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EDITORIAL

More than meets the eye: 2-[^{18}F]FDG PET-based radiomics predicts lymph node metastasis in colorectal cancer patients to enable precision medicine

Wenpeng Huang[1] · Mai Hong Son[2] · Le Ngoc Ha[2] · Lei Kang[1] · Weibo Cai[3]

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Colorectal cancer (CRC) ranks as the third most prevalent cancer and the fourth leading cause of cancer-related mortality worldwide [1, 2]. Lymph node metastasis (LNM) stands as the primary route of metastasis in CRC, intricately influencing the surgical scope, the formulation of adjuvant chemotherapy programs, and the postoperative survival rates of patients [3, 4]. Consequently, the accurate and comprehensive assessment of lymph node (LN) status is pivotal in CRC, holding the potential to optimize personalized therapy—often referred to as precision medicine—thus advancing individualized patient care. The conventional gold standard for diagnosing LNM involves preoperative invasive lymph node biopsy and pathology. However, the pathological examination has several limitations, including invasiveness, high cost, and susceptibility to sampling errors.

Diagnostic imaging plays a crucial role in diagnosing, staging, and monitoring the treatment of patients with CRC. However, the diagnostic accuracy of computed tomography (CT) and magnetic resonance imaging (MRI) in identifying LNM, primarily relying on size shape and structure of LNs, remains inadequate and unsatisfactory due to low sensitivity. While LNs with active FDG metabolism can be detected using 2-[^{18}F]FDG PET/CT [5], this approach is hindered by complications such as false-positive findings in cases of inflammatory, granulomatous, and infectious diseases, limiting its applicability to CRC N staging [6, 7]. Consequently, there is a pressing need for a non-invasive and more effective method to assess the preoperative LNM status.

Over the last decade, in addition to traditional imaging techniques, nuclear medicine explored the field of radiomics, emerging as an increasingly explored subject [8, 9]. In brief, radiomic analysis involves extracting a multitude of imaging features from radiologic images, with these features often pertaining to the spatial distribution of the signal and pixel interrelationships, rather than having a direct association with clinically determined features [10, 11]. These features elucidate the heterogeneity and spatial complexity of lesions and are broadly categorized into aspects related to tumor shapes, voxel intensities, spatial interrelationships between neighboring voxels, and other higher-dimensional features [12, 13].

In this issue of the *European Journal of Nuclear Medicine and Molecular Imaging (EJNMMI)*, Xu and colleagues from Ren Ji Hospital, Shanghai Jiao Tong University, China, reported a superbly designed and executed study on the prediction of LNM in CRC patients using 2-[^{18}F]FDG PET-based radiomics [14]. We believe this study represents a new perspective in the prediction of LNM through radiomics. The retrospective, randomized, comparative imaging study adhered to clearly defined inclusion/exclusion criteria and utilized preoperative 2-[^{18}F]FDG PET/CT images for LNM identification. A total of 264 patients with pathologically confirmed adult CRC from the authors' academic medical center were divided into a training cohort ($n = 132$), used to construct the radiomics signature, and a validation cohort ($n = 132$), employed to assess the signature's performance. The Rad score was built by two imaging specialists with 8 and 10 years of experience using 3D slicer software to segment volumes of interest of LN from CT and PET images, with only one LN segmented per patient. From 1702 radiomics features extracted from CT and PET images, 8 features

✉ Lei Kang
kanglei@bjmu.edu.cn

✉ Weibo Cai
wcai@uwhealth.org

[1] Department of Nuclear Medicine, Peking University First Hospital, No.8 Xishiku Str, Xicheng District, Beijing 100034, China

[2] Department of Nuclear Medicine, Hospital 108, Hanoi, Vietnam

[3] Departments of Radiology and Medical Physics, University of Wisconsin - Madison, K6/562 Clinical Science Center, 600 Highland Ave, Madison, WI 53705-2275, USA

were selected through robust statistical analysis to establish the Rad scores. One notable advantage of this paper lies in the substantial amount of data and the statistical robustness of its implementation. Simultaneously, LN status was defined based on preoperative CT and PET/CT and recorded as CT-reported LN status and PET/CT-reported LN status. The manuscript itself is highly satisfactory, from the presentation to the figures. In conclusion, this work on radiomics is exemplary, representing a state-of-the-art contribution that aligns seamlessly with the standards of *EJNMMI*.

This study was meticulously designed to demonstrate the potential of radiomics in a multifaceted manner. The key findings are summarized below: (1) Five radiomic features were extracted from PET, and three from CT. The "Idmn" feature derived from PET images and the "gray-level nonuniformity normalized (GLNUN)" feature from CT images were identified as the most influential predictors of LN status. (2) The AUCs of the Rad score for forecasting LN status were documented as 0.908 and 0.840 for the training and test datasets, respectively, surpassing the diagnostic efficiency of traditional CT-reported LN status and PET/CT-reported LN status. (3) Clinical risk factors did not contribute synergistically to predicting LNM; incorporating clinical variables into the predictive model did not enhance the model's performance over the radiomics signature. (4) The calibration curves demonstrated harmony. Decision curve analysis results showed that, for a threshold probability ranging between 0 and 0.88, the radiomics signature provided a greater net benefit compared to the "treat none," "treat all," "treat based on CT-reported," and "treat based on PET/CT-reported" approaches. (5) The author conducted a comparative analysis to identify N1 and N2 using both the radiomics signature and conventional parameter approaches. In the training cohort, the radiomics signature exhibited superior performance with an AUC of 0.885, surpassing the performance of conventional CT-reported LN status (AUC, 0.587) and PET/CT-reported LN status (AUC, 0.621). In the testing cohort, the radiomics signature continued to demonstrate the highest performance.

The potential of radiomics in detecting tumor LNM is increasingly emphasized by a growing number of similar studies. To our knowledge, the 2017 study by Giesel et al. [15] marked the first attempt to assess the correlation between SUVmax in PET examinations and semi-automatic density measurements in CT components within PET/CT examinations for the evaluation of radiomics. Subsequently, PET/CT radiomics analysis was employed to predict LNM in various cancers, including breast cancer, lung cancer, stomach cancer, esophageal cancer, colorectal cancer, cervical cancer, endometrial cancer, and prostate cancer [16–25]. However, in these studies, radiomic analysis focused on delineated primary tumor volumes rather than directly assessing LN volumes. The potential of utilizing metabolic heterogeneity in LN for predicting LNM has not been explored. In contrast, this study focuses in the direct extraction of PET/CT radiomic features from the most likely metastatic LN. Furthermore, this study serves as a crucial proof of concept, indicating that Rad scores have superior predictive capabilities for lymph node metastasis compared to current CT and PET reports. This suggests that incorporating radiomic features into routine clinical practice may significantly enhance the assessment of LNM status in tumor patients. In summary, these intriguing results imply that 2-[^{18}F]FDG PET-based radiomics addresses the limitation of relying solely on morphological signs for assessing metastasis in LNs.

While the adoption of radiomics in clinical practice remains limited, studies such as these suggest that the era of radiomics and artificial intelligence (AI) in diagnostic imaging is on the horizon. However, acknowledging the study's limitations, as highlighted by the authors, the retrospective nature prevented the mapping of selected LNs with those confirmed by postoperative pathology for tumor metastasis. Future investigations should consider adopting a multicenter prospective design with larger patient cohorts, specifically focusing on correlating preoperative PET/CT findings with histopathologic results. Moreover, the next logical step, as suggested by this study, involves exploring the potential combinatorial predictive value of assessing intratumoral and intranodal metabolic heterogeneity. This step may lead to a more comprehensive understanding, with the aim of determining whether predictive accuracy for lymph node metastasis can be further enhanced.

Despite these findings, the reliance on manual segmentation for feature extraction introduces subjectivity and variability. In comparison to CT and MRI, PET generates images with relatively low spatial resolution. While CT and MRI can detect structures smaller than a millimeter, the spatial resolution of PET in human body imaging is 8–10 mm [26]. The necessity for manual lesion segmentation will impede the consistency and clinical application of Rad scores until an automated segmentation tool becomes available for clinical use, thereby reducing analysis time and inter-reader variability. This represents a critical question eagerly anticipated by many in the field of medical imaging, and we look forward to the findings in the near future.

Due to limitations in case collection, this study did not validate the Rad score in an external cohort. All images were obtained from the Biograph mCT scanner. One major unaddressed challenge in radiomics is the development of a Rad score applicable across different medical centers, limiting the ability to assess the generalization, particularly the robustness and generalizability [27]. Notably, radiomic analysis in 2-[^{18}F]FDG PET/CT imaging is significantly influenced by image acquisition. Factors such as imaging protocol, scanner type, postprocessing, and the presence of

motion can negatively impact the robustness of radiomics analysis. In a recent study, scholars from multiple research centers globally collaborated to form the Image Biomarker Standardization Initiative (IBSI). The initiative aims to establish a standardized radiomics image processing scheme for calculating features from imaging and provide reporting guidelines for studies involving radiomics analysis [28, 29]. These reference values enable the verification of radiomics software, enhancing the reproducibility of radiomics studies and facilitating the clinical translation of radiomics. Consequently, to make radiomics a viable tool for clinical decision-making, further efforts are required towards standardizing the workflow. In addition, the primary obstacle to clinical implementation lies in the lack of practices for sharing models, codes, and data. Akinci D'Antonoli et al. [30] have explored the sharing practices in the current radiomics research landscape and introduced a large radiomics research database (RadBase) to facilitate the retrieval of radiomics models, code, and data when shared. For future systematic and routine radiomics studies, the number of included patients may not be a limiting factor; instead, reproducibility will be the primary consideration.

Extensive and promising research has consistently affirmed the utility of radiomics, showcasing significant value in diagnosing, characterizing diseases, and predicting outcomes [31]. Despite these advancements, it is noteworthy that, to date, no FDA-approved device based on radiomics has been integrated into clinical practice [32]. For real-life clinical applications before commercialization, including acquisition protocol and image quality optimization, workflow improvement, disease detection and classification, and likely reporting, licensing of radiomics programs as a "medical device" will be mandatory as a diagnostic aid. This prerequisite not only brings forth challenges related to validation standards, approval criteria, and novel quality control parameters but also underscores the need to determine the clinical utility of radiomics in routine practice.

In summary, this meticulously designed study by Xu et al. [14] marks an exciting milestone in the application of 2-[^{18}F]FDG PET-based radiomics, opening avenues for larger clinical trials to validate these radiomic signatures in diverse settings and populations. The Rad scores outperformed traditional CT-reported LN status and PET/CT-reported LN status in diagnostic efficiency, thereby enhancing individualized care and precision medicine. We encourage researchers to embrace open science practices, ensuring the reproducibility of radiomics research both now and in the future.

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Declarations

Ethics approval and consent to participate This article does not contain any studies with human participants or animals performed by any of the authors.

Conflict of interest Weibo Cai declares conflict of interest with the following corporations: Actithera, Inc., Rad Source Technologies, Inc., Portrai, Inc., rTR Technovation Corporation, and Four Health Global Pharmaceuticals, Inc. All other authors declare no conflict of interest.

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