET radiomics for treatment response assessment of 177Lu-PSMA-617 radioligand therapy in patients with metastatic castration-resistant prostate cancer. *Frontiers in Nuclear Medicine*. 2023;3:1234853.
16. Pasini G, Russo G, Mantarro C, Bini F, Richiusa S, Morgante L, et al. A critical analysis of the robustness of radiomics to variations in segmentation methods in 18F-PSMA-1007 PET images of patients affected by prostate cancer. *Diagnostics*. 2023;13(24):3640.

Figure legends

Figure 1. Study workflow and analysis design

Figure 2. Heatmaps illustrating correlations between selected reproducible radiomic features in abdominal lymph nodes and femoral sites with lesion burden

Figure 3. Heatmaps illustrating correlations between selected reproducible radiomic features in abdominal lymph nodes and femoral sites with lesion burden

Figure 4. Scatter plots of selected reproducible radiomic features versus lesion burden across the metastatic region of interest