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Review

Radiomics in Gynaecological Imaging: A State-of-the-Art Review

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Abstract: Radiomics is an emerging field of research based on extracting mathematical descriptive features from medical images with the aim of improving diagnostic performance and providing increasing support to clinical decisions. In recent years, a number of studies have been published regarding different possible applications of radiomics in gynaecological imaging. Many fields have been explored, such as tumour diagnosis and staging, differentiation of histological subtypes, assessment of distant metastases, prediction of response to therapy, recurrence, and patients' outcome. However, several studies are not robust, do not include validation cohorts, or lack reproducibility. On these bases, the purpose of this narrative review is to provide an overview of the most relevant studies in the literature on radiomics in gynaecological imaging. We focused on gynaecological malignancies, particularly endometrial, cervical, mesenchymal, and ovarian malignant pathologies.

Keywords: radiomics; gynaecological imaging; MRI; CT; endometrial cancer; cervical cancer; ovarian cancer; mesenchymal tumours

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1. Introduction

Nowadays, cross-sectional imaging is widely used in clinical practice for diagnosis, treatment planning, and monitoring of various diseases and conditions, as in the case of gynaecological pathologies, both benign and malignant [1]. One of the most used cross-sectional imaging techniques is computed tomography (CT), particularly useful for evaluating different anatomical structures and organs. CT has low accuracy for the characterization of pelvic masses, but it is helpful to evaluate the presence of secondary lesions to the thorax and abdominal organs [2,3].

The most commonly and widely used cross-sectional imaging modality to characterize and correctly stage gynaecological conditions is magnetic resonance imaging (MRI). Thanks to the high soft tissues' spatial and contrast resolutions, MRI can offer detailed images of the female pelvis, with no risk related to radiation dose exposure. Particularly, MRI is considered the non-invasive standard of reference technique in the gynaecological field, both for diagnosis and management [1]. Classical CT and MRI semiotics have, however, some limitations in the precise characterization and prediction of prognosis of some gynaecological malignancies.

During the last few years, several studies aimed at investigating the role of radiomics in gynaecological malignancies, including assessment of diagnosis, response to treatment, and risk of relapse or recurrence, have been published [4–7]. The increase in radiomics papers in gynaecological conditions, as in the case of other topics, can be due to the high number of freeware and user-friendly software available for everyday clinical practice and sometimes due to the simplicity of publications. However, in this large number of papers,

many of them are not sufficiently robust, do not include validation cohorts, are affected by lack of reproducibility, and have too different main objectives.

On these bases, we aimed to collect, summarize, discuss, and underline the most important and robust papers regarding radiomics applied to gynaecological conditions in order to sort out the large amount of data published in the literature and guide further studies in this field. Therefore, the authors of this present study searched MEDLINE (PubMed interface) and EMBASE (Elsevier interface) in August 2023, by using appropriate keywords regarding radiomics applied to gynaecological conditions. For each paper, we included the name of the first author, year of publication, study type (prospective, retrospective), geographical area based on the first author's affiliation, and the main findings of the study.

2. Application of Radiomics in the Female Pelvis: From Segmentation to Features Extraction

To obtain a quantitative reliable result in radiomics studies, it is fundamental to follow a precise radiomics pipeline, composed of five necessary steps: (1) image acquisition, (2) segmentation, (3) features extraction, (4) features selection, and (5) statistical analysis and modelling [8]. All of them should be provided in the most robust way possible, especially to allow reproducibility between studies and centres.

Image acquisition is the first and one of the most important steps. When setting up a radiomics study, imaging protocol(s) must be well delineated (e.g., contrast media administration, timing of dynamic sequences, mandatory and optional MRI sequences). Data regarding CT and MRI protocols for the study of the female pelvis have been comprehensively detailed in the literature [9,10].

Segmentation is a fundamental step in medical image analysis as it allows for the identification and isolation of specific anatomic structures or pathological regions within an image. For computing this aspect, region(s) of interest (ROIs) or volume(s) of interest (VOIs) should be drawn in the interested lesion, organ, or tissue. ROIs can be manually drawn by human readers, semi-automatically or automatically, each of them with advantages and disadvantages.

Manual segmentation has the main disadvantage of being time consuming: the reader should sketch the contours slice by slice using pointing devices. Moreover, this procedure can lead to a reduction in the robustness of radiomics features [11].

On the other hand, semi-automatic and automatic approaches are based on available software or custom-made algorithms; in the case of the semi-automatic approach, the preliminary segmentation will be refined by a human reader [11,12]. Semi-automatic segmentation strategies, providing putative contours that the expert operator is asked to refine or correct, represent a solution to reduce both times and inter-operator variability. Automatic segmentation techniques rely on deep or machine learning (DL and ML, respectively) strategies [13]. These models learn step by step how to segment images if trained on a large amount of already labelled images.

Once the ROI or VOI is segmented, a wide range of quantitative features can be extracted. These features can be categorized into different groups such as shape-based features, intensity-based features, texture-based features, and spatial-relationship-based features. The process that leads to obtaining this quantitative data is named "feature extraction". After that, feature selection is employed to identify the most relevant and discriminative features for a specific clinical task. This step helps reduce the computational burden and improve the robustness of subsequent analysis.

Finally, the extracted and selected radiomic features are subjected to statistical analysis and modelling. Various statistical methods, machine learning algorithms, or deep learning architectures can be applied to explore the relationships between these features and clinical outcomes or other relevant parameters [14].

One of the most important limitations to be underlined regards radiomics features obtained by different scanners and institutions. In fact, radiomic features are usually

strictly dependent on different factors, such as acquisition data, MR technical features, and contrast media, being employed. For these reasons, whether it is necessary to compare radiomics data deriving from different scanners or from multiple institutions, it is of utmost importance to provide a post-processing step, in order to reduce potential bias. Different methods were proposed, including denoising [15], N4 bias field correction [16], voxel size resampling and interpolation, discretization [17], and ComBat harmonization [18]. Technical information regarding these aspects are out of the scope of this present review.

3. Endometrial Cancer

Endometrial cancer (EC) is the most common gynaecological malignancy in industrialized countries, with an expected increasing incidence worldwide [19–21]. EC usually affects postmenopausal patients (75–80% of cases), with a peak between 55 and 65 years, and its most frequent clinical manifestation is abnormal postmenopausal bleeding [19,22].

Diagnosis is based on minimally invasive procedures (hysteroscopy, endometrial biopsy, dilatation, and curettage) and transvaginal ultrasound (TVUS) [22,23]. However, MRI is considered the best technique for pre-operative staging [24,25].

EC is classified according to the recently updated International Federation of Gynaecology and Obstetrics (FIGO) staging system [26] and is traditionally grouped into two major prognostic groups (type I and type II), based on the histological type and FIGO histological grading system [27–29]. Type I tumours account for approximately 80% of endometrial neoplasms and include endometrioid histotypes with pathological grading G1 and G2. This category of EC is characterized by a good prognosis and is typically estrogen responsive. Type II represents approximately 20% of overall endometrial tumours and includes high-grade (G3) endometrioid and non-endometrioid forms (clear-cell, mucinous, carcinosarcomas, undifferentiated forms). This group usually shows a more aggressive course and does not correlate with estrogenic exposure.

In order to provide therapeutic management guidelines, the European Society of Gynaecological Oncology (ESMO), European Society for Radiotherapy and Oncology (ESTRO), and European Society of Gynaecological Oncology (ESGO) guidelines stratify EC into four risk categories (low, intermediate, high intermediate, and high risk) according to histology, grade, stage, and the presence of lymph vascular space invasion (LVSI), which describe tumour behaviour and the likelihood of recurrences, directing toward possible adjuvant therapy [22]. EC clinical behaviour is also influenced by its genomic features; therefore, a reclassification of EC based on genomics has been recently proposed considering four categories (POLE ultramutated, microsatellite instability hypermutated, copy-number low, and copy-number high) [30].

Deep myometrial invasion (DMI) allows for the differentiation between the FIGO stages IA and IB, the most important morphological prognostic factor [31,32]. Even if MRI is the most accurate technique for the evaluation of DMI, its detection is not always straightforward and has shown relatively high inter-observer variability, particularly when the endometrium is thinned (i.e., older patients, endometrial cavity distension), when the endometrial–myometrial interface is obscured by fibroids or adenomyosis, and when the lesion is located in uterine cornual regions [31–34].

Another key prognostic factor is the presence of pelvic or para-aortic nodes metastases (LNM), which is also essential in guiding the therapeutic approach. The principal criterion for suspecting nodes metastases is based on nodal size (short axis > 1 cm). However, this criterion has a low specificity because hyperplastic nodes can also be enlarged, which may lead to a high percentage of false-positive results. At the same time, it has been demonstrated that nodes with a short axis lower than 1 cm are sometimes proved as metastatic at pathology [24,35].

Many studies investigated the possible role of radiomics in improving the assessment of EC [36,37]. The most common imaging modality employed in radiomics investigation studies for EC diagnosis and staging was MRI, using standard diagnostic MRI protocols. According to the latest guidelines of the European Society of Urogenital Radiology (ESUR),

pelvic MRI protocol for EC assessment includes T2WI, diffusion-weighted (DWI), and dynamic contrast-enhanced (DCE) imaging [24].

Multicentric and prospective radiomic studies applied to EC are summarised in Table 1.

3.1. Deep Myometrial Invasion

Due to its clinical and prognostic significance, approximately 10 studies investigated the role of radiomics in assessing DMI. Ueno et al. [38] extracted 11 features from MRI of a small cohort of patients with EC using a random forest model. Areas under the receiver operating characteristic curve (AUC), sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV) to assess DMI were estimated at 0.84, 79.3%, 82.3%, 81.0%, 76.7%, and 84.4%. Stanzione et al. analysed an MRI radiomics-powered machine learning (ML) model to increase radiologists' performance in assessing DMI. After a three-dimensional segmentation of the EC, the authors extracted several radiomic features from a small number of patients (n = 54), concluding that the radiologist's performance increases from 82% to 100% with the radiomics support [39]. In another prospective study, the authors extracted radiomics features from two-dimensional ROIs in 180 patients. Their results proved that high tumour entropy on apparent diffusion coefficient (ADC) maps independently predicted DMI (odds ratio [OR] 3.2, $p < 0.001$) [40]. Another radiomic model, based on whole-tumour features, showed a good performance for DMI prediction, with an AUC of 0.84 and 0.76 in the training and test cohorts, respectively [41]. Zhu and co-workers defined a geometric feature to describe the irregularity of tissue structure inside the corpus uteri caused by EC and built a model combining it with texture features extracted by the whole uterus region. Compared with models in other studies, this model showed better performance in predicting DMI in terms of sensitivity (94.7%) and specificity (93.3%) [42]. Han et al. built three radiomics models on T2WI and DWI. The models based only on T2WI or DWI, and the model which combined T2WI and DWI, which included 24, features obtained in the validation set AUCs of 0.76, 0.80, and 0.85, respectively. Nevertheless, the authors did not observe a statistically significant difference between diagnostic values obtained by the model based on both T2WI and DWI and those obtained by two radiologists' subjective assessments [43]. More recently, three other studies evaluated the performance of MRI radiomics-based machine learning models to predict DMI, obtaining comparable AUC values, including between 0.79 and 0.83 [44–46]. However, in the research performed by Otani and colleagues, the diagnostic performance for DMI of four radiologists did not show statistically significant improvement with the support of radiomic classifiers [46], contrary to a previous investigation [39].

3.2. Nodal Involvement

Due to the limitations of conventional imaging in assessing nodal status and its prognostic relevance, many studies investigated this topic. Ytre-Hauge et al. reported that five texture features correlated with the presence of LNM, even if their accuracy and specificity were lower compared with conventional MRI features [40]. For the evaluation of nodal status, the AUC of a whole tumour radiomics model established by Fasmer and colleagues yielded 0.73 and 0.72 in training and test cohorts, respectively [41]. Xu and colleagues developed four different predictive models, one based on clinical features exclusively, one based solely on radiomic features, and two based on both radiomics and clinical features. Moreover, the authors evaluated the diagnostic performance of the MRI reading of two specialized radiologists. One of the models based on radiomic features, node size, and cancer antigen 125 (CA125) showed the best discrimination ability in the training cohort (AUC: 0.892) and test cohort (AUC: 0.883). On a sub-analysis based on node size, this model achieved the highest sensitivity (97%) and specificity (86%) in the subgroup of enlarged nodes (diameter > 8 mm), which was comparable with radiologists' diagnostic performance (accuracy: 0.970; sensitivity 81%). For the normal-sized nodes (diameter: 3–8 mm) and the small-sized nodes subgroup (diameter < 3 mm) analysis, this

model displayed an accuracy of 0.846 and 0.849, respectively, and a sensitivity of 64.7% and 47.1%, respectively. In both cases, the model outperformed radiologists' reports [47]. A multicentre study established a radiomics model for assessing pelvic LNM on preoperative MRI of a large cohort of patients (n = 662), divided into one training set and two validation sets. The authors compared the performance of the radiomics model with the performance of two experienced radiologists based on MRI findings alone and with the aid of the radiomics model. The AUC values of the model were 0.935 for the training set, and 0.909 and 0.885 for the validations sets. Moreover, with the support of the radiomics model, the authors demonstrated an improvement in radiologists' diagnostic performance in predicting LNM [48]. Finally, a recently published study reported mean AUCs of radiomics classifiers for the assessment of pelvic and para-aortic nodes metastasis of 0.72 and 0.82, respectively [46].

3.3. Lymph Vascular Space Invasion and Tumour Grading

LVSI, defined as the presence of tumour cells in a space lined by endothelial cells outside the invasive border, is another key prognostic factor in EC [49]. In Ueno et al.'s research, 12 texture features extracted from tumour segmentation of 137 MRIs finally correlated with LVSI. AUC, sensitivity, specificity, and accuracy were estimated at 0.80, 80.9%, 72.5%, 76.6%, and 74.3% [38]. A further study performed on a small cohort of MRIs (n = 73) demonstrated that texture analysis may have a limited role in the diagnosis of LVSI since it yielded low diagnostic values (AUC: 0.59; sensitivity: 71%; specificity: 59%) [50]. Almost comparable values were observed by Celli and colleagues. They evaluated an LVSI predictive model based on a single feature from ADC as a predictor, which achieved an AUC of 0.59, a sensitivity of 50%, and a specificity of 61% [51]. More recently, four investigations registered more promising performances of radiomics analysis for LVSI assessment, with reported AUC values between 0.79 and 0.85 [44–46,52].

Several authors also investigated how radiomics may be useful for the assessment of EC histological grades. In a prospective investigation, a texture feature obtained from DCE images was capable of independently predicting a high-risk histological EC subtype (OR 1.01, p = 0.004) [40]. In a recently published multicentric research, Zheng et al. developed a model based on clinical and radiomic features for pathological grade prediction, which outperformed clinical and radiomics-only models, yielding AUCs of 0.920, 0.882, and 0.881 for the training, internal validation, and external validation sets, respectively [53]. Moreover, the classification model based on clinical and T2WI signatures generated by Li et al. obtained very promising results for histological type prediction (AUC: 0.91) on the independent external testing dataset [45]. Lefebvre et al. explored the possible role of harmonic signatures for predicting EC high tumour grade, describing a good performance with an AUC, a sensitivity, and a specificity of 0.81, 93%, and 63%, respectively [54].

With regard to the assessment of the clinical risk category, one of the most robust studies in the literature was published in 2020 by Yan and colleagues on a cohort of 717 pathologically confirmed ECs, divided into a primary group and two validation groups. The authors developed a radiomics nomogram by combining selected radiomics MRI features and clinical parameters. The AUC for the prediction of high-risk EC for the radiomics nomogram in the primary group and the validation groups were 0.896, 0.877, and 0.919, respectively [55]. Chen et al. compared the performance for predicting low-risk EC in a cohort of 102 patients with pathologically proven stage I EC of a model based on clinical and conventional MRI characteristics with those of a model based only on radiomic features extracted from T2WI. Their results showed that the radiomic model had a better performance (AUC of 0.946 vs. AUC of 0.756) [56]. Conversely, the model proposed by Celli et al. for predicting low-risk EC, which was based on two features from ADC maps and T2WI, had a less promising performance (AUC: 0.74) [51]. Moreover, the abovementioned model generated by Li et al. was also tested for predicting high-risk categories, reporting an AUC of 0.82 [45].

3.4. Prognosis

With regards to EC prognosis, a prospective study demonstrated that high kurtosis in post-contrast T1WI was a good predictor of reduced recurrence and progression-free survival (HR 1.5, $p < 0.001$), after adjusting for MRI-measured tumour volume and histological risk at biopsy [40]. In order to assess EC outcome, Jacob et al. generated and validated a radiomic prognostic model based on MRI studies of 177 EC patients. They found that the model predicted 46 genes that were associated with poorer disease survival rates and a statistically significant correlation of the model with poor disease-specific survival ($p < 0.001$) [57]. Concerning EC recurrence risk assessment, Lin and co-workers in their retrospective multicentric research built a model based on clinicopathological and radiomics features extracted from the intra-tumoral area of 421 MRIs. This mode showed optimal performance in predicting the recurrence in terms of AUCs (0.87 and 0.85 in the internal and external validation cohorts, respectively), calibration curve, and decision curve analysis [58].

Table 1. Overview of most relevant radiomic studies applied to uterine endometrial cancer.

First Author	Publication Year	Study Type	Geographical Area	Sample Size	Main Findings	ML Method	PMID
Ytre-Hauge S [40]	2018	Prospective	E	180	ADC can predict DMI while contrast-enhanced T1WI high-risk histological subtype, recurrence- and progression-free survival	N/A	30102441
Yan BC [48]	2020	Retrospective, Multicentre	A	622	The model had an AUC of 0.935 for the training set, and 0.909 and 0.885 for validation sets 1 and 2, in the assessments of pelvic LNM	RF	32749583
Yan BC [55]	2020	Retrospective, Multicentre	A	717	The nomogram showed an AUC of 0.896 in the primary group, 0.877 in the validation group 1, and 0.919 in the validation group 2 in predicting high-risk patients preoperatively	LASSO, LiR, LoR	32681608
Celli V [51]	2022	Retrospective, Multicentre	E	64	ADC can predict the LVSI predictive model based on an AUC of 0.59. By combining ADC and T2WI, the AUC raised to 0.74	LoR	36497362
Lefebvre TL [44]	2022	Retrospective, Multicentre	A	157	Radiomics models for DMI, LVSI, high-grade, and FIGO stages led to AUCs of 0.81, 0.80, 0.74, and 0.84, respectively, in the test and training sets	RF	35819326
Lin Z [58]	2023	Retrospective, Multicentre	A	421	The model based on clinicopathological and radiomics features showed better performance for the prediction of recurrence	LASSO	37171486
Li X [45]	2023	Retrospective, Multicentre	A	413	The signature model based on T2WI reported AUCs of 0.79, 0.82, 0.91, and 0.85 for DMI, high-risk EC, histological type, and LVSI, respectively	LASSO	37190137
Zheng T [53]	2023	Retrospective, Multicentre	A	403	Compared with the clinical model and radiomics model, the combined model showed superior performance; the AUCs were 0.920, 0.882, and 0.881 for the training, internal validation, and external validation sets, respectively	N/A	37097730

ML: machine learning; PMID: PubMed identifier; E: Europe; A: Asia–Pacific; MRI: magnetic resonance imaging; DMI: deep myometrial invasion; LNM: lymph node metastases; EC: endometrial cancer; ADC: apparent diffusion coefficient; T1WI: T1-weighted imaging; OR: odds ratio; HR: hazard ratio; AUC: area under the curve; LVSI: lymph vascular space invasion; T2WI: T2-weighted imaging; FIGO: International Federation of Gynaecology and Obstetrics; N/A: not applicable/not present; RF: random forest regression; LASSO: least absolute shrinkage and selection operator logistic regression; LoR: logistic regression; LiR: linear regression.

3.5. CT-Based Radiomics

To the best of our knowledge, only one study explored the performance of texture analysis based on CT imaging for EC assessment. Ytre-Hauge et al. developed a model to predict DMI, cervical stroma invasion (CSI), and LNM by analysing the tumour texture features from 155 preoperative pelvic contrast-enhanced CTs. They found that high tumour entropy independently predicted DMI and CSI with an AUC of 0.71 and 0.67, respectively. Another CT feature (Kurtosis5) correlated with LNM (AUC = 0.69). Furthermore, high tumour kurtosis tended to independently predict reduced recurrence- and progression-free survival [59].

4. Cervical Cancer

Cervical cancer (CC) is ranked fourth among malignancies in terms of incidence, prevalence, and mortality in women worldwide; however, when early diagnosis is made, CC is one of the most successfully treatable forms of cancer [60]. Patients with CC are staged according to the TNM classification, and the clinical staging is based on the FIGO staging system [61]. The initial workup for assessment of pelvic tumour extent and to guide treatment options is based on pelvic MRI according to consensus recommendations by the ESMO, ESTRO, and European Society of Pathology (ESP) guidelines [62].

Radiological assessment of cervical malignancy for the initial staging, response monitoring, and evaluation of disease recurrence is performed on pelvic MRI according to the ESUR guidelines [63]. The standard pelvic MRI protocol includes T1WI without and with saturation, T2WI with a slice thickness of 4 mm or less, and DWI sequences while contrast-enhanced MRI remains optional. However, pelvic MRI has some limitations in the assessment of CC, mainly related to the limited accuracy for nodes status, largely based on the size criteria (i.e., $\geq$1.0 cm in short axis) which yields a low pooled sensitivity of 56–61% [64], in the assessment of parametrial invasion with a pooled sensitivity of 76% and specificity of 94% [65], as well as in the evaluation of residual disease after chemoradiation therapy with sensitivity and specificity of 80% and 55%, respectively [66]. Given the current limitations of standard imaging techniques, over the last decade, there has been an increasing number of studies investigating if radiomics applied to CT or MRI may fill the current gaps in patients with CC.

Most of these radiomics studies proved a moderate to high performance of radiomics or combined clinical–radiomics models suggesting that radiomics might be used as a prognostic biomarker and helpful in tailoring therapeutic management. In addition, some papers addressed technical issues about radiomics, including the development of a fully automatic whole-volume tumour segmentation tool [67], evaluation of robustness, stability, and reproducibility of radiomic features in pelvic MRI, suggesting the application of normalization prior to features extraction [68–71] and the definition of the best volume of interest to achieve a specific outcome [72].

Multicentric and prospective radiomic studies applied to CC are summarised in Table 2.

4.1. Primary Tumour

With regard to diagnosis, radiomics analysis of cervical mucosa combining contrast-enhanced T1WI images and T2WI seems promising for predicting MRI invisible early stage CCs, and machine learning MRI-based radiomics models may allow for the detection of carcinogenic HPV status in CC [72]. Whole-tumour volumetric 3D radiomics analysis had a good performance in stratifying the histological grade of CC and performed better than the radiomics evaluation of the centre slice of the tumour alone [73]. Wang et al. [74], instead investigated the role of radiomics for predicting different histological subtypes of CC, discovered that multiparametric MRI-based radiomics models may be a promising method to differentiate adenocarcinoma and squamous cell carcinoma, achieving a specificity of 94% by using five combined MRI sequences. More recently, Liu et al. [75] investigated the evaluation of pathological types and the FIGO stage. These authors found that MRI

radiomics features, obtained using T2WI and contrast-enhanced T1WI, achieved an AUC of 0.777 and 0.750, respectively, for differentiating between adenocarcinoma and squamous cell carcinoma. From these two sequences, the AUC that distinguished low from high FIGO stages was 0.716 and 0.676, respectively, while the AUC for node status was 0.730 and 0.618 on T2WI and contrast-enhanced T1WI, respectively.

4.2. Nodal Involvement, Lymph Vascular Space Invasion, and Parametrial Invasion

With regard to the detection of metastatic nodes, multiple original radiomics studies are available so far [76–89]; these studies included a number of patients ranging from almost 100 to more than 700 and only four of these studies were multicentric [86–89] (Table 2). In addition, two metanalyses investigating the accuracy of radiomics for the assessment of nodes status have been published in 2022 by Li et al. [90] and Ren et al. [91]. Based on the metanalysis by Li et al. [92], the pooled diagnostic odds ratio, sensitivity, specificity, and AUC of radiomics in detecting nodes metastasis were 12, 80%, 76%, and 0.83, respectively; in addition, the assessment of multiple sequences and radiomics combined with clinical factors seemed to improve the diagnostic odds ratio compared with the human reading. However, this metanalysis also highlighted the high heterogeneity among the included studies [90]. The metanalysis by Ren et al. [91] concluded that compared with the radiomics analysis, ADC values are more clinically promising because they are more easily accessible and widely applied, with similar pooled diagnostic values. It is worth saying that some additional studies investigated MRI-based radiomics in the prediction of the LVSI preoperatively [92–96], but only the study by Wu et al. [96] was multicentric. In this multicentric study with 168 patients, the authors developed an MRI-based nomogram by combining contrast-enhanced T1WI and T2WI and obtained a moderately high AUC (0.830) for predicting LVSI in the test cohort [96]. To the best of our knowledge, only one study investigated the role of radiomics for predicting parametrial invasion in a retrospective single-centre study with 137 patients; in this study, radiomics signatures obtained with T2WI and joint T2WI and DWI yielded an AUC of 0.797 vs. 0.946 and 0.780 vs. 0.921, respectively, in the primary and validation cohorts [97].

4.3. Response to Treatment

Another interesting and widely studied field of radiomics research in patients with CC is the assessment of response to treatments including conization [98], radiotherapy, chemotherapy, and chemo-radiation therapy [99–109], the evaluation of recurrence [110–113], and toxicity related to radiotherapy [114–116]. Among all studies on the assessment of response to treatments, there are four multicentric studies and one prospective study that deserve attention (Table 2). Three multicentric studies were focused on the response to neoadjuvant chemotherapy. The study by Sun et al. [100] included 275 patients with locally advanced CC and showed that the combined model of the intratumoural zone of T1WI, intratumoural zone of T2WI, and peritumoural zone of T2WI achieved an AUC of 0.998 in the training set and 0.999 in the testing set. Tian et al. [101] included 277 patients and developed a radiomics signature containing pre- and post-contrast imaging features that were able to distinguish responders from non-responders in both primary and validation cohorts with an AUC of 0.773 and 0.816, respectively, and that remained relatively stable across centres. In addition, the combined model incorporating radiomics signature with clinical factors yielded an even better predictive performance compared with radiomics signature alone. More recently, Zhang et al. [109] developed a deep-learning radiomics nomogram to predict response to neoadjuvant chemotherapy with high accuracy; this nomogram performed better than the clinical model and was strongly correlated with disease-free survival. The prospective observational study by Bowen et al. [99] investigated the role of radiomics in predicting the response of PET and MRI in FIGO IB2 -IVA patients receiving external radiotherapy and brachytherapy. Finally, the multicentre retrospective study by Gui et al. [104] analysed 183 patients from two institutions and created a radiomics model to predict pathological complete response after neoadjuvant chemoradiotherapy,

yielding promising results (the RF_DEF model showed a mean AUC of 0.80). It is also interesting to mention that some studies have investigated the role of radiomics in predicting malnutrition after intervention [117], as well as haematological toxicities, changes in the pelvic bone marrow, and proctitis related to radiotherapy [114–116].

Several radiomics original studies also looked for radiomics features and signatures that could help in prognostication [113,118–130]. Among these, five multicentre studies, one prospective study, and one metanalysis are worth mentioning. Some of these studies have focused their attention on radiomics applied to ADC maps [120], yielding high accuracy. Other papers have analysed radiomics of T2WI alone [127,129] and combined it with contrast-enhanced T1WI [119] or with ADC [126]. These models identified radiomics signatures that are promising in predicting several prognostic outcomes. A recently published meta-analysis aimed to determine the impact of radiomics in overall and disease-free survival. The authors demonstrated that current predictive models for treatment toxicity, local or distant recurrence, and survival prediction yield promising results with reasonable predictive accuracy [131]. Nevertheless, studies with large data sets, external validation, validation in prospective clinical trials, and evaluation of the integration of these models into clinical practice are still needed before routine implementation of radiomics in patients with CC.

Table 2. Overview of most relevant radiomic studies applied to uterine cervical malignancies.

First Author	Publication Year	Study Type	Geographical Area	Sample Size	Main Findings	ML Method	PMID
Bowen SR [99]	2018	Prospective	N	21	Histogram quantiles change throughout radiotherapy; some intensity histogram quantiles appeared to be associated with favourable tumour response, including large early RT changes in ADC skewness (AUC = 0.86)	N/A	29044908
Meng J [113]	2018	Prospective	A	34	Two radiomics feature (one from T2WI and one from ADC) were the best-selected predictors of recurrence, yielding an AUC of 0.885	LoR	30061666
Lucia F [120]	2019	Retrospective, Multicentre	E	190	The ADC model can predict disease-free survival with an accuracy of 90% (sensitivity 92–93%, specificity 87–89%)	N/A	30535746
Sun C [100]	2019	Retrospective, Multicentre	A	275	The combined model of the intratumoural zone of T1WI and T2WI and intratumoural zone of T2WI achieved an AUC of 0.998 for predicting the clinical response to neoadjuvant chemotherapy	RF	31395503
Fang J [119]	2020	Retrospective, Multicentre	A	248	The radiomics score demonstrated better prognostic performance in estimating disease-free survival in comparison with clinicopathological features	LASSO, Cox regression	32089742
Tian X [101]	2020	Retrospective, Multicentre	A	277	Radiomics signature can adequately distinguish chemotherapeutic responders from non-responders in both primary and validation cohorts and remain relatively stable across centres, with an AUC of 0.803–0.821	LoR	32117732
Dong T [86]	2020	Retrospective, Multicentre	A	226	A logistic regression model incorporating five radiomic features and two clinicopathological features had an accuracy of 89.20% for predicting the LN status	LoR	32373511

Table 2. *Cont.*

First Author	Publication Year	Study Type	Geographical Area	Sample Size	Main Findings	ML Method	PMID
Hou L [87]	2020	Retrospective, Multicentre	A	168	Radiomics features on T2WI, ADC, and contrast-enhanced T1WI are associated with LNM. Moreover, the radiomic signature can depict LNM with an AUC of 0.825	LASSO	32974143
Gui B [104]	2021	Retrospective, Multicentre	E	183	A radiomics model can predict pathological complete response after neoadjuvant chemoradiotherapy by using T2WI with an AUC of 0.80	N/A	33807494
Liu Y [88]	2021	Retrospective, Multicentre	A	219	A CT-based radiomic model can predict normal-size LNM with an AUCs of 0.912 in the training cohort, 0.859 in the internal validation cohort, and 0.800 in the external validation cohort	SVM	33975178
Ikushima H [111]	2022	Retrospective, Multicentre	A	204	Radiomics combined with clinical parameters can increase the prediction of OFR after chemotherapy, with an AUC of 0.709	LASSO	34865079
Liu Y [75]	2023	Retrospective	A	235	Radiomics can differentiate adenocarcinoma and squamous cell carcinoma with an AUC of 0.777 and 0.750 on T2WI and T1WI. AUC can depict low- and high-FIGO stages (AUC = 0.716 and 0.676). Good results were found also in the detection of tumour grade.	LASSO	34918963
Shi J [89]	2022	Retrospective, Multicentre	A	169	A radiomic signature nomogram can predict LNM status better than a radiomics or clinical model alone (AUC = 0.891 vs. 0.830 vs. 0.812)	LASSO	34968703
Liu B [126]	2022	Retrospective, Multicentre	A	263	A radiomic signature consisting of four radiomic features for disease-free survival prediction demonstrated better prognostic performance in both primary and validation cohorts (C-index: 0.736 and 0.758, respectively) compared with a clinical-based model (C-index: 0.603 and 0.649, respectively)	LASSO, Cox regression	35145910
Autorino R [127]	2022	Retrospective, Multicentre	E	175	A radiomic model can predict overall survival before starting chemoradiotherapy with an AUC of 0.73	LoR	35325372
Wei G [129]	2022	Retrospective, Multicentre	A	83	Authors developed two radiomics models to predict the overall survival by concurrent chemoradiotherapy alone or concurrent chemoradiotherapy followed by adjuvant chemotherapy, with AUCs of 0.832 and 0.879, respectively	Elastic Net Regression, LASSO, Cox regression	35636572
Wu Y [96]	2023	Retrospective, Multicentre	A	168	The nomogram showed high predictive performance in the training (AUC: 0.883) and test cohort (AUC: 0.830) for predicting LVSI	Spearman, LASSO	36929220
Zhang Y [109]	2023	Retrospective, Multicentre	A	285	Radiomics signature showed favourable predictive values in differentiating responders from non-responders to neoadjuvant chemotherapy with high AUCs (over 0.90)	LoR, LASSO	36980381

ML: machine learning; PMID: PubMed identifier; N: North America; A: Asia–Pacific; E: Europe; MRI: magnetic resonance imaging; DWI: diffusion-weighted imaging; FDG: fluorodeoxyglucose; PET: positron emission tomography; CT: computed tomography; CC: cervical cancer; ADC: apparent diffusion coefficient; RT: radiotherapy; AUC: area under the curve; 2D: two-dimensional; 3D: three-dimensional; T2WI: T2-weighted imaging; T1WI: T1-weighted imaging; LNM: lymph node metastases; LN: lymph nodes; OFR: out-of-field recurrence; ROC: receiver operating characteristic; LASSO: least absolute shrinkage and selection operator; FIGO: International Federation of Gynaecology and Obstetrics; SPAIR: spectral attenuated inversion recovery; LVSI: lymph vascular space invasion; N/A: not applicable/not present; RF: random forest regression; LASSO: least absolute shrinkage and selection operator logistic regression; LoR: logistic regression; SVM: support vector regression.

5. Mesenchymal Tumours

Uterine mesenchymal tumours arise from uterine smooth muscle, endometrial stroma, or a combination of both [132]. Benign leiomyomas (LM) are the most common mesenchymal uterine tumours, affecting up to 80% of women of reproductive age [133]. Conversely, uterine sarcomas (US) are a rare form of mesenchymal tumours, accounting for approximately 1% of gynaecological neoplasms and 3–7% of all uterine malignancies, and have a poor prognosis [134]. Currently, there are no reliable imaging criteria for distinguishing US, especially leiomyosarcomas, from LM with atypical features, including degeneration or unusual pattern of growth [135]. The final diagnosis is usually made only after the surgery, based on postoperative histopathological assessment.

Considering the overlap imaging features in atypical LM and US, several authors investigated the possible role of MRI texture analysis in aiding radiologists in the differential diagnosis between these two entities [136]. However, the majority of these publications are retrospective and monocentric, beyond being limited by small sample cohorts of patients, particularly those with malignant lesions.

Malek et al. developed a radiomic model based on MR perfusion, which showed good diagnostic values (accuracy, sensitivity, and specificity of 91%, 100%, and 90%, respectively) [137]. The same authors aimed to develop a decision tree and a complex algorithm to differentiate US and LM, with accuracies of 96% and 100%, respectively. However, the algorithm was reported to be time consuming, with a special limit for everyday clinical practice [138].

Finally, Xie et al. reported that a radiomic model based on ADC map can predict pathological results of patients with sarcomas and atypical leiomyomas with an AUC of 0.83 [139].

Nakagawa and colleagues compared the performance of ML using multiparametric MRI and positron-emission tomography (PET), concluding that the MRI-based model was superior to the PET one and comparable with that of experienced radiologists [140]. Another investigation compared the diagnostic performance of three different volumes of interests (VOIs)—lesion, lesion and surrounding tissue, and whole uterus—in ADC map-based radiomic analysis for distinguishing US and LM. The results showed that the model based on features extracted from VOIs covering the whole uterus had the best diagnostic performance (AUC: 0.876, sensitivity: 76.3%, and specificity: 84.5%) [141]. Yang and Stamp focused their research on distinguishing low-grade US and LM, testing different ML models and various cutting-edge deep learning techniques. For the classic techniques considered, the highest classification accuracy was 0.85, while the most accurate learning model achieved an accuracy of approximately 0.87 [142].

6. Ovarian Pathologies

Ovarian lesions are a frequent cause of gynaecological pathologies with both benign and malignant conditions frequently encountered in clinical practice. Ovarian cancer is in the seventh place for cancer incidence in females and it is associated with high mortality [143]. Epithelial tumours are the most common cause of ovarian cancer, and they include a wide spectrum of lesions with different histopathological features, risk factors, treatment options, and prognosis [143]. Particularly, the most common ovarian lesions are serous and mucinous tumours. In this complex clinical context, radiomics can serve as a relevant tool to improve the diagnosis, management, and prediction of prognosis in patients with ovarian pathologies [144]. Several studies explored the performance of radiomics with a plethora of different aims and outcomes in ovarian pathologies. Relevant multicentric studies are summarized in Table 3.

Ultrasound, CT, and MRI are the most used imaging techniques in patients with ovarian pathologies. Ultrasound is the first imaging modality for the assessment of ovarian pathologies but the differential diagnosis between different entities may be challenging based only on the qualitative assessment. Initial single-centre studies applied the radiomics analysis on ultrasound images to predict the histopathological types and grades of epithe-

lial ovarian cancers [145,146] and prognosis [147] with reported good performances but validation can be problematic as the ultrasound images' acquisitions depend on operator experience. Considering the main aim of this review and the application of CT and MRI in clinical practice, further discussion will be focused on the application of cross-section imaging in different scenarios.

6.1. CT

Contrast-enhanced CT is performed for the preoperative staging in patients with ovarian tumours, providing information on the primary mass and presence of distant metastases. Pan et al. [148] proposed a nomogram with combined radiomics and conventional contrast-enhanced CT features for the preoperative classification between serous and mucinous cystadenomas with an AUC of 0.92 in the external validation cohort. Using non-contrast CT images, Li et al. [149] constructed and externally validated a radiomics model and nomogram with good-to-excellent performance (AUC of 0.83 and 0.95, respectively) for the differential diagnosis between benign and malignant ovarian tumours. A large study including 1329 patients with ovarian tumours provided an AUC of 0.91 of the machine-learning-based radiomics model for the differentiation between the benign and malignant tumours on contrast-enhanced CT [150]. Furthermore, a multicentric study involving 665 patients from four centres reported an AUC of 0.836 for differentiating high-grade and non-high-grade serous carcinoma [151].

CT-based radiomics can also be used to predict overall survival and progression-free survival in patients with ovarian cancer [152,153]. In this setting, a multicentric study performed by Wei et al. [154] demonstrated good accuracy of the radiomics signature on preoperative contrast-enhanced CT and nomogram for the prediction of 18-month and 3-year recurrence risks in patients with advanced high-grade serous ovarian cancer. Fotopoulou et al. [155] recently validated a radiomics prognostic vector, which was independently associated with progression-free survival, in an independent cohort of high-grade serous ovarian cancer imaged with contrast-enhanced CT. Radiomics was also able to predict response to neoadjuvant treatment in patients with high-grade serous ovarian carcinoma based on the segmentation of omental tumour deposits [156].

6.2. MRI

MRI is the most accurate imaging modality for the assessment of ovarian pathologies, and it may be particularly helpful for lesion characterization and stratification of the risk of malignancy. MRI is often performed as a second-line imaging modality in patients with indeterminate adnexal masses detected on other imaging exams. Radiomics analysis in ovarian pathologies has been applied to different MRI sequences, with the more promising results reported for the radiomics features extracted from the T2WI. In a multicentric study, Wei et al. [157] provided a combined model, including radiomics features extracted from the segmentation of T2WI, which achieved a good performance (AUC of 0.86) in the external validation set for the differential diagnosis between benign and borderline epithelial ovarian tumours. Jian et al. [158] applied radiomics to multiple MRI sequences to differentiate type I from type II epithelial ovarian cancers. Li and co-workers [159] proposed an MRI-based radiomics signature for the prediction of recurrence-free survival in patients with high-grade serous ovarian carcinoma. In that study, radiomics features were extracted from the T2WI and post-contrast sequences, with similar performances. In a study including 186 patients, Wang et al. [160] reported that the radiomics model based on T2WI had the highest performance among different MRI sequences of the prediction of prognosis in patients with epithelial ovarian cancers. MRI-based radiomics models have also been tested and validated for the prediction of postoperative residual tumour, peritoneal metastases, or chemotherapy response in patients with ovarian cancers [161–163].

Radiomics can also predict genomics markers, such as BRCA mutations, proteomics, and immunological markers in patients with ovarian cancers, as explored in recent studies [164–166]. Nevertheless, Avesani and co-workers [167] found a low performance of

the radiomics model in predicting BRCA mutation (AUC of 0.46–0.59) when applied to a multicentric cohort of 218 patients from four different centres.

Optimistic results of the current radiomics studies should be balanced by the challenges for the applications of radiomics in ovarian pathologies. Most of the current radiomics research are retrospective single-centre studies lacking external validation. Heterogeneity of imaging acquisition parameters and lack of standardized protocol can limit the application of the radiomics models in external centres [168]. Moreover, inter-reader variability and reproducibility of the radiomics features are crucial for the validation of the radiomics model, and they are often missing in current studies. A recent systematic review pointed out that the methodological rigor and quality of radiomics studies are still unsatisfactory in ovarian pathologies, with a reported radiomics quality score of 6, corresponding to 16.7% of the total score, which is lower compared with other fields of research in radiomics studies [169–171].

Table 3. Overview of most relevant radiomic studies applied to ovarian cancer.

First Author	Publication Year	Study Type	Geographical Area	Sample Size	Main Findings	ML Method	PMID
Wei W [154]	2019	Retrospective, Multicentre	A	142	Radiomics signature's accuracy was 79.7% and 70% for the prediction of 18-month and 3-year recurrence risk in the independent external validation cohort	LASSO, Cox regression	31024855
Veeraraghavan H [164]	2020	Retrospective, Multicentre	N	75	The clinical–genomic model revealed an association between progression-free survival to chemotherapy	Cox regression	33212885
Pan S [148]	2020	Retrospective, Multicentre	A	103	The combined nomogram had an AUC of 0.92 for the differentiation in the external validation cohort	LASSO	32547958
Li S [149]	2021	Retrospective, Multicentre	A	134	Good performance of the radiomics (AUC 0.83) and nomogram (AUC 0.95) for the differential diagnosis between benign and malignant ovarian tumours in the external validation tests	LASSO	33888749
Jian J [158]	2021	Retrospective, Multicentre	A	294	The combined radiomics model had an AUC of 0.847 in the external validation cohort for differentiation between type I and type II epithelial ovarian cancers	LASSO	32743768
Song X [161]	2021	Prospective	A	89	The radiomics model and nomogram had an AUC of 0.928 and 0.944 in the validation cohort, respectively, for the prediction of peritoneal metastasis	LASSO, LoR	33948702
Rundo L [156]	2022	Retrospective, Multicentre	E	109	CT radiomic model based on omental deposits predicted response to neoadjuvant chemotherapy treatment	Elastic Net regression	35785153
Wang M [151]	2022	Retrospective, Multicentre	A	665	Radiomics model had an AUC of 0.836 for differentiating high-grade and non-high-grade serous carcinoma in the testing cohort	LoR	36469315
HU J [153]	2022	Retrospective	A	217	The radiomics model had a c-index of 0.858 for the prediction of overall survival and 0.700 for the prediction of disease-free survival in patients with high-grade serous ovarian cancer	Cox regression	35800777

Table 3. *Cont.*

First Author	Publication Year	Study Type	Geographical Area	Sample Size	Main Findings	ML Method	PMID
Li J [150]	2022	Retrospective	A	1329	The machine learning classifier provided an AUC of 0.91 for the radiomics model and 0.96 for the mixed model for the differential diagnosis between benign and malignant ovarian tumours	KNN, SVM, RF, LoR, MLP, XGBoost	36016613
Wei M [157]	2022	Retrospective, Multicentre	A	417	The combined model had an AUC of 0.86 for the differentiation between benign and borderline epithelial ovarian tumours in the external validation set	LoR	35943620
Fotopolou C [155]	2022	Retrospective, Multicentre	E	323	The radiomic prognostic vector score was independently associated with significantly worse progression-free survival	Cox regression	34923575
Lu J [162]	2023	Retrospective	A	128	The radiomic–clinical nomogram had an AUC of 0.900 for the prediction of residual tumour in the separate validation cohort	LASSO	36587996
Li H [163]	2023	Retrospective, Multicentre	A	301	The combined radiomics nomogram had an AUC of 0.799 for the prediction of platinum resistance in the testing cohort	LoR	36995415

ML: machine learning; PMID: PubMed identifier; A: Asia–Pacific; N: North America; E: Europe; CT: computed tomography; MRI: magnetic resonance imaging; AUC: area under the curve; T2WI: T2-weighted imaging; LASSO: least absolute shrinkage and selection operator logistic regression; LoR: logistic regression; KNN: k-nearest neighbour; SVM: support vector machines; RF: random forest; MLP: multi-layer perceptron; XGBoost: extreme gradient boosting.

7. Conclusions

In conclusion, several radiomics studies applied to gynaecological pathologies have shown promising results in terms of diagnostic and prognostic efficacy. However, many radiomics models were developed using small populations and did not include validation cohorts, which raises doubts about the reproducibility of their results. Moreover, these investigations were mostly performed using manual segmentation methods and thus can be extremely time consuming, especially in the case of radiomics features extracted from multiple acquisitions. For these reasons, researchers' efforts in the future should concentrate on improving the reproducibility and feasibility of radiomics models, in order to accelerate the path to their effective clinical application and, hopefully, to increase their diagnostic and therapeutic impact.

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