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MRI radiomics: A machine learning approach for the risk stratification of endometrial cancer patients

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ABSTRACT

Purpose: To investigate radiomics and machine learning (ML) as possible tools to enhance MRI-based risk stratification in patients with endometrial cancer (EC).
Method: From two institutions, 133 patients (Institution1 = 104 and Institution2 = 29) with EC and pre-operative MRI were retrospectively enrolled and divided in two a low-risk and a high-risk group according to EC stage and grade. T2-weighted (T2w) images were three-dimensionally annotated to obtain volumes of interest of the entire tumor. A PyRadiomics based and previously validated pipeline was used to extract radiomics features and perform feature selection. In particular, feature stability, variance and pairwise correlation were analyzed. Then, the least absolute shrinkage and selection operator technique and recursive feature elimination were used to obtain the final feature set. The performance of a Support Vector Machine (SVM) algorithm was assessed on the dataset from Institution 1 via 2-fold cross-validation. Then, the model was trained on the entire Institution 1 dataset and tested on the external test set from Institution 2.
Results: In total, 1197 radiomics features were extracted. After the exclusion of unstable, low variance and intercorrelated features least absolute shrinkage and selection operator and recursive feature elimination identified 4 features that were used to build the predictive ML model. It obtained an accuracy of 0.71 and 0.72 in the train and test sets respectively.
Conclusions: Whole-lesion T2w-derived radiomics showed encouraging results and good generalizability for the identification of low-risk EC patients.

1. Introduction

Personalized medical approaches are based on the concept that there are unique underlying characteristics behind diseases with significant inter-individual variability [1]. They are not only highly promising in several fields, but likely to become unavoidable in certain contexts [2]. Oncology represents one of these areas and gynecologic malignancies are by no means an exception, although the actual application of personalized medicine is still a work in progress [3].

Endometrial cancer (EC) is the most common gynecologic tumor and

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its incidence is on the rise [4]. Radical surgery is considered the pillar for EC treatment, with the role of lymphadenectomy and adjuvant therapy still debated and systemic treatment being indicated for advanced or recurrent disease [5,6]. Choices regarding treatment strategy are guided by the stratification of risk, which at present mainly takes into account imaging (e.g. disease stage) and pathological (e.g. tumor grade and histology) parameters [7]. In particular, MRI is currently considered the most accurate imaging modality for EC staging, being able to assess important features like deep myometrial invasion or cervical stroma involvement [8]. On the other hand, biopsy is needed to evaluate recognized negative prognostic factors such as high grade and non-endometrioid histotypes [9]. In patients at low risk, less invasive treatment options could be considered to minimize the possible downsides on the quality of life without undermining oncological outcomes, which appear particularly relevant for those women that wish to preserve their fertility [10,11].

The high-throughput extraction of quantitative parameters from medical images, a complex multi-step process known as radiomics, has been recently proposed to enhance the value of diagnostic imaging and is regarded as a potential tool to help the transition towards personalized medicine in clinical practice [12–15]. Radiomics has been successfully paired with machine learning with promising applications in oncologic patients [16–20] With specific regard to EC, there are recent evidences suggesting that MRI-powered radiomics could serve to build support decision tools for various difficult medical tasks, such as predicting the extent of myometrial infiltration or nodal involvement [21–25]. In this study, we aimed to explore the potential of radiomics features extracted from T2-weighted (T2w) MR images training and testing a machine learning model for the stratification of risk in patients with EC.

2. Materials and methods

Approval from the Institutional Review Board was obtained for this retrospective study and the requirement for written informed consent was waived.

2.1. Patient population and reference standard

Subjects who underwent surgical treatment for EC at University of Naples "Federico II" (Institution 1) or Pineta Grande Hospital (Institution 2) between January 2016 and May 2020 were retrospectively collected. To be included in the study, the availability of a pre-treatment MRI performed at either Institution 1 or 2 no longer than one month prior to surgery was required. The following exclusion criteria were applied: 1) previous treatment for EC; 2) presence of artifacts; 3) tumor either undetectable on T2w images or smaller than 10 mm in maximum diameter (as measured on sagittal plane); 4) patients with distant metastases. Hysterectomy specimens were analyzed by two experienced pathologists to serve as reference standard, as previously described [26]. Information regarding tumor grade, histologic type, local T stage and nodal involvement were used to divide our population in two risk groups. Specifically, patients with Type 1 EC (G1 or G2 endometrioid tumors) confined to the endometrium or infiltrating the myometrium for less than 50% of its thickness (pT1a) and without proofs of nodal involvement (N0 or Nx) were considered as low risk patients, whereas patients with either Type 2 EC (G3 endometrioid tumors and non-endometrioid variants), local stage $>$ pT1a or evidence of nodal involvement were considered as high risk patients [27]. Institution 1 cases were used for the feature selection process as well as model training, while Institution 2 cases served exclusively as an external test set for the final model.

2.2. Image acquisition and segmentation

Technical parameters of the MRI protocol employed in both Institution 1 (3 T scanner, Magnetom Trio, Siemens Healthineers, Erlangen, Germany) and Institution 2 (1.5 T scanner, Siemens Aera, Siemens Healthineers, Erlangen, Germany) have been detailed elsewhere [26]. For the present study, a radiologist experienced in genitourinary imaging annotated all the sagittal T2w images slice by slice to obtain a volume of interest (VOI) encompassing the entirety of the lesion [28]. Two additional readers also performed segmentations for a random subset of 30 patients from Institution 1, to allow inter-reader reproducibility analysis.

2.3. Radiomics features extraction and selection

The radiomics feature extraction process followed a previously validated pipeline [29] based on the Imaging Biomarker Standardization Initiative-compliant PyRadiomics software package [30,31]. Image preprocessing steps included voxel resampling to isotropic values, grey level z-score normalization and fixed-bin width discretization prior to the extraction. These settings were identical to those employed in a previous T2w-radiomics study in patients with EC and the settings file is available in a freely accessible online repository (https://rcuocolo.github.io/MRadEC/) [28].

Extracted features underwent a multi-component selection process to identify the best subset to build a predictive model, all conducted on the training data extracted from Institution 1 cases. First, non-reproducible features were eliminated through Intraclass Correlation Coefficient (ICC) analysis, based on data extracted from the annotations by the 3 readers. A two-way random effect, single rater, absolute agreement ICC model was employed, and a $\geq$0.75 threshold identified "stable" features [32]. A MinMax scaler (range = 0–1) was fitted on the training data and used to transform datasets from both Institution 1 and 2. The scaler is provided as a pickled Python object in the repository accompanying this study. Then, low variance ($<$0.01) features were removed, as well as those highly correlated ($>$0.80) at a pairwise Pearson correlation analysis. An automated least absolute shrinkage and selection operator (LASSO) automatically identified 8 features whose coefficients did not shrink to 0. After balancing the training data with the Synthetic Minority Oversampling Technique, recursive feature elimination (RFE) paired with a linear Support Vector Machine (SVM) identified the final feature set to build the model.

The feature selection process was conducted using the "irr" R package and the "pandas", "scikit-learn" and "imbalanced-learn" Python packages [33,34].

2.4. Machine learning model training and testing

A SVM was trained on the dataset from Institution 1, and its performance was assessed in the training data with 2-fold cross-validation. No hyperparameters were modified outside of enabling probability estimates to allow further analysis of the model's output. The final model was then fitted on the entire training dataset and tested on the external test set from Institution 2. A confusion matrix was constructed to obtain commonly employed accuracy metrics (precision, recall) for each class as well as the area under the Receiver Operating Curve (AUC), calibration metrics (Brier score) and calibration plot. To explore the processes behind the model's predictions, the "SHAP" Python package was used to obtain the Shapley values (reflecting the importance of each feature for the classification) for all features in the train set.

Model training and testing was conducted with the "scikit-learn" Python package [33]. The complete radiomics pipeline is schematically depicted in Fig. 1.

2.5. Statistical analysis

The normality of the distribution of continuous clinical variables was assessed with the Shapiro-Wilk test. In absence of normal distribution, the differences in continuous clinical variables (age, lesion size) between the populations of the two institutions were assessed using the Mann-

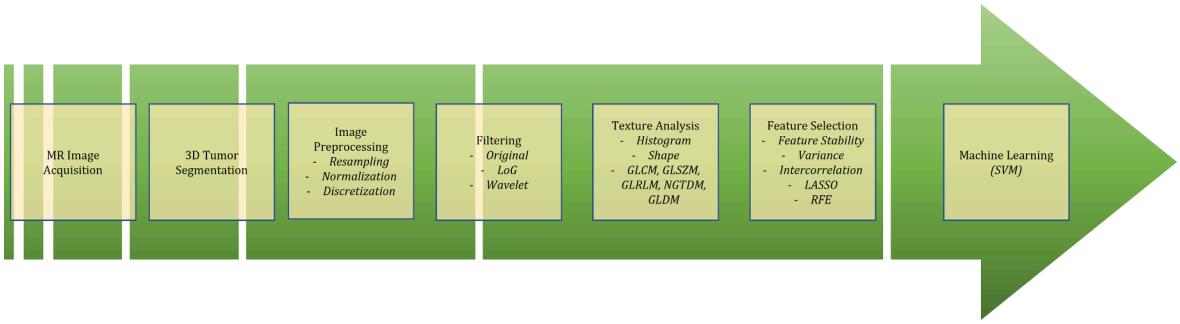

Fig. 1. The multi-step radiomics pipeline employed in the study. LoG (Laplacian of Gaussian), GLCM (Gray-Level Co-Occurrence Matrix), GLSZM (Gray Level Size Zone Matrix), GLRLM (Gray Level Run Length Matrix), NGTDM (Neighboring Gray Tone Difference Matrix), GLDM (Gray Level Dependence Matrix), LASSO (Least Absolute Shrinkage And Selection Operator), RFE (Recursive Feature Elimination), SVM (Support Vector Machine).

Whitney and Fisher exact tests, as appropriate. The same statistical tests were applied for evaluating the differences between categorical variables (EC type, T stage, N stage, class label). Categorical variables are presented as counts and percentages. A p value < 0.05 was used to identify statistical significance. All statistical analyses were conducted with the "stats" R package [34].

3. Results

3.1. Patient population and reference standard

The patient selection flowchart can be found in Fig. 2. The final study population included a total of 133 patients, of which 104 from Institution 1 and 29 from Institution 2. The main clinical characteristics are reported in Table 1.

3.2. Statistical analysis

The distribution of continuous clinical variables was not normal and therefore these are presented as medians and interquartile range (IQR). The results of the comparisons for clinical data between the datasets are presented in Table 1. The only variable with a significant difference was T stage ($p = 0.03$).

Table 1
Main clinical characteristics of the study population and results of the comparison between patients from sites 1 and 2.

	Site 1 (train set, n = 104)	Site 2 (test set, n = 29)	*p value*
Age (years)*	63 (12,5)	60 (12)	0.28
Lesion size (mm)*	41.5 (35,5)	40 (15)	0.72
Type 1 EC#	60/104 (58%)	22/29 (76%)	0.09
pT1a#	72/104 (69%)	13/29 (45%)	0.03°
N0 or Nx#	97/104 (93%)	25/29 (86%)	0.25
Low risk group#	56/104 (54%)	11/29 (38%)	0.15

EC = Endometrial cancer.
* Median values are reported, with interquartile range in parenthesis.
# Counts are reported, with percentages in parenthesis.
° Statistically significant difference for $p < 0.05$.

3.3. Feature selection and machine learning analysis

In total, 1197 radiomics features were extracted, of which 214 (18%) were stable at ICC analysis. Then, 4/214 (2%) had low variance and were also excluded, together with 175/210 (83%) presenting high pairwise correlation. At LASSO, of the remaining 35 features only 8 (23%) were selected, half of which (4) remained after RFE:

1. original_shape_Flatness

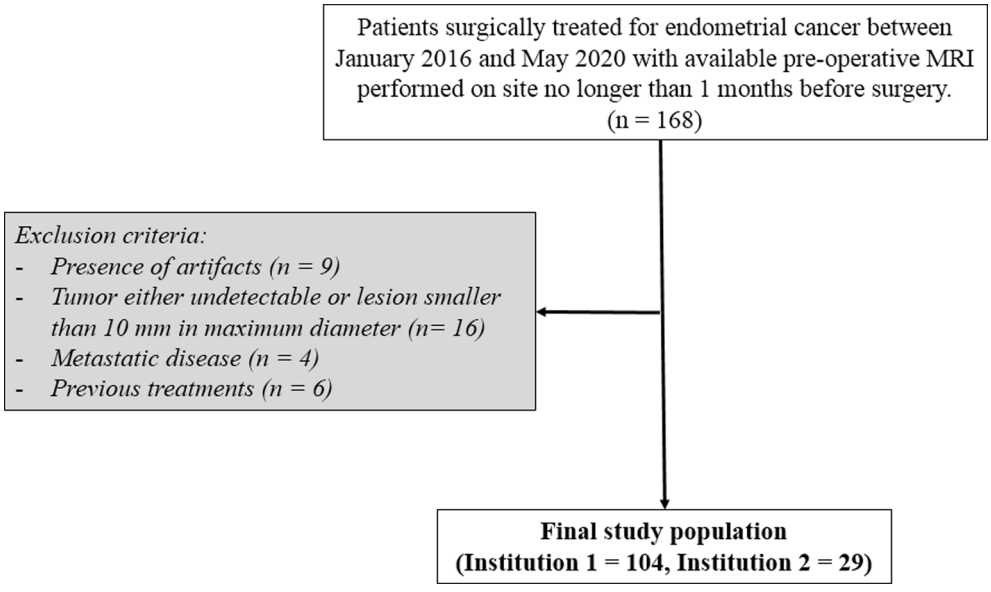

Fig. 2. Patients' selection flowchart.

2. original_glrlm_RunLengthNonUniformityNormalized
3. log-sigma-2–0-mm-3D_firstorder_Median
4. wavelet-LLH_glszm_ZoneEntropy

The final SVM model is available as a pickled Python object in the study repository. It obtained an accuracy of 0.71 in the balanced training data for the classification of risk in EC, with an AUC of 0.78. The confusion matrix and accuracy metrics are shown in Table 2. The overall accuracy was 0.72 in the test set, with an AUC of 0.71 (95% confidence interval 0.50–0.92) and a Brier score of 0.21 (Fig. 3). Shapley values for the train set are plotted and depicted in Fig. 4.

4. Discussion

Our results suggest that a ML model powered by handcrafted T2w radiomics features could be considered as a feasible tool to identify low-risk patients among EC subjects who might benefit from a more conservative management. Although the performance of the model is not as high as desirable, it is noteworthy that the model did not suffer from performance losses when presented with previously unseen data during the external validation process. It can be hypothesized that the risk of overfitting was avoided with a robust feature selection process that led to finally include in the model a reasonably low number of informative features. It also deserves to be underscored that the external validation group was composed of T2w images acquired on a scanner with different field strength, which is another finding supporting the good generalizability of our model.

Comparing the main clinical characteristics of patients included in the train and test partitions, a single statistically significant difference emerged in terms of EC local stage. However, this did not generate a difference in the prevalence of low-risk patients between the two groups. Furthermore, the overall homogeneity of the two groups indicates that the study sample size could be representative of the general EC population, which might be an important point to ensure the reliability of the model.

Preliminary investigations have been previously conducted to explore the potential role of MRI radiomics for the prediction of high-risk characteristics in EC patients with encouraging results that were however limited by the lack of external validation and that were exclusively focused on first-order textural features [22,23]. Furthermore, in these exploratory studies images were segmented to obtain two-dimensional regions of interest, an approach conceptually resembling a "virtual biopsy", but which does not allow for a comprehensive evaluation of the entire tumor. Indeed, it has been recently found that three-dimensional may be superior to two-dimensional radiomics when phenotyping EC, although further confirmations are needed to support this claim [24]. In their study, *Fasmer and colleagues* evaluated independently single EC high-risk features rather than using them to define risk-groups prior to model building [24]. Moreover, their approach was based on T1 weighted contrast enhanced MR images, making it difficult to formally compare these previous results with the present study. Since abbreviated, unenhanced MRI protocols for the evaluation of EC have been proposed and might be profitable in terms of cost-effectiveness, we believe that radiomics models employing unenhanced images might be more advantageous and possibly easier to be implemented in clinical practice. Recently, *Chen et al.* proposed a radiomics model based on T2w MR images for the risk stratification of EC patients [35]. They exclusively focused on subjects with locally confined disease (pT1a or pT1b) and took into account lesion grade, with their model reaching an AUC in the validation cohort of 0.815 (95% confidence interval: 0.588–1), in the identification of low-risk patients (pT1a and either G1 or G2 endometrioid EC). However, while this finding might confirm the great value of T2w radiomics applications for EC, it should be taken cautiously. Indeed, the authors did not validate the performance of the model on an external dataset from a different institution, and a potential performance loss could occur. Moreover, feature stability testing for multiple segmentations was not performed and thus there is a risk that insufficiently robust features were inadvertently included in the model, leading to an overly optimistic claim of performance. Finally, the wide range of the confidence interval at least partly due to the relatively lower sample size introduces an additional concern regarding the potential generalizability of the proposed model. On the other hand, in a recent study with a large multicenter cohort, a radiomics signature for the pretreatment identification of high-risk EC was developed and validated on two different, independent and external datasets, with notable outcomes (AUCs of 0.75 and 0.85 in validation groups 1 and 2 respectively) [36]. This model however, despite showing a higher performance compared to the one achieved with the model presented in our study, requires data from three different MRI sequences to work (i.e., T2w, diffusion weighted and contrast enhanced images). Hence, the performance gain comes at the cost of higher complexity and more time-consuming segmentation workload, as well as at the risk of not being universally applicable (e.g. patients with contraindication to the administration of contrast medium could not be evaluated by such a model). Interestingly, in their study *Yan and colleagues* found that, after feature selection, T2w features were those with the highest weight in the radiomics signature in comparison the other sequences. We believe that this finding supports our choice to build a T2w-only radiomics model.

The present study suffers from some limitations that deserve to be acknowledged and discussed. Firstly, the retrospective design implies a possible risk of selection bias making it necessary to validate our findings in a prospective setting. Secondly, the assumption that Nx and N0 status are equal was made to allow patients grouping; while this has been previously done in similar settings [36], the ideal reference standard is clearly represented by the pathological confirmation of N0 status. Nevertheless, this issue could not be addressed retrospectively due to the nature of current management of EC, which often does not require lymphadenectomy. Thirdly, more advanced risk stratification approaches integrating additional features such as EC molecular profile have been proposed and might have been considered for patients grouping [37,38]. However, their use is not widespread, and the data was not available, warranting for further, more comprehensive investigations in the future. Fourthly, while an external dataset was available for validation, the sample size was relatively small and further data from more institutions would have provided even more robust grounds to support the claims of generalizability. Finally, there are additional quantitative parameters that could be extracted with relative from MRI sequences other than T2w (e.g. diffusion weighted imaging) without a radiomics pipeline and it could be worthy to explore them in combination with the present approach [39–41].

In conclusion, whole-lesion T2w-derived radiomics, have demonstrated an interesting potential in the identification of high-risk EC patients in our study. Of note, our pipeline has proven good generalizability with reproducible results across different Institutions, scanner model and field strength. This non-invasive strategy for the pre-operative stratification of risk in endometrial cancer could aid in the

Table 2
Confusion matrix (A) obtained by the model in the test and accuracy metrics (B) for both train (mean, with standard deviation in parentheses) and test sets (exact values derived from the confusion matrix).

A.

	Low-risk patients	High-risk patients
Predicted low-risk	7	4
Predicted high-risk	4	14

B.

	Accuracy	Precision	Recall	F1 score	AUC
Train	0.71 (± 0.05)	0.70 (± 0.05)	0.71 (± 0.07)	0.71 (± 0.06)	0.78 (± 0.09)
Test	0.72	0.78	0.78	0.78	0.71

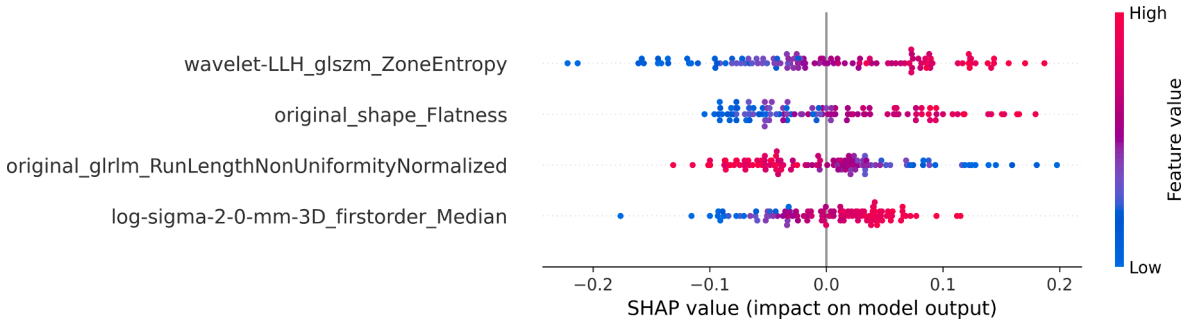

Fig. 3. Calibration plot for the model.

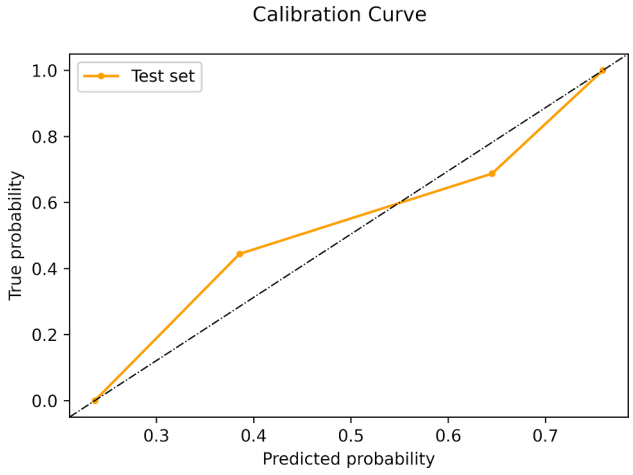

Fig. 4. Shapley values for the features in the train set.

identification of the most appropriate management. Thus, our findings support the need for future investigations in this field, ideally within a prospective trial framework.

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None.

Code availability

https://rcuocolo.github.io/MRadEC/

Ethics approval

IRB approved.

Informed consent

IRB waived.

CRediT authorship contribution statement

Pier Paolo Mainenti: Conceptualization, Methodology, Investigation, Writing – review & editing. **Arnaldo Stanzione:** Conceptualization, Methodology, Investigation, Writing – original draft. **Renato Cuocolo:** Data curation, Writing – original draft, Investigation, Visualization, Validation, Formal analysis. **Renata Del Grosso:** Data curation, Formal analysis. **Roberta Danzi:** Data curation. **Valeria Romeo:** Writing – review & editing, Supervision. **Antonio Raffone:** Data curation, Writing – review & editing. **Attilio Di Spiezio Sardo:** Data curation, Supervision. **Elena Giordano:** Data curation. **Antonio Travaglino:** Data curation, Writing – review & editing. **Luigi Insabato:** Data curation, Supervision. **Mariano Scaglione:** Data curation, Investigation. **Simone Maurea:** Writing – review & editing. **Arturo Brunetti:** Conceptualization, Methodology, Investigation, Writing – review & editing, Supervision.

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