Magnetic resonance imaging-radiomics in endometrial cancer: a systematic review and meta-analysis

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ABSTRACT

Objective Endometrial carcinoma is the most common gynecological tumor in developed countries. Clinicopathological factors and molecular subtypes are used to stratify the risk of recurrence and to tailor adjuvant treatment. The present study aimed to assess the role of radiomics analysis in pre-operatively predicting molecular or clinicopathological prognostic factors in patients with endometrial carcinoma.

Methods Literature was searched for publications reporting radiomics analysis in assessing diagnostic performance of MRI for different outcomes. Diagnostic accuracy performance of risk prediction models was pooled using the metandi command in Stata.

Results A search of MEDLINE (PubMed) resulted in 153 relevant articles. Fifteen articles met the inclusion criteria, for a total of 3608 patients. MRI showed pooled sensitivity and specificity 0.785 and 0.814, respectively, in predicting high-grade endometrial carcinoma, deep myometrial invasion (pooled sensitivity and specificity 0.743 and 0.816, respectively), lymphovascular space invasion (pooled sensitivity and specificity 0.656 and 0.753, respectively), and nodal metastasis (pooled sensitivity and specificity 0.831 and 0.736, respectively).

Conclusions Pre-operative MRI-radiomics analyses in patients with endometrial carcinoma is a good predictor of tumor grading, deep myometrial invasion, lymphovascular space invasion, and nodal metastasis.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Radiomics applications could add pre-operative information for appropriate counseling and treatment planning.

WHAT THIS STUDY ADDS

⇒ MRI-radiomics is a good predictor of grade, myometrial infiltration, lymphovascular space invasion, and nodal metastasis in endometrial carcinoma.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Applications of MRI-radiomic models in clinical practice could help tailor management of endometrial carcinoma.

INTRODUCTION

Endometrial cancer is one of the most common female genital tract malignancies, ranking first in developed countries.[1] Nowadays, molecular classification combined with traditional clinicopathological prognostic factors represents the mainstay of risk classification and has been correlated with prognosis, clinical management, and personalization of patient therapy.[2] The main limitation of molecular and clinicopathological prognostic factors is the need of post-operative surgical specimens, obtained through comprehensive surgical staging. Since pre-operative endometrial sampling performed for tumor diagnosis represents the collection of only a portion of the whole tumor, it may result in undersampling or in sampling errors,[3] and often pre-operative specimen collection can deal with heterogeneity of tumor cell molecular and clinicopathological characteristics. Therefore, an accurate pre-operative tumor characteristics assessment could be highly beneficial for risk stratification, treatment planning, and patient counseling.

In this scenario there is a need for a pre-operative tool that is able to estimate prognostic factors in order to properly frame gynecologic pathology and plan treatment, also and especially in resource-poor setting, where additional tests are often unavailable. In recent years there has been a growing interest in the use of artificial intelligence in a wide range of fields for creating algorithms and statistical models. Machine learning techniques enable computer systems to automatically improve their performance of specific tasks by learning from data, without being explicitly programmed.

The increasing demand for a non-invasive method to extract quantitative and qualitative information from pre-treatment imaging techniques led to the development of radiomics, defined as the "capacity to see more than the human eye". This method aims to attain information contained in each voxel, the minimal component of the three-dimensional radiological image, reflecting the intrinsic pathophysiology

of the tumor tissue, to build a predictive model with machine learning techniques.

An increasing number of studies have examined radiomics analysis in different non-gynecological and gynecological cancers.[4] However, non-unanimous statistical methods and data machine learning approaches have been used. The present meta-analysis aimed to evaluate the role of radiomics in predicting molecular or clinicopathological prognostic factors and survival in patients diagnosed with endometrial cancer.

METHODS

Search Strategy

A search was performed up to October 2022 by two authors (IC, LS) independently, within several databases (MEDLINE, PubMed, Embase) to ensure all relevant studies evaluating the use of radiomics analysis to assess pre-operatively molecular or clinicopathological prognostic factors and survival. The preferred reporting items for systematic reviews and meta-analyses (Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)) guidelines were used for this study.

The process of evidence acquisition combined the following keywords and their MESH terms: "endometrial cancer", "endometrium", "endometrial atypical hyperplasia", "endometrial carcinoma", "radiomics", "texture analysis", "invasion to one-half or more of myometrium", "lymphovascular invasion", "histological grade", "endometrial cancer risk categories", "endometrial cancer high-risk", "endometrial cancer low-risk", "lymph node metastasis", "fluorodeoxyglucose positron emission tomography–computed tomography (PET-CT) imaging and radiomics", "computed tomography (CT) imaging and radiomics", "magnetic resonance (MR) imaging and radiomics".

Article abstracts, full-text articles, and cross-referenced studies identified from retrieved articles were screened for pertinent information. All duplicate records were removed.

Selection of Studies and Methodologic Quality Assessment

Key criteria for inclusion were: (1) original studies published in English in peer-reviewed journals; (2) pathological diagnosis of endometrial cancer; and (3) radiomics analysis on pre-treatment MRI. Studies with incomplete or absent outcomes reports were excluded from the present analysis. The selected studies were comprehensively examined, and relevant data extracted for each paper. The information selected included: author, year of publication, main objective, study design (retrospective or prospective, mono or multicentric), age of patients, histotype, grading, International Federation of Gynecology and Obstetrics (FIGO) staging, histopathological features, deep myometrial infiltration, lymphovascular space invasion, lymph node metastasis, molecular profile, oncologic outcomes, pre-treatment imaging, softwares used for radiomics analysis, and statistical methods used for the selection of features.

The two authors (IC, LS) carried out data extraction and quality assessment from all the retrieved studies based on full-text articles. Discrepancies between the investigators were resolved by consensus. The studies were then classified qualitatively according to the guidelines published in the Cochrane Handbook for Systematic Reviews of Interventions.[5] The risk of bias of studies included in the meta-analysis were assessed according to the Risk of Bias In Non-randomized Studies of Interventions (ROBINS-I).[6] In accordance with the Journal's guidelines, the authors will provide their data for independent analysis by a selected team by the Editorial Team for the purposes of additional data analysis or for the reproducibility of this study in other centers if so requested.

Outcomes

The primary outcome was to evaluate the capability of two-dimensional MRI-based texture analysis features in predicting: high grade (FIGO grading 3 vs grading 1/grading 2); high risk according to European Society of Gynecological Oncology (ESGO)/European Society for Medical Oncology (ESMO)/European Society for Radiotherapy & Oncology (ESTRO) consensus; deep myometrial infiltration; lymphovascular space invasion; lymph node metastasis; oncologic outcomes (progression-free survival, overall survival, disease-specific survival, disease-free survival, and recurrence-free survival); and molecular profile.

Statistical Analysis

Diagnostic accuracy performance of risk prediction models was pooled using the metandi command in Stata,[7] which requires a minimum of four studies and fits a bivariate normal model for the logit (log-odds) transforms of sensitivity and specificity between studies, also modeling correlation between sensitivity and specificity, which is expected to be negative.[8]

RESULTS

Study Selection

The study selection is illustrated in Figure 1A. A search of the MEDLINE (PubMed) database resulted in 153 relevant articles. Fifteen articles met the inclusion criteria, for a total of 3608 patients.[9–23]

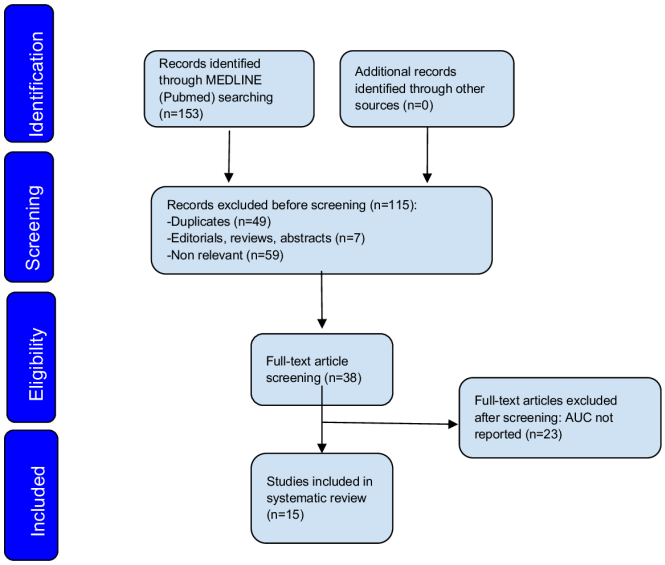

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram. AUC, area under the curve.

Table 1 Characteristics of 15 included studies comprising 3608 patients.

Study characteristic	Studies	N (%)
Publication years		
Before 2019	1	137 (3.8)
2019–2020	3	911 (25.2)
2021–2022	11	2560 (71.0)
Study design		
Prospective	1	177 (4.9)
Retrospective	14	3431 (95.1)
Institutional setting		
Monocentric	11	2256 (62.5)
Multicentric	4	1352 (37.5)
Geographic location		
Europe	3	383 (10.6)
Canada	1	137 (3.8)
Asia	11	3088 (85.6)

Study Characteristics and Patient Characteristics

The characteristics of the included studies are detailed in Table 1. Among the 15 studies included, 1 study (6.7%) was prospective[13] and 14 (93.3%) were retrospective.[9–12 14–23] One study was published in 2017,[9] 3 studies were published between 2019 and 2020,[10–12] and 11 studies were published between 2021 and 2022.[13–23] The risk of bias assessment for the included studies is detailed in online supplemantal table S1.

Software of mage segmentations and feature extraction and selection are detailed in Table 2. Of the included patients, 3139 (87.0%) had endometrioid histotype endometrial carcinoma, while 336 (9.3%) had non-endometrioid histotype endometrial carcinoma; for 133 (3.7%) patients the histotype was not specified. A total of 2640 patients (73.2%) were diagnosed with low/intermediate grade 1 or 2 and 414 (26.8%) were diagnosed with grade 3 endometrial carcinoma; for 554 patients the grade was not specified. Finally, 3126 patients (86.6%) had FIGO stage I and II, while 349 had stage III and IV endometrial carcinoma (9.7%), and for 133 (3.7%) patients the FIGO stage was not specified.

Outcomes

The results for all outcomes are detailed in Table 3. Histologic grade was investigated in six studies for a total of 1099 patients, of which 359 patients (32.7%) were grade 3 and 692 patients (63%) were grade 1 or 2. In 48 patients (4.3%) grading was not specified. Three studies[24–26] were excluded from the analysis for missing data regarding area under the curve (AUC) or true-positive, false-positive, true-negative, and false-negative values for validation cohort or training cohort or both. The pooled sensitivity and specificity were estimated to be 0.785 (95% CI: 0.672 to 0.867) and 0.814 (95% CI: 0.743 to 0.0.869), respectively (Figure 2A).

Histological class of risk was investigated in three studies for a total of 952 patients, of which 411 patients (43.2%) were high-risk class and 541 patients (56.8%) were low/intermediate class. Two studies[27 28] were excluded from the analysis for missing data regarding AUC or true-positive, false-positive, true-negative, and false-negative values for validation cohort or training cohort or both. Unfortunately, metandi requires a minimum of four studies so there was insufficient data for a proper analysis.

Deep myometrial invasion was investigated in five studies for a total of 959 patients, of which 454 patients (47.4%) had myometrial invasion<50% and 503 patients (52.4%) had myometrial

Table 2 Characteristics of radiomics analysis

Authors	Publication year	Study type	Patients (n)	Imaging	Software segmentation	Software extraction	Software selection
Ueno[9]	2017	R	137	MRI	Tex-Rad	Tex-Rad	Tex-Rad
Yamada[10]	2019	R	121	MRI	Life-x	Life-x	XL-STAT
Bereby-Kahanea[11]	2020	R	73	MRI	Tex-Rad	Tex-Rad	Tex-Rad
Yan[12]	2020	R	717	MRI	MITK-Sof	PyRadiomics	LASSO
Jacob[13]	2021	P	177	MRI	Tex-Rad	Tex-Rad	LASSO
Long[14]	2021	R	184	MRI	PhilipsRadiomicsTool	Python	–
Yan[15]	2021	R	209	MRI	MITK-Sof	PyRadiomics	LASSO
Chen[16]	2021	R	102	MRI	ITK-SNAP	AIK	LASSO
Zhang[17]	2022	R	210	MRI	ITK-SNAP	AK-SOFT	SPSS 26.0+RSOFT
Zhao[18]	2022	R	163	MRI	ITK-SNAP	PyRadiomics	LASSO
Otani[19]	2022	R	200	MRI	Life-x	Life-x	Python
Bo[20]	2022	R	136	MRI	ITK-SNAP	AK-SOFT	LASSO
Mainenti[21]	2022	R	133	MRI	–	PyRadiomics	LASSO
Liu[22]	05/2022	R	707	MRI	MITK-Sof	PyRadiomics	LASSO
Liu[23]	08/2022	R	339	MRI	MITK-Sof	PyRadiomics	LASSO

AIK, Artificial Intelligent Kit; AK, Analysis Kit; IBM SPSS 26.0, IBM Statistical Package for the Social Sciences; LASSO, least absolute shrinkage and selection operator; LIFEx, LIFEx freeware; MITK-Sof, Medical Imaging Interaction Toolkit software; MRI, magnetic resonance imaging; P, prospective study; R, retrospective study; RSOFT, R software; Tex-Rad, Texture+Radiology; XL-STAT, XL-STAT software.

Table 3 Results of the statistical analysis

Outcome	Sensitivity (95% CI)	Specificity (95% CI)	Covariance
Grade 3 vs grade 1/2	0.785 (0.672 to 0.867)	0.815 (0.743 to 0.869)	0.032
Deep myometrial invasion	0.743 (0.607 to 0.844)	0.816 (0.740 to 0.874)	0.018
Lymphovascular space invasion	0.656 (0.561 to 0.741)	0.753 (0.597 to 0.862)	0.042
Lymph node metastasis	0.831 (0.634 to 0.933)	0.736 (0.596 to 0.841)	0.146

CI, confidence interval.

invasion>50%. In two patients deep myometrial invasion was not specified. Four studies[24 29–31] were excluded from the analysis for missing data regarding AUC or true-positive, false-positive, true-negative, and false-negative values for validation cohort or training cohort or both. The pooled sensitivity and specificity were estimated to be 0.743 (0.607–0.844) and 0.816 (0.740–0.874), respectively (Figure 2B).

Lymphovascular space invasion was investigated in five studies for a total of 1006 patients, of which 234 patients (23.3%) had lymphovascular space invasion while 772 patients (76.7%) did not. One study[32] was excluded from the analysis for missing data regarding AUC or true-positive, false-positive, true-negative, and false-negative values for validation cohort or training cohort or both. The pooled sensitivity and specificity were estimated to be 0.656 (0.561–0.741) and 0.753 (0.597–0.862), respectively (Figure 2C).

Lymph node metastasis was investigated in five studies for a total of 1430 patients, of which 150 patients (10.5%) had positive lymph node metastasis while 1254 patients (87.7%) had negative lymph node metastasis. In 26 patients lymph node metastasis could not be assessed. Five other studies were excluded[24 33–36] from the analysis for missing data regarding AUC or true-positive, false-positive, true-negative, and false-negative values for validation cohort or training cohort or both. The pooled sensitivity and specificity were estimated to be 0.831 (0.634–0.933) and 0.736 (0.596–0.841), respectively (Figure 2D).

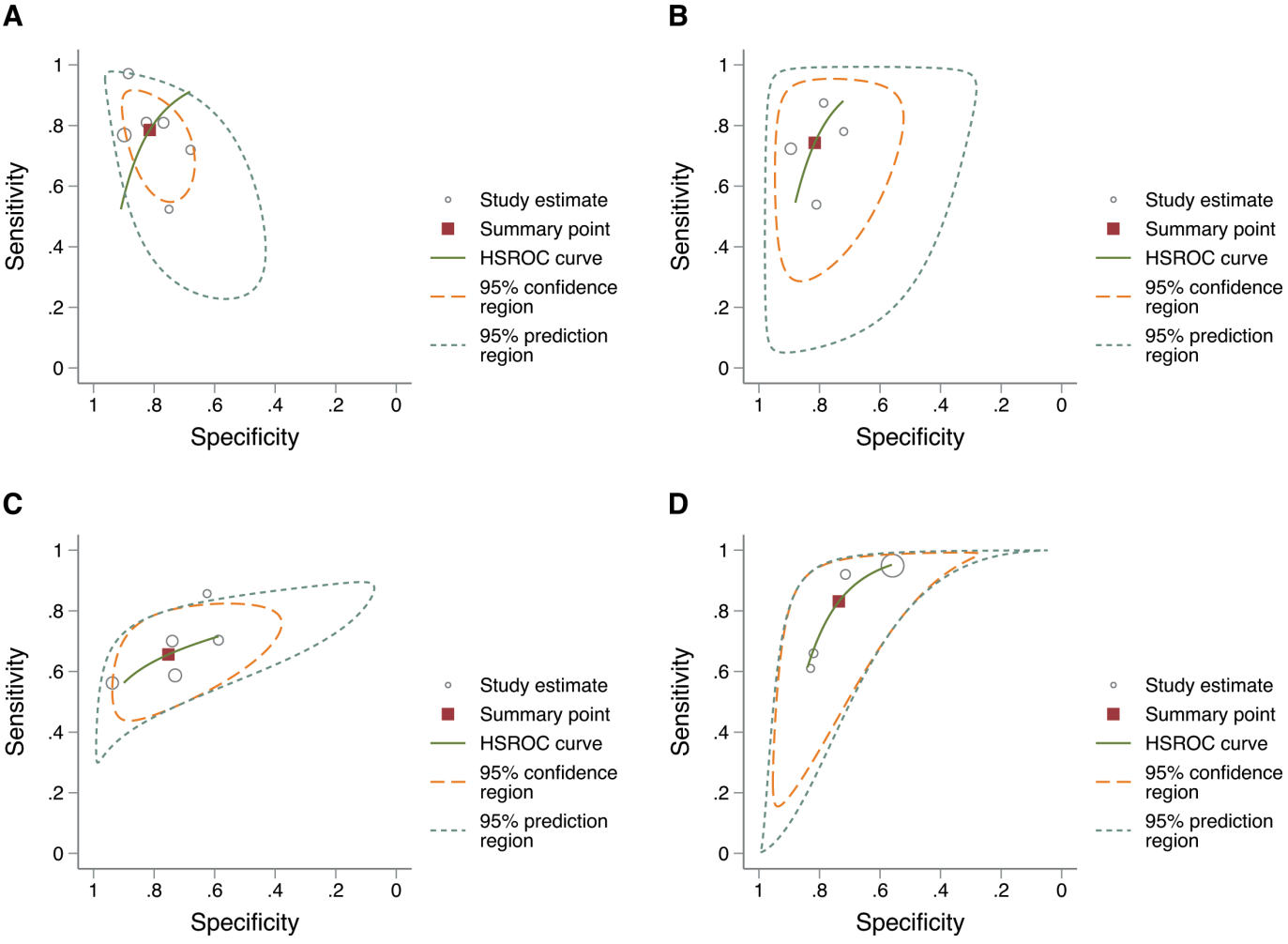

Figure 2 Summary receiver operating characteristic (SROC) plots: (A) Grading 3/high grade. (B) Deep myometrial invasion. (C) Lymphovascular space invasion. (D) Lymph node metastasis. HSROC, hierarchical summary receiver operating characteristic.

Progression-free survival, overall survival, disease-specific survival, disease-free survival, and recurrence-free survival were investigated in four,[24 28 37 38] one,[37] one,[13] one,[39] and one[10] studies, respectively. Unfortunately, the data were not comparable and metandi requires specific data from a minimum of four studies which was not attained, making any statistical analysis impractical. Molecular profile was investigated in three studies.[13 40 41] Unfortunately, the data were not comparable and metandi's specific data requirement was not reached, making any statistical analysis impractical.

DISCUSSION

Summary of Main Results

Radiomics applied to pre-operative MRI in patients diagnosed with endometrial carcinoma has high sensitivity and specificity in predicting lymph node metastasis and grade, and adequate sensitivity and specificity in predicting deep myometrial invasion and lymphovascular space invasion. One of the major findings of the present analysis was the high sensitivity and specificity of radiomics in the evaluation of lymph node involvement, especially for small lymph nodes or in populations considered at low risk.

Results in the Context of Published Literature

Some authors have evaluated the role of radiogenomic analysis in endometrial cancer; however, there are currently no meta-analyses on the topic. Veeraraghavan et al reported a good performance (AUC values of 0.75 and 0.78 in training and validation cohorts) of radiomics on predicting DNA mismatch repair deficiency in 150 patients with endometrial carcinoma.[40] Wang et al reported an excellent performance (AUC values of 0.94 and 0.893 in training and validation cohorts) of radiomics on predicting programmed death-1 (PD-1) expression and association with Lynch syndrome in 100 patients affected by endometrial carcinoma.[41] Jacob et al developed and validated a radiomic prognostic index based on four tumor texture features on pre-operative MRI. High radiomic prognostic index was associated with poor disease-specific survival. Moreover, the association between radiomic prognostic index and gene expression profiles revealed 46 significantly differentiated genes in patients with high radiomic prognostic index.[13]

Therefore, the possibility of radiomics to stratify high-risk endometrial carcinoma by predicting these classical prognostic factors before surgery could be of value.[42] Radiomics is a quantitative approach to medical imaging, which aims at enhancing the existing data available to clinicians by means of advanced mathematical analysis. Several studies from different areas in imaging have been published to date, highlighting the potential increase in using radiomics for decision-making support. However, scientific evidence in gynecologic oncology is generally limited. Some authors have analyzed the role of radiomics in ovarian cancer, investigating the potential predictivity on survival, BRCA mutation status, or possibility to triage benign and malignant lesions or type I and type II epithelial ovarian cancer.[43] Moreover, in cervical cancer, the accuracy in detecting parametrial and nodal invasion has been evaluated.[44]

In endometrial cancer, the choice of performing a surgical evaluation of nodal station and the extension of nodal dissection are both still very much a matter of debate, translated into wide variability across operating centers, ranging from fully systematic pelvic and aortic lymphadenectomy to no nodal evaluation at all. Surgical nodal assessment of early-stage endometrial carcinoma may guide adjuvant treatment; although conversely it does not improve survival, but increases post-operative morbidity and costs.[45 46] Although currently lymph node staging represents the standard, in the near future the combination of MRI radiomic analysis and molecular biology on diagnostic biopsy could enable the omission of lymph node staging. This in turn could lead to a reduction in morbidity associated with surgical procedures, as adjuvant therapy could be based on molecular and radiomic characteristics rather than lymph node status. Increasing the use of pre-operative MRI in low-risk endometrial cancer would potentially provide additional and precise prognostic or diagnostic information that can assist healthcare providers and patients in planning treatment, and in the future it may eventually replace other more expensive assessments. Radiomics analysis represents a reproducible diagnostic support tool that is able to overcome the limitations of standard image techniques, such as the reader's experience and high interobserver variability. The pre-operative applications of MRI-based whole-tumor radiomic and radiogenomic analysis to categorize endometrial cancer risk could potentially help in the pre-operative selection of patients for tailored treatment.

Strengths and Weaknesses

This study is the first meta-analysis with the aim of establishing the diagnostic accuracy of pre-operative MRI-radiomic analysis to risk stratify patients with endometrial cancer, in order to tailor surgical and adjuvant therapy. The subanalysis includes the main prognostic factors of endometrial cancer by assessing individual values of specificity and sensitivity for each outcome. In addition, the main studies in the literature have been included, respecting the inclusion criteria to obtain uniform results from statistical analysis.

We recognize that this study has a number of limitations. First, the studies included were all retrospective in nature. Second, the lack of standardization among methodologies used to create the radiomics models, mathematical methodologies, and data analysis (segmentation and extraction of features). Third, there was limited information on external validation of the radiomics model used. Although more studies and better methods of standardization are needed, improvements in radiomics accuracy and availability would make radiomics an essential support tool for clinicians in tailoring therapeutic choice.

Implications for Practice and Future Research

Future applications of radiomics in the management of endometrial cancer could include determining whether to perform sentinel lymph node mapping versus lymphadenectomy, adjuvant treatment selection, characterizing the disease more than classical histological data, and potentially replacing the molecular findings, thus saving time and resources. Future objectives will be the standardization of radiomics methods and models, and investigations of findings from different imaging techniques

(positron emission tomography–computed tomogrpahy (PET-CT) or CT scan).

CONCLUSIONS

The MRI-radiomics pre-operative analyses in patients diagnosed with endometrial cancer is a good predictor of lymph node metastasis, tumor grade, myometrial invasion, and lymphovascular space invasion in endometrial cancer patients. Applications of MRI-radiomic models in clinical practice could help in tailoring a more personalized management of endometrial cancer treatment, potentially reducing the time and cost of further investigations. Standardization of methodology and more data are needed for radiogenomic evaluation.

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