Radiomics systematic review in cervical cancer: gynecological oncologists' perspective

Nicolò Bizzarri ,[1] Luca Russo ,[2] Miriam Dolciami,[2] Konstantinos Zormpas-Petridis,[2] Luca Boldrini,[2] Denis Querleu ,[1] Gabriella Ferrandina,[1,3] Luigi Pedone Anchora,[1] Benedetta Gui ,[2] Evis Sala,[2,3] Giovanni Scambia [1,3]

For numbered affiliations see end of article.

Correspondence to
Dr Nicolò Bizzarri, UOC Ginecologia Oncologica, Dipartimento per la salute della Donna e del Bambino e della Salute Pubblica, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Roma 00168, Italy; nicolo.bizzarri@yahoo.com

NB and LR contributed equally.

Received 24 April 2023
Accepted 7 August 2023
Published Online First 15 September 2023

Check for updates

To cite: Bizzarri N, Russo L, Dolciami M, *et al. Int J Gynecol Cancer* 2023;**33**:1522–1541.

ABSTRACT

Objective Radiomics is the process of extracting quantitative features from radiological images, and represents a relatively new field in gynecological cancers. Cervical cancer has been the most studied gynecological tumor for what concerns radiomics analysis. The aim of this study was to report on the clinical applications of radiomics combined and/or compared with clinical-pathological variables in patients with cervical cancer.

Methods A systematic review of the literature from inception to February 2023 was performed, including studies on cervical cancer analysing a predictive/prognostic radiomics model, which was combined and/or compared with a radiological or a clinical-pathological model.

Results A total of 57 of 334 (17.1%) screened studies met inclusion criteria. The majority of studies used magnetic resonance imaging (MRI), but positron emission tomography (PET)/computed tomography (CT) scan, CT scan, and ultrasound scan also underwent radiomics analysis. In apparent early-stage disease, the majority of studies (16/27, 59.3%) analysed the role of radiomics signature in predicting lymph node metastasis; six (22.2%) investigated the prediction of radiomics to detect lymphovascular space involvement, one (3.7%) investigated depth of stromal infiltration, and one investigated (3.7%) parametrial infiltration. Survival prediction was evaluated both in early-stage and locally advanced settings. No study focused on the application of radiomics in metastatic or recurrent disease.

Conclusion Radiomics signatures were predictive of pathological and oncological outcomes, particularly if combined with clinical variables. These may be integrated in a model using different clinical-pathological and translational characteristics, with the aim to tailor and personalize the treatment of each patient with cervical cancer.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Radiomics analysis in cervical cancer is a relatively new field of research.

WHAT THIS STUDY ADDS

⇒ The best predictive performance was obtained by the integration of radiomics features with different clinical, radiological, and pathological parameters.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Integration of radiomics features with known prognostic factors might help clinicians to tailor cervical cancer treatment and follow-up.

INTRODUCTION

Radiomics in gynecological cancers is a relatively new field of research.[1] Cervical cancer is the most studied gynecological tumor,[2] with the first report on radiomics published in 2014.[3] The International Federation of Gynecology and Obstetrics (FIGO) introduced the use of imaging for cervical cancer staging in 2018,[4] and it is known that magnetic resonance imaging (MRI) and positron emission tomography (PET)/computed tomography (CT) are currently the most accurate imaging modalities for local disease and distant metastases staging, respectively.[5]

Radiological evaluation is currently based on qualitative assessment and simple metrics, such as tumor size/evaluation of disease extent on MRI or metabolic activity, and evaluation of lymph node and distant metastases on PET/CT; but images do contain high-dimensional quantitative data that may reflect the 'unseen' tumor characteristics and biological hallmarks.[6]

Radiomics is the process of extracting quantitative features from radiological images (Figure 1). Different radiomics features are typically extracted after contouring the region of interest, generally corresponding to the site of disease. Radiomics quantify the phenotype, which is subsequently correlated with various outcomes, such as prediction of response to treatments, probability of recurrence, and survival.[7]

Texture analysis, histogram analysis and morphometric analysis represent the three main families of features currently analysed in radiomics studies.[6] As a non-invasive method of assessing the tumor and its surrounding microenvironment, radiomics holds the potential to evaluate and monitor tumor characteristics, such as temporal and spatial heterogeneity, thereby potentially reducing the need for invasive procedures.[6 8 9]

Cervical cancer represents an ideal tumor in which radiomics evaluation can be applied, as it spreads in a step-by-step way with parametrial invasion/lymph nodes being the first site of extra cervical metastasis.[4]

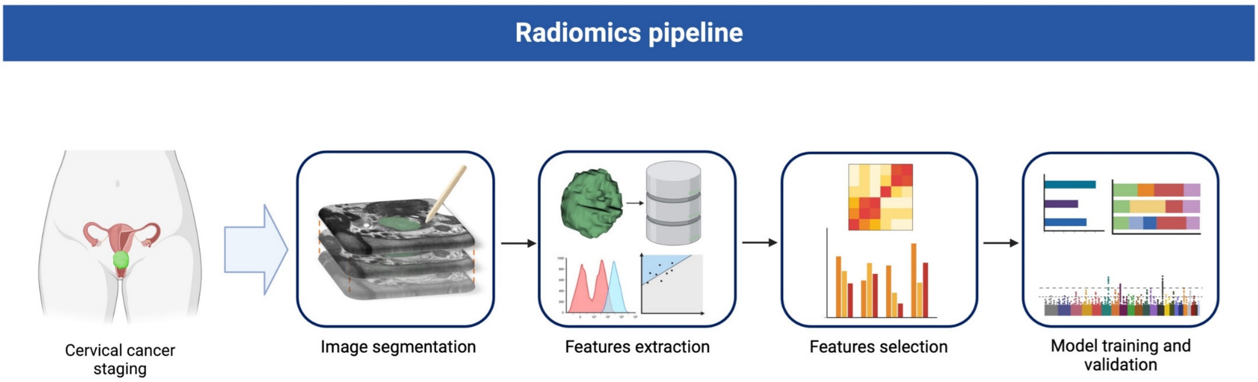

Figure 1 Radiomics standard pipeline. Radiological images are segmented to obtain the region of interest (ROI), corresponding to the tumor volume. The ROI is processed, and high-dimensional radiomic features of different classes are extracted with dedicated software. The feature selection procedure then reduces the number of features, eliminating redundant ones. Afterwards, selected features are combined to build the model for the prediction of the chosen outcome.

Also, the majority of patients are diagnosed with two histological types,[10] with already known clinical-radiological prognostic factors[11] and a limited clinical application of other -omics analyses (such as genomics or proteomics) to date.[12]

The aim of this systematic review was to report on the clinical applications of radiomics combined and/or compared with clinical-pathological variables in patients with cervical cancer.

METHODS

The methods for this review were specified a priori based on the recommendations in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[13]

A systematic search for articles on radiomics and cervical cancer in PubMed and Scopus Database was performed in February 2023. No limit on date of publication was applied (articles from inception to 1 February 2023 were screened). No restriction on the country was applied.

The search terms used the following key words combinations: [((cervix) OR (cervical)) AND ((tumor) OR (cancer) OR (neoplasm)) AND ((radiomic) OR (radiomics) OR (texture))].

Inclusion criteria were:

- ► peer-reviewed original articles;
- ► studies that included patients with diagnosis of cervical cancer;
- ► all FIGO stages;
- ► all type of images; and
- ► studies including a predictive/prognostic radiomics model, which was combined or compared with a radiological or clinical-pathological model.

Reviews, case reports, editorial comments, conference abstracts, short communications, pre-clinical or technical studies, animal studies, and non-English language studies were excluded. Studies analysing pre-invasive disease or colposcopy texture/images were also excluded.

Lastly, studies not including comparison or combination of a radiomics model with a radiological or clinical-pathological model were also excluded.

Data extraction was performed manually and independently by two reviewers (NB and LR), and any disagreement was discussed with a third reviewer (MD). Citations and references of the retrieved studies were used as additional sources. All included articles were evaluated for potential conflicts of interest.

RESULTS

A total of 334 studies were retrieved, and 57 (17.1%) were selected according to the aforementioned criteria. The detailed list of articles included after the selection process is reported in OnlineSupplementalTable 1. The PRISMA flowchart describes the applied selection steps and reports the reasons for exclusion (Figure 2).

Early-Stage Cervical Cancer

Prediction of 'Intermediate' Risk Factors

Patients with apparent early-stage cervical cancer undergoing radical surgery might have the so-called 'intermediate' risk factors at final histology, represented by the combination of tumor size, depth of stromal infiltration, and lymphovascular space invasion (LVSI) status.[14]

A potential application of radiomics is the prediction of 'intermediate' risk factors on pre-operative images.

LVSI

Table 1 demonstrates the different studies investigating the role of different imaging modalities-based radiomics in predicting LVSI. Almost all studies evaluated MRI-based radiomics,[15–19] with only one study evaluating PET/CT-based radiomics.[20] Three of these studies proposed a nomogram including clinical-pathological and radiological variables.[16 18 19] In general, radiomics models reached better concordance indexes in predicting LVSI in cervical cancer than clinical and radiological models alone.

Depth of Stromal Infiltration

The only study analysing depth of stromal infiltration was published by Ren et al,[21] and showed that MRI-based radiomics analysis outperformed radiologists for the pre-operative diagnosis of middle or deep stromal invasion in early-stage cervical cancer. The probability of invasion could be predicted by a nomogram, which included radiomics signature.

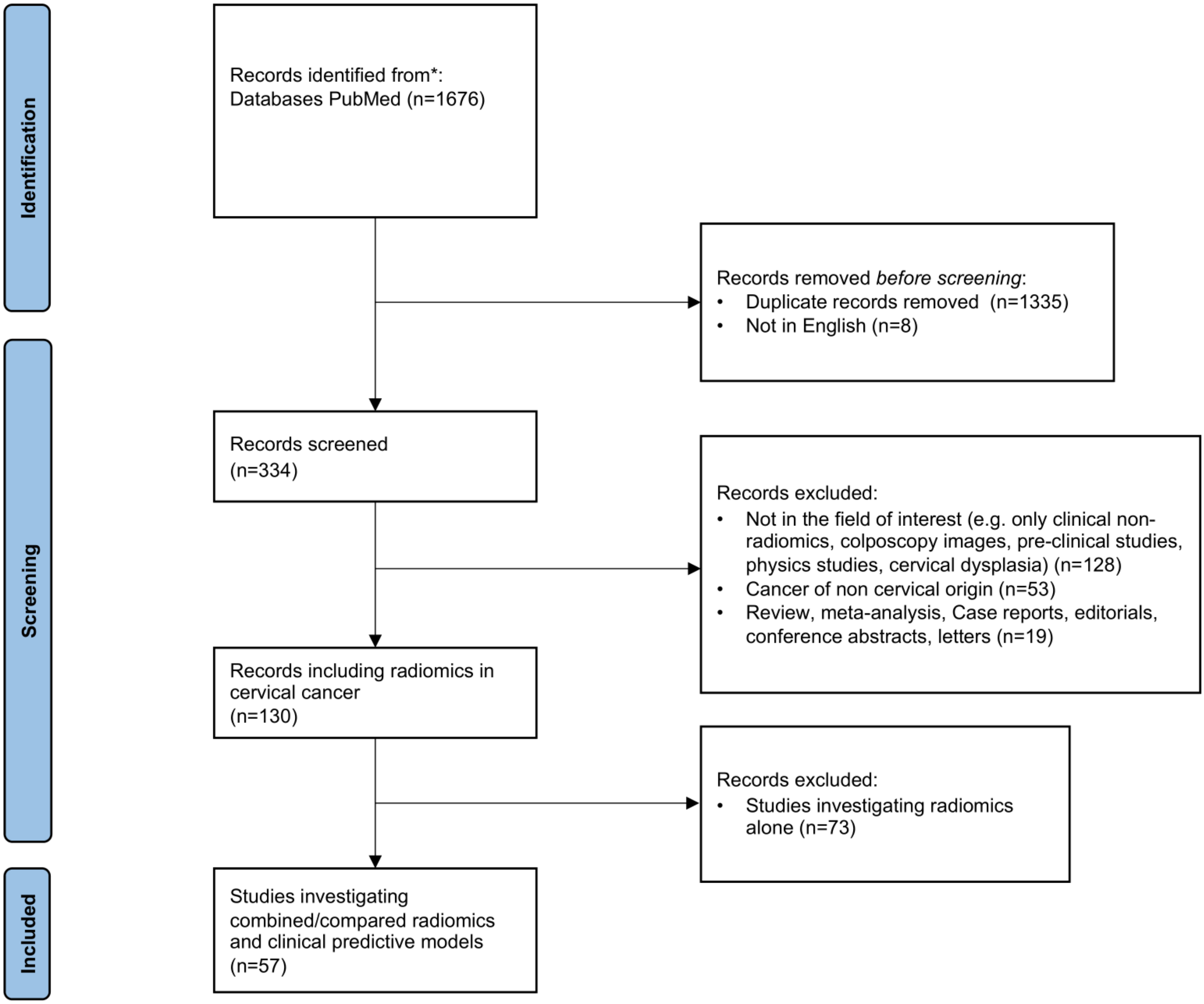

Figure 2 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart.

Prediction of 'High' Risk Factors

High-risk factors include lymph nodes metastasis, parametrial infiltration, and positive surgical margins.[22] When pre-operatively identified, these factors can represent an indication to avoid radical surgery and refer patients to chemoradiotherapy. Surgical margins involvement has not been the specific aim of any study involving radiomics. In fact, prediction of free surgical margins derives from a combination of patient selection and surgical technique. Therefore, this high-risk factor is not accessible pre-operatively. Several studies have assessed the ability of radiomics to predict high-risk factors such as occult lymph node metastases and parametrial invasion, otherwise occult at standard imaging.

Lymph Node Metastasis

Prediction of lymph node metastases in patients with cervical cancer has been the most investigated topic in radiomics studies. Table 2 shows the studies analysing the radiomics prediction of lymph node metastases.

Of the 16 included studies, 11 (68.8%) performed radiomics analysis by contouring the tumor,[23–33] three (18.8%) by contouring the tumor and the peri-tumoral area,[34–36] and two (12.5%) by contouring the lymph nodes.[37 38] One of the first studies evaluating the role of PET/CT-based radiomics in predicting lymph node metastases[23] showed that the combination of radiomic features and vascular-endothelial growth factor (VEGF) expression had a significantly superior predictive value (area under the curve 0.878, 95% CI 0.772 to 0.947), compared with that of the conventional metabolic parameters.

Other authors showed that the performance of MRI-based radiomics model was significantly better than that of each predictive factor alone (including clinical stage and MRI-reported lymph node status).[24] Several studies[25–32 34–38] evaluated the role of MRI-based radiomics in the prediction of nodal metastases; the majority concluded that the radiomics signatures are more accurate in predicting lymph node metastases compared with clinical-radiological features. The best performance was reached by the model which combined radiomics and clinical-radiological features.

Two studies evaluated the predictivity of CT-based radiomics to predict lymph node metastases with promising results, especially

Table 1 Studies comparing or combining clinical and radiomics models in predicting LVSI in cervical cancer

Authors	Title	Year	Journal	Design	No of participants	Internal validation set	External validation set	Imaging	Nomogram	Machine learning or deep learning	AUC radiomics model (max)	AUC radiomics model external validation set	Clinical model compared or combined with radiomics model	Main conclusion
Wu et al[15]	Radiomics analysis of multiparametric MRI evaluates the pathological features of cervical squamous cell carcinoma	2019	J Magn Reson Imaging	Retrospective	56	No	No	MRI (T2, T2 FS, ADC, Ktrans, Ve, Vp)	No	Machine learning	0.831	No	Combined	Functional maps exhibit better discriminative values than anatomical images.
Li et al[16]	MR-based radiomics nomogram of cervical cancer in prediction of the lymph-vascular space invasion preoperatively	2019	J Magn Reson Imaging	Retrospective	105	Yes	No	MRI (T1)	Yes	Machine learning	0.754	0.727	Combined	Radiomics model performed better than MRI model in predicting LVSI.
Li et al[20]	Prediction of lymphovascular space invasion using a combination of tenascin-C, cox-2, and PET/CT radiomics in patients with early-stage cervical squamous cell carcinoma	2021	BMC Cancer	Retrospective	112	Yes	No	PET/CT	No	Machine learning	0.914	0.806	Combined	Combination of PET radiomics with COX-2 and tenascin-C provides a new tool for detecting LVSI.
Huang et al[17]	Multi-parametric magnetic resonance imaging-based radiomics analysis of cervical cancer for preoperative prediction of lymphovascular space invasion	2022	Front Oncol	Retrospective	125	Yes	No	MRI (sFOV, T2, ADC, T2WI, FS-T2WI, T1c)	No	Machine learning	0.922	No	Combined	The multi-parametric MRI-combined radiomics model reached a better performance than the clinical parameters.
Xiao et al[18]	Multiparametric MRI radiomics nomogram for predicting lymph-vascular space invasion in early-stage cervical cancer	2022	Br J Radiol	Retrospective	233	Yes	No	MRI (T1, FS-T2WI, DWI, ADC, CE)	Yes	Machine learning	0.810	No	Combined	The nomogram and rad-score could be used conveniently and individually to predict LVSI.
Cui et al[19]	Multi-parametric MRI-based peri-tumoral radiomics on prediction of lymph-vascular space invasion in early-stage cervical cancer	2022	Diagn Interv Radiol	Retrospective	163	Yes	No	MRI (CE T1W, T2W)	Yes	Machine learning	0.771	0.788	Combined	Radiomics nomogram from peri-tumoral regions and the degree of cellular differentiation can be used as a non-invasive tool for predicting LVSI.

ADC, apparent diffusion co-efficient; AUC, area under the curve; CE, Contrast-Enhanced; COX-2, cyclooxygenase-2; DWI, Diffusion-weighted imaging; FS, Fat-saturation; Ktrans, volume transfer constant; LVSI, lymphovascular space invasion; MRI, magnetic resonance imaging; PET, positron emission tomography; sFOV, scanning field of view.

Table 2 Studies comparing or combining clinical and radiomics models in predicting lymph node metastases in cervical cancer

Authors	Title	Year	Journal	Design	No of participants	Countoured region	Internal validation set	External validation set	Imaging	Nomogram	Machine learning or deep learning	AUC radiomics model (max)	AUC radiomics model external validation set	Clinical model compared or combined with radiomics model	Main conclusion
Li et al[23]	Value of [^{18}F]FDG PET radiomic features and VEGF expression in predicting pelvic lymphatic metastasis and their potential relationship in early-stage cervical squamous cell carcinoma	2018	Eur J Radiol	Retrospective	94	Tumor	Yes	No	FDG PET/CT	No	Machine learning	0.803	No	Combined	Radiomic features in combination with the VEGF expression level improved the prediction accuracy.
Kan et al[25]	Radiomic signature as a predictive factor for lymph node metastasis in early-stage cervical cancer	2019	J Magn Reson Imaging	Retro	143	Tumor	Yes	No	MRI (T1CE, T2)	No	Machine learning	0.754	No	Compared	The radiomic signatures allowed good discrimination of lymph node metastasis (better than conventional radiology).
Yu et al[24]	Feasibility of an ADC-based radiomics model for predicting pelvic lymph node metastases in patients with stage IB-IIA cervical squamous cell carcinoma	2019	Br J Radiol	Retro	153	Tumor	Yes	No	MRI (ADC)	No	Machine learning	0.870	No	Combined (no comparison with clinical/radiomic model alone)	The radiomics model was significantly better than that of each predictive factor alone.
Wang et al[26]	Preoperative prediction of pelvic lymph nodes metastasis in early-stage cervical cancer using radiomics nomogram developed based on T2-weighted MRI and diffusion-weighted imaging	2019	Eur J Radiol	Retro	96	Tumor	Yes	No	MRI (T2, DWI)	Yes	Machine learning	0.909	No	Comparison combined model versus clinical-pathological	The radiomics nomogram demonstrated an improved prediction ability for lymph node metastasis. The radiomics nomogram integrating the radiomics signature with clinical-pathologic risk factors showed a significant improvement over the nomogram based only on clinical-pathologic risk factors in the primary cohort and validation cohort.
Wu et al[34]	Radiomics analysis of MRI improves diagnostic performance of lymph node metastasis in patients with cervical cancer	2019	Radiother oncol	Retro	189	Tumor+peri-tumor	Yes	No	MRI (T2 tumor +peritumoral)	No	Machine learning	0.895	No	Combined	The decision tree that combines radiomics model of MRI and clinical lymph node status achieved best diagnostic performance.
Yan et al[27]	A preoperative radiomics model for the identification of lymph node metastasis in patients with early-stage cervical squamous cell carcinoma	2020	Br J Radiol	Retro	190	Tumor	Yes	No	MRI (T2FS)	Yes	Deep learning	0.852	No	Combined	Radiomics signature and SCC-Ag demonstrated good performance in identifying lymph node metastasis.

Continued

Table 2 Continued

Authors	Title	Year	Journal	Design	No of participants	Countoured region	Internal validation set	External validation set	Imaging	Nomogram	Machine learning or deep learning	AUC radiomics model (max)	AUC radiomics model external validation set	Clinical model compared or combined with radiomics model	Main conclusion
Wu et al[35]	Development of a deep learning model to identify lymph node metastasis on MRI in patients with cervical cancer	2020	JAMA Netw Open	Retro	894	Tumor+peri-tumor	No	Yes	MRI (T1CE, T2, DWI)	No	Deep learning	0.963	0.933	Combined	The deep learning model that used both intratumoral and peri-tumoral regions on contrast-enhanced T1-weighted imaging showed the best performance. These results were further improved in a hybrid model that combined tumor image information mined by deep learning model and MRI-reported lymph node status. Moreover, the hybrid model was significantly associated with disease-free survival from cervical cancer.
Song et al[37]	Feasibility of T(2)WI-MRI-based radiomics nomogram for predicting normal-sized pelvic lymph node metastasis in cervical cancer patients	2021	Eur Radiol	Retro	132	Tumor+LNs	Yes	No	MRI (T2)	Yes	Machine learning	0.820	No	Combined	The combination of lymph node radiomics signature with lymph node clinical morphological features could discriminate lymph node metastasis relatively well.
Xia et al[28]	Radiomics based on nomogram predict pelvic lymphnode metastasis in early-stage cervical cancer	2022	Diagnostics	Retro	150	Tumor	Yes	No	MRI (T2)	Yes	Machine learning	0.988	No	Combined	The combined radiomics-clinical model had highest performance in discriminating lymph node metastasis.
Qian et al[29]	RESOLVE DWI based deep learning nomogram for prediction of normal sized lymph node metastasis in cervical cancer: a preliminary study	2022	BMC Med Imaging	Retro	169	Tumor	Yes	No	MRI (DW, ADC)	Yes	Deep learning	0.890	No	Combined (comparison with radiomic model only)	The deep learning nomogram showed the best performance in development cohort and test cohort.
Xiao et al[30]	MRI texture analysis for preoperative prediction of lymph node metastasis in patients with nonsquamous cell cervical carcinoma	2022	Acad Radiol	Retro	104	Tumor	Yes	No	MRI (T1CE, T2, DWI)	No	Machine learning	0.79	No	Combined	The MRI-based support vector machine models performed better than morphologic criteria of lymph node status MRI and yielded similar discrimination abilities in predicting lymph node metastasis in the training and testing cohorts. In addition, the MRI-based support vector machine models showed robust performance in the adenocarcinoma and adenosquamous carcinoma subgroups.

Continued

Table 2 Continued

Authors	Title	Year	Journal	Design	No of participants	Countoured region	Internal validation set	External validation set	Imaging	Nomogram	Machine learning or deep learning	AUC radiomics model (max)	AUC radiomics model external validation set	Clinical model compared or combined with radiomics model	Main conclusion
Zhang et al[38]	Feasibility of predicting pelvic lymph node metastasis based on IVIM-DWI and texture parameters of the primary lesion and lymph nodes in patients with cervical cancer	2022	Acad Radiol	Retro	143+83	Tumor+LNs	Yes	No	MRI (IVIM-DWI)	No	Machine learning	0.937	0.937	Combined	Models based on intravoxel incoherent motion diffusion weighted imaging and texture parameters of primary lesions and lymph nodes both performed well in diagnosing pelvic lymph node metastasis of cervical cancer and were superior to morphological features of lymph nodes. Especially, parameters of lymph nodes showed higher diagnostic efficiency and clinical significance.
Liu et al[31]*	Development of a deep learning-based nomogram for predicting lymph node metastasis in cervical cancer: A multicenter study	2022	Clin Transl Med	Retro	1123	Tumor	Yes	Yes	CT	Yes	Deep learning and machine learning	0.867	0.804	Combined	The performance of deep learning nomogram surpassed the diagnosis of experienced gynecologists. Therefore, deep learning nomogram can serve as a non-invasive tool for lymph node metastasis determination and thus assist treatment decision-making.
Shi et al[36]	MRI-based peri-tumoral radiomics analysis for preoperative prediction of lymph node metastasis in early-stage cervical cancer: a multi-center study	2022	MRI	Retro	169	Tumor+peri-tumor	Yes	Yes	MRI (T1CE, T2)	Yes	Machine learning	0.891	0.804	Combined	High clinical potential for intra-tumoral and peri-tumoral radiomics with multi-modal MRI for pre-operative predicting lymph node metastasis.
Huang et al[32]	Reduced field-of-view DWI-derived clinical-radiomics model for the prediction of stage in cervical cancer	2023	Insights into Imaging	Retro	94	Tumor	Yes	No	MRI (ADC)	Yes	Machine learning	0.887	0.887	Combined	The reduced field-of-view DWI-derived combined clinical-radiomics model has the potential for staging cervical cancer, thereby facilitating clinical decision-making.
Chen et al[33]	Noninvasive CT radiomic model for preoperative prediction of lymph node metastasis in early cervical carcinoma	2020	Br J Radiol	Retro	150	Tumor	Yes	No	CT	No	Machine learning	0.800	No	Combined (no comparison with clinical/radiomic model alone)	Radiomics and FIGO stage, predicted lymph node status. A noninvasive radiomic model, combining two radiomic features and a FIGO stage, was built for prediction of lymph node status in early cervical carcinoma.

*The article was not published as an original article but rather as a letter to the editor; nevertheless, it has been included as it provides original data.
ADC, apparent diffusion co-efficient; AUC, area under the curve; CE, contrast-enhanced; CT, computed tomography; DWI, diffusion weighted imaging; FDG, fluorodeoxyglucose; FIGO, International Federation of Gynecology and Obstetrics; FS, Fat-saturation; IVIM, intravoxel incoherent motion; LN, lymph node; MRI, magnetic resonance imaging; PET, positron emission tomography; SCC, squamous cell carcinoma; VEGF, vascular endothelial growth factor.

when a deep learning-based analysis was performed.[31 33] In particular, Liu et al showed that the radiomics models surpassed the radiological prediction of lymph node metastases,[31] while Chen et al developed a combined radiomics-FIGO stage model with high prediction of nodal involvement.[33]

Parametrial Invasion

Only a few studies showed that radiomics signature of the primary tumor is able to predict the likelihood of occult parametrial involvement at pre-operative MRI scan with high accuracy. This information could be used as a supplementary tool to provide individualized treatment plans for patients with cervical cancer.[39 40]

Survival

Two studies showed that radiomics signature was more accurate in predicting disease-free survival compared with clinical-pathological features alone.[41 42] However, conflicting results were reported on the performance of combined radiomics-clinical-pathological models in predicting survival,[41 42] with one study showing no significant survival improvement given by the combined model,[41] and the other demonstrating that the combined model performed better than the clinical model in disease-free survival prediction in both the training and validation set.[42] In particular, in the study by Fang et al,[41] 18 features were identified to be predictive for disease-free survival, including 10 features derived from contrast-enhanced T1-weighted (CET1w) images and eight features extracted from T2-weighted (T2w) images. This might indicate that CET1w images probably contains more prognostic information than T2w images. Importantly, shape flatness was included in the 10 CET1w-derived features, whereas small flatness value indicated an irregular tumor shape.

In the other study by Zhou et al,[42] 4/8 (50.0%) of the selected features were derived from CET1w, indicating that intra-tumoral and peri-tumoral tumor enhancing features are potentially associated with tumor perfusion and vascularization; thus, providing a prognostic signature in early cervical cancer.

Locally Advanced Cervical Cancer

Table 3 includes studies on radiomics signatures in locally advanced cervical cancer.

The majority of studies (21/30, 70.0%), analysed radiomics models in patients undergoing exclusive chemoradiotherapy.[3 43–63] Most of these studies reported on survival (both disease-free survival and overall survival),[43–45 47 49–54 56–62 64] or response to therapy[3 43 44 46 48 55 63 65 66] as main predictive outcome of interest.

MRI-based[3 43 44 46 50 52 55–59 61–65] and PET/CT-based[43–45 47–49 51 54 60] radiomics were mainly used, with only two studies using CT-based radiomics.[53 66] Overall, the radiomics signature predicted the above-mentioned outcomes of interest better than clinical-pathological-radiological models. The combined models were the best predictors in most of studies, with only a few studies concluding that combined/integrated models did not perform better than clinical models.[3]

Distant Metastasis and Recurrent/Persistent Cervical Cancer

None of the analysed studies included patients with diagnosis of distant metastasis or with recurrent/persistent cervical cancer.

DISCUSSION

Summary of Main Results

This systematic review reports the application of radiomics on images acquired in different cervical cancer settings (Figure 3). It showed that the best predictive performance was obtained by the integration of radiomics with different parameters including clinical, radiological, and histopathological ones.[67] The majority of studies on early-stage disease focused on prediction of lymph node metastases; in locally advanced disease they focused on prediction of response to treatment and survival. No radiomics studies evaluated distant metastases or recurrence.

Radiomics analysis in cervical cancer represents an opportunity to pre-operatively predict intermediate and high-risk factors that would change the type of surgery or the indication to surgery.

Results in the Context of Published Literature

Radiomics was born with the aim to bridge the gap between standard medical imaging and personalized medicine.[68 69] In-depth analysis of bioimages can provide the detailed information needed to guide gynecological oncologists to tailor the treatment according to the characteristics of the tumor. Radiomics can be indeed considered part of precision medicine in the multi-omics approach.

Recently, there has been a significant evolution in the clinical decision-making process, which can now benefit from multiple approaches to assist the physicians in the diagnosis, treatment, and prediction of outcomes, leading to personalized care for every single patient. The integration of different -omics information can improve on the integrated system by objectively quantifying the disease features and more accurately predicting different outcomes.[70] Prediction of 'intermediate risk factors' in early-stage disease (LVSI and depth of stromal invasion) represents an important tool that can aid surgeons to tailor the radicality of the surgery.[14]

It is known that lymph node metastasis represents the worst prognostic factors in apparent early-stage disease.[11] Lymph node involvement is currently assessed using morphologic features (short axis >8–10 mm, shape, margins, and signal intensity) on MRI and glucose uptake at ^{18}FDG-PET/CT, with high specificity (93%) and low sensitivity (53–66%). The low sensitivity is due to the limited capability for conventional imaging to detect small metastatic lymph nodes (short axis <5 mm). The addition of diffusion weighted imaging (DWI) increases sensitivity of MRI up to 87%, even if it suffers from low specificity.[71]

The prediction of lymph node metastasis in apparent early-stage cervical cancer has been one of the most studied topics in radiomics analyses, with two meta-analyses recently published. The first involved 12 studies with a total of 793 patients, and showed that pre-operative MRI-based radiomics features perform well in predicting lymph node metastasis with pooled sensitivity of 80% and an area under the curve of 76%.[72] The second, more recent, meta-analysis included 22 studies with a total of 2314 patients, and showed that both apparent diffusion co-efficient values and radiomics analysis demonstrated good diagnostic performance for the detection of lymph node metastasis. Radiomics demonstrated higher pooled sensitivity than conventional imaging features. Compared with radiomics analysis, apparent diffusion co-efficient values were clinically more promising, as they are more easily accessible and widely applied, and show a non-statistically significant trend to outperform radiomics analysis. Given the generally

Table 3 Studies analysing radiomics signature in locally advanced cervical cancer

Authors	Title	Year	Journal	Design	No of participants	Stage	Treatment	Outcome	Internal validation set	External validation set	Imaging	Nomogram	Machine learning or deep learning	AUC radiomics model (max)*	AUC radiomics model external validation set	Clinical model compared or combined with radiomics model	Main conclusion
Torheim et al[3]	Classification of dynamic contrast enhanced MR images of cervical cancers using texture analysis and support vector machines	2014	IEEE Trans Med Imaging	Retrospective	81	LACC	CCRT	Response to therapy	Yes	No	MRI (DCE)	No	Machine learning	Accuracy*	No	Compared and combined	Pre-treatment dynamic contrast-enhanced MRI of locally advanced cervical cancer contained information relevant for prediction of treatment response. For predicting outcome of chemoradiotherapy for cervical cancer patients, texture features appear to be better predictors than first-order statistical features, and can compete with the clinical factors (tumor volume and stage). Combining the three significant models based on radiomics features with the clinical features volume and stage did not improve classification performance.
Lucia et al[43]	Prediction of outcome using pretreatment 18F-FDG PET/CT and MRI radiomics in locally advanced cervical cancer treated with chemoradiotherapy	2017	Eur J Nucl Med Mol Imaging	Retrospective	102	LACC	CCRT	DFS+LRC	Yes	No	18F-FDG PET/CT+MRI	No	Machine learning	0.950	No	Compared	In LACC treated with CRT, radiomics features from functional imaging diffusion-weighted imaging (MRI and PET, respectively) are independent predictors of recurrence and loco-regional control with significantly higher prognostic power than usual clinical parameters.
Lucia et al[44]	External validation of a combined PET and MRI radiomics model for prediction of recurrence in cervical cancer patients treated with chemoradiotherapy	2018	Eur J Nucl Med Mol Imaging	Retrospective	78	LACC	CCRT	DFS+LRC	No	Yes	18F-FDG PET/CT+MRI	No	Machine learning	No	0.930	Compared (vs clinical-pathological features: FIGO stage, volume, tumor size, nodal status, histology)	The previously developed PET/MRI radiomics predictive models were successfully validated in two independent external cohorts. The DFS model reached a high accuracy better than prediction using standard clinical variables.
Chen et al[45]	Textural features of cervical cancers on FDG-PET/CT associate with survival and local relapse in patients treated with definitive chemoradiotherapy	2018	Sci Rep	Retrospective	142	LACC	CCRT	OS+PFS + DMFS * PRFS	Yes	No	18F-FDG PET/CT		None	Survival analysis with HR by single characteristic (textural or clinical features)*	No	Compared	In cervical cancer patients receiving definitive chemoradiotherapy, pre-treatment textural features on 18F-FDG-PET/CT can supplement the prognostic information.

Continued

Table 3 Continued

Authors	Title	Year	Journal	Design	No of partici pants	Stage	Treatment	Outcome	Internal validation set	External validation set	Imaging	Nomogram	Machine learning or deep learning	AUC radiomics model (max)*	AUC radiomics model external validation set	Clinical model compared or combined with radiomics model	Main conclusion
Sun C et al[65]	Radiomic analysis for pretreatment prediction of response to neoadjuvant chemotherapy in locally advanced cervical cancer: a multicentre study	2019	EBioMedicine	Retrospective	275	LACC	NACT	Response to therapy	Yes	No	MRI (T2 intra-tumoral and peri-tumoral, T1 intra-tumoral)	No	Machine learning	0.998 (multi-sequence model)	0.999	Compared	This study demonstrated that MRI-based radiomic features hold potential in the pre-treatment prediction of response to NACT in LACC, which could be used to identify rightful patients for receiving NACT and avoiding unnecessary treatment.
Fang et al[46]	Multi-habitat based radiomics for the prediction of treatment response to concurrent chemotherapy and radiation therapy in locally advanced cervical cancer	2020	Front Oncol	Retrospective	120	LACC	CCRT	Response to therapy	No	No	MRI (T2+T1 CE + DWI)	No	Machine learning	0.820	0.798	Compared	A radiomic model employing features from multiple tumor habitats held the ability for predicting treatment response in patients with locally advanced cervical cancer before chemoradiation. The radiomic model has shown good predictive performance, and proved to perform better than each single signature or clinical characteristic.
Mu et al[47]	18F-FDG PET/CT habitat radiomics predicts outcome of patients with cervical cancer treated with chemoradiotherapy	2020	Radiol Artif Intell	Retrospective	154	LACC	CCRT	PFS+OS	Yes	No	18F-FDG PET/CT	Yes	Machine learning	0.860	0.850	Combined (Comparison of combined model vs clinical-pathological-FIGO staging system)	The radiomics nomograms constructed with T stage, lymph node status, and radiomics signatures, resulted in significantly better performance for the estimation of DFS compared with the FIGO staging system.
Tian et al[66]	Prediction of response to preoperative neoadjuvant chemotherapy in locally advanced cervical cancer using multicenter CT-based radiomic analysis	2020	Front Oncol	Retrospective	277	LACC	NACT+surgery or RT	Response to therapy	Yes	No	CT (with and without contrast)	No	Machine learning	0.803	0.821	Combined (no comparison with radiomic model alone)	Radiomics signature containing pre-contrast and post-contrast imaging features can adequately distinguish chemotherapeutic responders from non-responders, and remain relatively stable across centers. The combined model has a better predictive performance than radiomics signature alone. Both models showed good discrimination, calibration.

Continued

Table 3 Continued

Authors	Title	Year	Journal	Design	No of partici pants	Stage	Treatment	Outcome	Internal validation set	External validation set	Imaging	Nomogram	Machine learning or deep learning	AUC radiomics model (max)*	AUC radiomics model external validation set	Clinical model compared or combined with radiomics model	Main conclusion
Zhou et al[48]	Quantitative PET Imaging and clinical parameters as predictive factors for patients with cervical carcinoma: implications of a prediction model generated using multi-objective support vector machine learning	2020	Technol Cancer Res Treat	Retrospective	75	LACC	CCRT	LR-failure D-failure	No	No	18F-FDG PET/CT	No	Machine learning	0.840	No	Combined (comparison with both radiomic and clinical model)	Based on a moderately high fixed sensitivity and optimized for specificity, the model using both clinical parameters and imaging features had the best performance in predicting both loco-regional failure and distant failure.
Yusufaly et al[49]	Improved prognosis of treatment failure in cervical cancer with nontumor PET/CT radiomics	2021	J Nucl Med	Retrospective	127	LACC	CCRT	DFS	Yes	No	18F-FDG PET/CT	No	Machine learning	Survival analysis with HR by single characteristic (textural or clinical features)*	No	Combined	Incorporating non-tumor radiomic biomarkers can improve the performance of prognostic models compared with using only clinical and tumor radiomic biomarkers. Optimal performance was seen in a Cox model including one clinical biomarker (whether or not a tumor was stage III–IVA), two radiomic biomarkers, one radiomic biomarker, and one whole-body radiomic biomarker.
Laliscia et al[50]	MRI-based radiomics: promise for locally advanced cervical cancer treated with a tailored integrated therapeutic approach	2021	Tumori	Retrospective	60	LACC	CCRT	PFS+OS	No	No	MRI (T2)	No	Machine learning	NR	No	Combined (only stated in conclusion)	The combination of clinical and radiomics features can provide information to predict behavior and prognosis of LACC and to make more accurate treatment decisions.
Nakajo et al[51]	Machine learning based evaluation of clinical and pretreatment 18F-FDG-PET/CT radiomic features to predict prognosis of cervical cancer patients	2021	Abdom Radiol	Retrospective	50	ESCC+LACC	Surgery +/ CRT or CHT	PFS	No	No	18F-FDG PET/CT	No	Machine learning	0.872	No	Combined	A machine learning approach based on clinical and pre-treatment 18F-FDG PET-based radiomic features may be useful for predicting tumor progression in cervical cancer patients. The five top predictors of disease progression were: stage, surface area, metabolic tumor volume, gray-level run length non-uniformity (GLRLM_RLNU), and gray-level non-uniformity for run (GLRLM_GLNU).

Continued

Bizzarri N, *et al*. *Int J Gynecol Cancer* 2023;**33**:1522–1541. doi:10.1136/ijgc-2023-004589

Table 3 Continued

Authors	Title	Year	Journal	Design	No of partici pants	Stage	Treatment	Outcome	Internal validation set	External validation set	Imaging	Nomogram	Machine learning or deep learning	AUC radiomics model (max)*	AUC radiomics model external validation set	Clinical model compared or combined with radiomics model	Main conclusion
Liu et al[52]	Predicting disease-free survival with multiparametric MRI-derived radiomic signature in cervical cancer patients underwent CCRT	2021	Front Oncol	Retrospective	263	LACC	CCRT	DFS	Yes	No	MRI (T2+ADC map)	No	Machine learning	0.816	0.787	Combined (comparison with both radiomic and clinical model)	The multi-parametric MRI-derived radiomic signature could be used as a non-invasive prognostic tool for predicting DFS in LACC patients. Higher radiomic signature was significantly associated with worse DFS. The radiomics signature demonstrated better prognostic performance in predicting DFS than the clinical model. However, the combined model showed no significant improvement.
Li et al[53]	Radiomic score as a potential imaging biomarker for predicting survival in patients with cervical cancer	2021	Front Oncol	Retrospective	106	LACC	CCRT	OS	Yes	No	CT (CE)	Yes	Machine learning	0.830	0.830	Combined	Radiomics has the potential for non-invasive risk stratification, and may improve the prediction of OS in patients with cervical cancer when added to the FIGO stage. Only the FIGO stage and radiomics score were independent risk factors associated with OS. The incorporation of the FIGO stage and radiomics score achieved better performance. The nomogram-based on the FIGO stage and radiomics score could individually predict the OS probability with good discrimination and calibration.
Cai et al[64]	MRI radiomic features: a potential biomarker for progression-free survival prediction of patients with locally advanced cervical cancer undergoing surgery	2021	Front Oncol	Retrospective	181	LACC	Surgery	PFS	Yes	No	MRI (T2+DWI)	Yes	Machine learning	0.879	0.820	Combined	The radiomics score demonstrated good performance in stratifying patients into high-risk and low-risk groups of progression in the training and validation cohorts. Otherwise, the combined nomogram, integrating the radiomics score and patient's age, hemoglobin, white blood cell, and lymph vascular space invasion, demonstrated prominent discrimination.

Continued

Table 3 Continued

Authors	Title	Year	Journal	Design	No of partici pants	Stage	Treatment	Outcome	Internal validation set	External validation set	Imaging	Nomogram	Machine learning or deep learning	AUC radiomics model (max)*	AUC radiomics model external validation set	Clinical model compared or combined with radiomics model	Main conclusion
Ferreira et al[54]	(18F)FDG PET radiomics to predict disease-free survival in cervical cancer: a multi-scanner/center study with external validation	2021	Eur J Nucl Med Mol Imaging	Retrospective	158	LACC	CCRT	DFS	No	Yes	PET/CT	No	Machine learning	0.780	0.57	Combined	(18F)FDG PET radiomic features combined with machine learning add relevant information to the standard clinical parameters in terms of LACC patient's outcome, but remain subject to variability across PET/CT devices. The best model was obtained using 10 tumor to liver features combined with clinical information.
Zhang et al[55]	IVIM-DWI and MRI-based radiomics in cervical cancer: prediction of concurrent chemoradiotherapy sensitivity in combination with clinical prognostic factors	2022	Magn Reson Imaging	Retrospective	163	LACC	CCRT	Response to therapy	Yes	No	MRI (IVIM+T2)	Yes	Machine learning	0.987	0.984	Combined	MRI-based radiomics and clinical prognostic factors showed high clinical value in predicting CCRT sensitivity for LACC with better predictive performance when combined.
Zhang et al[56]	The value of whole-tumor texture analysis of ADC in predicting the early recurrence of locally advanced cervical squamous cell cancer treated with concurrent chemoradiotherapy	2022	Front Oncol	Retrospective	219	LACC	CCRT	RFS	Yes	No	MRI (ADC)	No	Machine learning	0.804	0.821	Combined	In the clinical variables, T stage and lymph node metastasis were independent risk factors. The combined texture and clinical model was established, it exhibited the highest AUC in the training cohort and in the testing cohort, which was significantly higher than the AUC of the clinical prediction model.

Continued

Table 3 Continued

Authors	Title	Year	Journal	Design	No of partici pants	Stage	Treatment	Outcome	Internal validation set	External validation set	Imaging	Nomogram	Machine learning or deep learning	AUC radiomics model (max)*	AUC radiomics model external validation set	Clinical model compared or combined with radiomics model	Main conclusion
Wei et al[57]	MRI radiomics in overall survival prediction of local advanced cervical cancer patients tread by adjuvant chemotherapy following concurrent chemoradiotherapy or concurrent chemoradiotherapy alone	2022	Magn Reson Imaging	Not stated in abstract	130	LACC	CCRT±ACT	OS	No	No	MRI (T2)	Yes	Machine learning	0.879	No	Combined	The two radiomics models were built based on radiomics features extracted from the primary tumor of T2-weight MRI. The radiomics model and nomograms based on radiomics signature and clinical features were predictors of OS, progression-free survival, local regional control, and metastasis free survival. Patients were stratified into low-risk group and high-risk group determined by radiomics models and nomograms, respectively. The low-risk group patients present significantly increased OS, progression-free survival, local regional control, and metastasis free survival compare with high-risk group. The prognosis prediction performance of radiomics model and nomogram was superior to the prognosis prediction performance of FIGO stage.
Ikushima et al[58]	Prediction of out-of-field recurrence after chemoradiotherapy for cervical cancer using a combination model of clinical parameters and MRI radiomics: a multi-institutional study of the Japanese Radiation Oncology Study Group	2022	J Radiat Res	Retrospective	180	LACC (IIB)	CCRT	OFR	Yes	No	MRI (T2+DWI)	No	Machine learning	0.734	No	Combined	Combining MRI radiomics with clinical parameters improved the accuracy of predicting out of field recurrence after chemoradiotherapy for locally advanced cervical cancer. The AUC was improved on combining the pretreatment status of para-aortic lymph node metastasis with that from the least absolute shrinkage and selection operator model for DWIs.

Continued

Table 3 Continued

Authors	Title	Year	Journal	Design	No of participants	Stage	Treatment	Outcome	Internal validation set	External validation set	Imaging	Nomogram	Machine learning or deep learning	AUC radiomics model (max)*	AUC radiomics model external validation set	Clinical model compared or combined with radiomics model	Main conclusion
Zhang et al[59]	Added-value of texture analysis of ADC in predicting the survival of patients with 2018 FIGO stage IIICr cervical cancer treated by concurrent chemoradiotherapy	2022	Eur J Radiol	Retrospective	91	LACC	CCRT	PFS+OS	No	No	MRI (ADC)	Yes	Machine learning	0.750 PFS; 0.832 OS (C-Index)	No	Combined (Comparison combined model vs clinical-pathological -FIGO staging system)	The texture analysis of the ADC maps could be used along with clinical prognostic biomarkers to predict PFS and OS in patients with stage IIICr cervical SCC treated by CCRT. The C-index values of the combined models for PFS and OS, were significantly higher compared with 2018 FIGO staging system values.
Pedraza et al[60]	The value of metabolic parameters and textural analysis in predicting prognosis in locally advanced cervical cancer treated with chemoradiotherapy	2022	Strahlenther Onkol	Retrospective	116	LACC	CCRT	RFS+OS		No	18F FDG-PET/CT+MRI	No	None	Survival analysis with HR by single characteristic (textural or clinical features)*	No	Compared	Classical prognostic factors and tumor heterogeneity on pre-treatment PET/CT were significantly associated with prognosis in patients with LACC. Univariate analyses indicated that FIGO stage, the presence of hydronephrosis, high CYFRA 21.1 levels, and textural features had a significant impact on OS and RFS. Metabolic tumor volume as well as SCC-Ag concentration were also significantly associated with OS. On multivariate analysis, the presence of hydronephrosis, CYFRA 21.1, and sphericity were independent prognostics factors for OS and RFS.
Zhang et al[61]	MRI-based radiomics value for predicting the survival of patients with locally advanced cervical squamous cell cancer treated with concurrent chemoradiotherapy	2022	Cancer Imaging	Retrospective	185	LACC	CCRT	PFS+OS	Yes	No	MRI (T2+ADC + CE multiparametric LAVA)	Yes	Machine learning	0.792 PFS; 0.822 OS	0.809 PFS and 0.785 OS	Combined (comparison with both radiomic and clinical model)	The radiomics score achieved significantly better predictive performance for the estimation of PFS and OS, compared with the 2018 FIGO staging system and clinical-predicting model. The combined model constructed with T stage, lymph node metastasis position, and radiomics score achieved the best performance for the estimation of PFS and OS, which were significantly higher than those of the radiomics score.

Continued

Table 3 Continued

Authors	Title	Year	Journal	Design	No of participants	Stage	Treatment	Outcome	Internal validation set	External validation set	Imaging	Nomogram	Machine learning or deep learning	AUC radiomics model (max)*	AUC radiomics model external validation set	Clinical model compared or combined with radiomics model	Main conclusion
Zhang et al[62]	Nomograms combining clinical and imaging parameters to predict recurrence and disease-free survival after concurrent chemoradiotherapy in patients with locally advanced cervical cancer	2023	Acad Radiol	Retrospective	115	LACC	CCRT	Recurrence+DFS	Yes	No	MRI (IVIM-DWI+T2 WI)	Yes	Machine learning	0.977		Combined (no comparison with clinical/radiomic model alone)	The nomograms based on clinical, incoherent motion diffusion weighted imaging-DWI and radiomics parameters have high clinical value in predicting recurrence and DFS of patients with LACC after CCRT. External beam radiotherapy dose, f-value, pre-treatment and post-treatment Radiomics-score were independent prognostic factors for recurrence and DFS in patients with cervical cancer.
Zhang et al[63]	MRI-based radiomics for pretreatment prediction of response to concurrent chemoradiotherapy in locally advanced cervical squamous cell cancer	2023	Abdom Radiol	Retrospective	198	LACC	CCRT	Response to therapy	Yes	No	MRI (T2+ADC map)	Yes	Machine learning	0.857	0.842	Combined (comparison with both radiomic and clinical model)	The combined model constructed with tumor grade, FIGO stage, and radiomics-score achieved the best performance, which were significantly higher than the clinical model. The radiomics-score, consisting of four radiomics features selected from 200 radiomics features, showed good predictive performance, which was higher than the clinical model, but the difference was not statistically significant.

*Might include combined radiomics and clinical (radiological/pathological) models AUC.
ACT, adjuvant chemotherapy; ADC, apparent diffusion co-efficient; AUC, area under the curve; CCRT, concurrent chemo-radiotherapy; CE, contrast-enhanced; CHT, chemotherapy; CT, computed tomography; DCE, Dynamic contrast-enhanced; DFS, disease-free survival; DMFS, distant metastasis-free survival; DWI, diffusion weighted imaging; 18F-FDG, 18F-fluorodeoxyglucose; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; IVIM, intravoxel incoherent motion; LACC, locally advanced cervical cancer; LAVA, Volume Interpolated; LRC, loco-regional control; MRI, magnetic resonance imaging; NACT, neoadjuvant chemotherapy; NR, not reported; OS, overall survival; PET, positron emission tomography; PRFS, pelvic relapse-free survival; SCC, squamous cell carcinoma; VEGF, vascular endothelial growth factor.

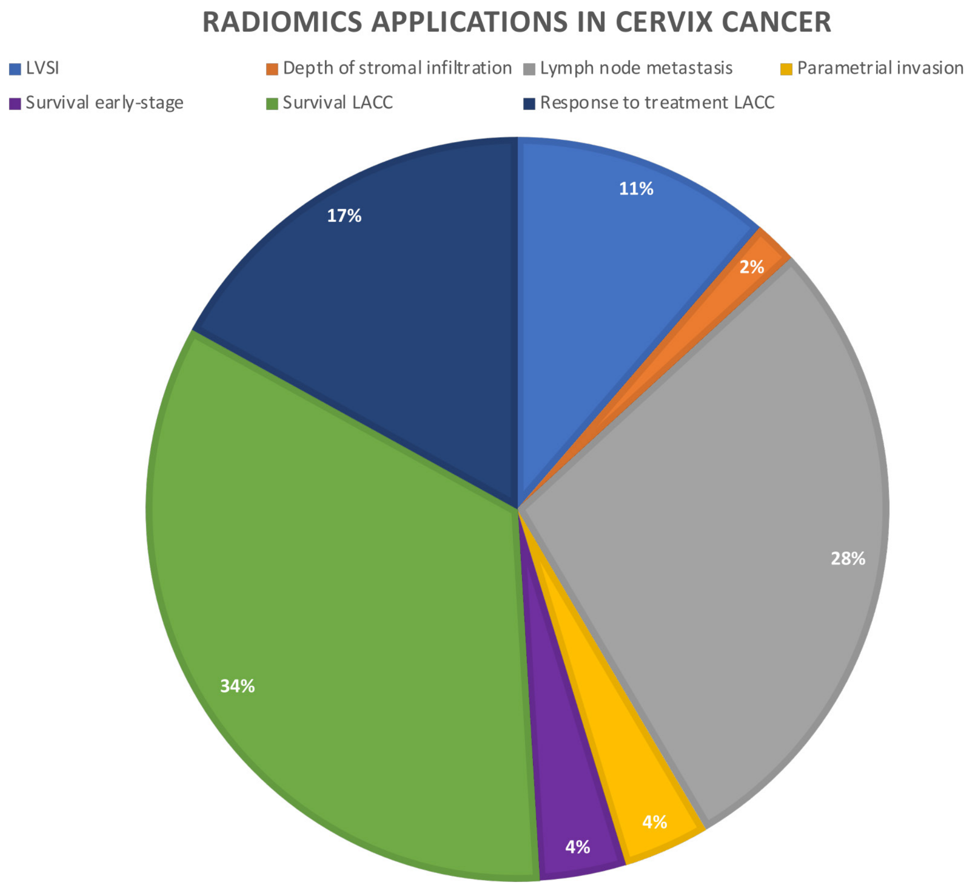

Figure 3 Current applications of radiomics in cervical cancer in the 57 articles included in this systematic review. LACC, locally advanced cervical cancer; LVSI, lymphovascular space involvement.

low-quality scores of included radiomics studies, well-designed studies are warranted to provide a more robust level of evidence for radiomics.[73]

The apparent diffusion co-efficient maps quantify the diffusivity of water molecules inside the tissue, with tumor regions of high cellular density being associated with increased restriction.[74] Apparent diffusion co-efficient values are more easily interpretable, while also having good repeatability, allowing for monitoring treatment response, and making their integration in clinical settings easier.[75]

In many cases, simple quantitative metrics from apparent diffusion co-efficient maps have outperformed more complex radiomics analysis. This could also be attributed to the fact that many of the considered radiomics studies do not provide enough evidence on a model's robustness or reproducibility. To facilitate the introduction of radiomic studies in clinical practice, it will be necessary to include similar repeatability experiments, as well as independent external datasets, to ensure the validity of the results.

With the high performance of radiomics in predicting risk of lymph node metastasis (Table 2), it was provocatively stated that radiomics signature could go beyond the concept of sentinel lymph node, being radiomics a non-invasive method able to discriminate the presence of lymph node metastasis with such high accuracy.[76] It is relevant to mention that, despite not being included in the results of this systematic review, different studies analysed the accuracy of radiomics signature extracted from ultrasound scan images.[77 78] Interestingly, ESGO guidelines accept 'expert' ultrasound scan as a staging method in cervical cancer,[79] making the use of radiomics in ultrasound an intriguing innovative field of research.

The ability of radiomics to predict high and intermediate risk factors in cervical cancer, as reported in our review, was also confirmed by a recent study by Li et al[80] showing that radiomics MRI improved the pre-treatment identification of multi-modality therapy candidates in early cervical cancer. It is known from ESGO and other international guidelines that surgery followed by adjuvant treatment in early-stage cervical cancer should be avoided, as it increases risk of morbidity.[79 81] The radiomics signature should be combined in a multi-omics framework, which integrates biological data and clinical parameters to obtain a final accurate tailored decision for the patient.

Concerning locally advanced disease, the included studies analysed patients treated either with exclusive chemoradiation or neoadjuvant chemotherapy followed by radical surgery. Other studies also showed that using radiomics indicators, it is possible to identify non-responders to chemoradiotherapy and modify the treatment accordingly, in patients undergoing chemoradiation and radical surgery.[82] It is also important to highlight that radiomics could be used as predictor of other outcomes, such as treatment-related toxicity, which is an important endpoint for all cancer survivors.[83–86]

Strengths and Weaknesses

The main strength of this study is that it describes the current evidence of radiomics analyses in cervical cancer from a clinical perspective. Moreover, we included only studies combining or comparing radiomics and clinical-pathological data, to directly test radiomics in a more clinical decisional environment. On the other hand, we have to acknowledge that the lack of standardization and interpretability of the radiomics pipeline significantly limits the comparison of the results from different studies, and especially with the ones published at the very beginning of this discipline. Moreover, studies on prediction of lymph node metastasis did not differentiate whether these were macroscopic or low-volume metastases. Lastly, despite it not being considered the treatment recommended by the guidelines, we included studies adopting neoadjuvant therapy; however, these were included within the systematic literature search.

Implications for Practice and Future Research

Radiomics signatures seem to be a promising tool in predicting pathological and oncological outcomes in patients with cervical cancer. For this reason, it would be ideal to integrate them within a clinical model in synergy with known prognostic factors. One potential application would be tailoring adjuvant treatment within known risk groups according to radiomics signatures. This is an interesting example of how radiomics could support gynecological oncologists to modulate or avoid the adjuvant treatments. Jiang et al[87] showed that the combination of radiomics signature and clinical-pathological features had a more accurate predictive ability than clinical-pathological features alone. The authors presented two cases with same clinical-pathological characteristic (same age, FIGO stage, histology, grade, tumor size, no lymph node metastasis, no LVSI), but one recurred after 17 months and the other was free from disease at 87 months. MRI-based radiomics characteristics of these cases were completely different (patient with 17 months recurrence: T1 contrast-enhanced radiomics score 2.60, T1 contrast-enhanced+T2 radiomics score 2.46; vs patient with 87 months: T1 contrast-enhanced radiomics score 0.53, T1 contrast-enhanced+T2 radiomics score 0.61), mirroring the disease-free survival. This represents a further step towards a personalized adjuvant treatment selection, based not only on clinical or pathological characteristics, but also on radiomics.

One could even hypothesize tailoring the radicality of hysterectomy according to pre-operative radiomics (or combined radiomics and clinical-pathologic) findings. A radiomics analysis of patients included in the ongoing robot-assisted approach to cervical cancer (RACC) trial[88] has been recently designed, and will provide further information on the predictivity of such approach on clinical-pathological outcomes of patients with early-stage cervical cancer treated with radical surgery.

MRI analysis of locally advanced cervical cancer treated with neoadjuvant chemotherapy and radical surgery showed that radiomics features hold potential in the pre-treatment prediction of response to neoadjuvant chemotherapy in locally advanced cervical cancer, which could be used to identify the right patients for receiving neoadjuvant chemotherapy; thus avoiding unnecessary treatment. This could spare the radiotherapy for a potential recurrence and avoid the use of triple treatment (chemotherapy, surgery, and radiotherapy) which is not advised by international guidelines owing to high morbidity.[79] Studies specifically looking at outcomes of patients diagnosed with distant metastases or with recurrent/persistent cervical cancer are needed. Lastly, recent evidence has shown that digital pathology approaches can aid in genotype classification, risk stratification, and outcomes prediction. 'Radio-pathomics' represents an emerging opportunity to bridge the existing knowledge gap between abstract mathematical image representation and underlying biology by matching radiological images and biopsy slides, paving the way for more innovative hybrid predictive models.[89]

CONCLUSION

Radiomics in cervical cancer is a new imaging research field. Radiomics models are highly predictive of pathological and oncological outcomes, particularly if combined with clinical variables. Most published studies are retrospective, and radiomics was not part of the original study design, thus reducing the overall quality of the produced evidence.

It is important to highlight that radiomics has to be considered part of an integrated model that should aim to harmonize different clinical-pathological and translational advances recently obtained in cervical cancer treatment, to offer patients a comprehensive multi-omics approach.

Author affiliations
[1]UOC Ginecologia Oncologica, Dipartimento per la salute della Donna e del Bambino e della Salute Pubblica, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy
[2]Department of Bioimaging, Radiation Oncology and Hematology, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy
[3]Università Cattolica del Sacro Cuore, Rome, Italy

Acknowledgements The authors acknowledge the work of the Gemelli Science and Technology Park Radiomics core research facility team.

Contributors Conceptualization: GS, NB. Methodology: NB, LR, MD. Data curation: NB, LR, MD, KZP, LB, DQ, GF, LPA, BG, ES. Writing- Original draft preparation: NB, LR, ES, GS. Supervision: ES, GS. Writing- Reviewing and Editing: all authors. Guarantor: NB.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

ORCID iDs
Nicolò Bizzarri http://orcid.org/0000-0002-1727-904X
Luca Russo http://orcid.org/0000-0002-0495-7462
Denis Querleu http://orcid.org/0000-0002-3984-4812
Benedetta Gui http://orcid.org/0000-0002-5130-2100
Giovanni Scambia http://orcid.org/0000-0003-2758-1063

REFERENCES

1 Shrestha P, Poudyal B, Yadollahi S, *et al*. A systematic review on the use of artificial intelligence in gynecologic imaging - background, state of the art, and future directions. *Gynecol Oncol* 2022;166:596–605.
2 Reuzé S, Orlhac F, Chargari C, *et al*. Prediction of cervical cancer recurrence using Textural features extracted from 18F-FDG PET images acquired with different scanners. *Oncotarget* 2017;8:43169–79.
3 Torheim T, Malinen E, Kvaal K, *et al*. Classification of dynamic contrast enhanced MR images of cervical cancers using texture analysis and support vector machines. *IEEE Trans Med Imaging* 2014;33:1648–56.
4 Bhatla N, Berek JS, Cuello Fredes M, *et al*. Revised FIGO staging for carcinoma of the cervix uteri. *Int J Gynaecol Obstet* 2019;145:129–35.
5 Manganaro L, Lakhman Y, Bharwani N, *et al*. Staging, recurrence and follow-up of uterine cervical cancer using MRI: updated guidelines of the European society of urogenital radiology after revised FIGO staging 2018. *Eur Radiol* 2021;31:7802–16.
6 Gillies RJ, Kinahan PE, Hricak H. Radiomics: images are more than pictures, they are data. *Radiology* 2016;278:563–77.
7 Lambin P, Rios-Velazquez E, Leijenaar R, *et al*. Radiomics: extracting more information from medical images using advanced feature analysis. *Eur J Cancer* 2012;48:441–6.
8 Limkin EJ, Sun R, Dercle L, *et al*. Promises and challenges for the implementation of computational medical imaging (Radiomics) in oncology. *Ann Oncol* 2017;28:1191–206.
9 Liu Z, Wang S, Dong D, *et al*. The applications of Radiomics in precision diagnosis and treatment of oncology: opportunities and challenges. *Theranostics* 2019;9:1303–22.
10 Cohen PA, Jhingran A, Oaknin A, *et al*. Cervical cancer. *Lancet* 2019;393:169–82.
11 Cibula D, Dostálek L, Jarkovsky J, *et al*. The annual recurrence risk model for tailored surveillance strategy in patients with cervical cancer. *Eur J Cancer* 2021;158:111–22.
12 Cancer Genome Atlas Research Network, Albert Einstein College of Medicine, Analytical Biological Services, *et al*. Integrated genomic and molecular characterization of cervical cancer. *Nature* 2017;543:378–84.
13 Moher D, Liberati A, Tetzlaff J, *et al*. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009;151:264–9.
14 Cibula D. Early-stage intermediate-risk—the group with the most Heterogenous management among patients with cervical cancer. *Int J Gynecol Cancer* 2022;32:1227–8.
15 Wu Q, Shi D, Dou S, *et al*. Radiomics analysis of multiparametric MRI evaluates the pathological features of cervical squamous cell carcinoma. *J Magn Reson Imaging* 2019;49:1141–8.
16 Li Z, Li H, Wang S, *et al*. MR-based radiomics nomogram of cervical cancer in prediction of the lymph-vascular space invasion preoperatively. *J Magn Reson Imaging* 2019;49:1420–6.
17 Huang G, Cui Y, Wang P, *et al*. Multi-parametric magnetic resonance imaging-based radiomics analysis of cervical cancer for preoperative prediction of lymphovascular space invasion. *Front Oncol* 2022;11:663370.
18 Xiao M, Li Y, Ma F, *et al*. Multiparametric MRI radiomics nomogram for predicting lymph-vascular space invasion in early-stage cervical cancer. *Br J Radiol* 2022;95:20211076.
19 Cui L, Yu T, Kan Y, *et al*. Multi-parametric MRI-based peritumoral radiomics on prediction of lymph-vascular space invasion in early-stage cervical cancer. *Diagn Interv Radiol* 2022;28:312–21.
20 Li X, Xu C, Yu Y, *et al*. Prediction of lymphovascular space invasion using a combination of tenascin-C, Cox-2, and PET/CT radiomics in patients with early-stage cervical squamous cell carcinoma. *BMC Cancer* 2021;21.
21 Ren J, Li Y, Yang J-J, *et al*. MRI-based radiomics analysis improves preoperative diagnostic performance for the depth of stromal invasion in patients with early stage cervical cancer. *Insights Imaging* 2022;13:17.
22 Peters WA III, Liu PY, Barrett RJ II, *et al*. Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. *JCO* 2000;18:1606–13.
23 Li K, Sun H, Lu Z, *et al*. Value of [^{18}F]FDG PET radiomic features and VEGF expression in predicting pelvic lymphatic metastasis and their potential relationship in early-stage cervical squamous cell carcinoma. *Eur J Radiol* 2018;106:160–6.
24 Yu YY, Zhang R, Dong RT, *et al*. Feasibility of an ADC-based radiomics model for predicting pelvic lymph node metastases in patients with stage IB-IIA cervical squamous cell carcinoma. *Br J Radiol* 2019;92:20180986.
25 Kan Y, Dong D, Zhang Y, *et al*. Radiomic signature as a predictive factor for lymph node metastasis in early-stage cervical cancer. *J Magn Reson Imaging* 2019;49:304–10.
26 Wang T, Gao T, Yang J, *et al*. Preoperative prediction of pelvic lymph nodes metastasis in early-stage cervical cancer using radiomics nomogram developed based on T2-weighted MRI and diffusion-weighted imaging. *Eur J Radiol* 2019;114:128–35.
27 Yan L, Yao H, Long R, *et al*. A preoperative radiomics model for the identification of lymph node metastasis in patients with early-stage cervical squamous cell carcinoma. *Br J Radiol* 2020;93:20200358.
28 Xia X, Li D, Du W, *et al*. Radiomics based on nomogram predict pelvic lymphnode metastasis in early-stage cervical cancer. *Diagnostics (Basel)* 2022;12:2446.
29 Qian W, Li Z, Chen W, *et al*. RESOLVE-DWI-based deep learning nomogram for prediction of normal-sized lymph node metastasis in cervical cancer: a preliminary study. *BMC Med Imaging* 2022;22:221.
30 Xiao ML, Wei Y, Zhang J, *et al*. MRI texture analysis for preoperative prediction of lymph node metastasis in patients with nonsquamous cell cervical carcinoma. *Acad Radiol* 2022.
31 Liu Y, Duan H, Dong D, *et al*. Development of a deep learning-based nomogram for predicting lymph node metastasis in cervical cancer: a multicenter study. *Clin Transl Med* 2022;12:e938.
32 Huang Q, Deng B, Wang Y, *et al*. Reduced field-of-view DWI-derived clinical-radiomics model for the prediction of stage in cervical cancer. *Insights Imaging* 2023;14:18.
33 Chen J, He B, Dong D, *et al*. Noninvasive CT radiomic model for preoperative prediction of lymph node metastasis in early cervical carcinoma. *Br J Radiol* 2020;93:20190558.
34 Wu Q, Wang S, Chen X, *et al*. Radiomics analysis of magnetic resonance imaging improves diagnostic performance of lymph node metastasis in patients with cervical cancer. *Radiother Oncol* 2019;138:141–8.
35 Wu Q, Wang S, Zhang S, *et al*. Development of a deep learning model to identify lymph node metastasis on magnetic resonance imaging in patients with Cervical cancer. *JAMA Netw Open* 2020;3:e2011625.
36 Shi J, Dong Y, Jiang W, *et al*. MRI-based peritumoral radiomics analysis for preoperative prediction of lymph node metastasis in early-stage cervical cancer: a multi-center study. *Magn Reson Imaging* 2022;88:1–8.
37 Song J, Hu Q, Ma Z, *et al*. Feasibility of T_2WI-MRI-based radiomics nomogram for predicting normal-sized pelvic lymph node metastasis in cervical cancer patients. *Eur Radiol* 2021;31:6938–48.
38 Zhang Y, Zhang K-Y, Jia H-D, *et al*. Feasibility of predicting pelvic lymph node metastasis based on IVIM-DWI and texture parameters of the primary lesion and lymph nodes in patients with cervical cancer. *Acad Radiol* 2022;29:1048–57.
39 Wang T, Gao T, Guo H, *et al*. Preoperative prediction of parametrial invasion in early-stage cervical cancer with MRI-based radiomics nomogram. *Eur Radiol* 2020;30:3585–93.
40 Li X, Lin T, Liu B, *et al*. Diagnosis of cervical cancer with parametrial invasion on whole-tumor dynamic contrast-enhanced magnetic resonance imaging combined with whole-lesion texture analysis based on T2- weighted images. *Front Bioeng Biotechnol* 2020;8:590.
41 Fang J, Zhang B, Wang S, *et al*. Association of MRI-derived radiomic biomarker with disease-free survival in patients with early-stage cervical cancer. *Theranostics* 2020;10:2284–92.
42 Zhou Y, Gu HL, Zhang XL, *et al*. Multiparametric magnetic resonance imaging-derived radiomics for the prediction of disease-free survival in early-stage squamous cervical cancer. *Eur Radiol* 2022;32:2540–51.
43 Lucia F, Visvikis D, Desseroit M-C, *et al*. Prediction of outcome using pretreatment^{18}F-FDG PET/CT and MRI radiomics in locally advanced cervical cancer treated with chemoradiotherapy. *Eur J Nucl Med Mol Imaging* 2018;45:768–86.
44 Lucia F, Visvikis D, Vallières M, *et al*. External validation of a combined PET and MRI radiomics model for prediction of recurrence in cervical cancer patients treated with chemoradiotherapy. *Eur J Nucl Med Mol Imaging* 2019;46:864–77.
45 Chen S-W, Shen W-C, Hsieh T-C, *et al*. Textural features of cervical cancers on FDG-PET/CT associate with survival and local relapse in patients treated with definitive chemoradiotherapy. *Sci Rep* 2018;8:11859.
46 Fang M, Kan Y, Dong D, *et al*. Multi-habitat based radiomics for the prediction of treatment response to concurrent chemotherapy and radiation therapy in locally advanced cervical cancer. *Front Oncol* 2020;10:563.

47 Mu W, Liang Y, Hall LO, *et al*. ^{18}F-FDG PET/CT habitat radiomics predicts outcome of patients with cervical cancer treated with chemoradiotherapy. *Radiol Artif Intell* 2020;2:e190218.
48 Zhou Z, Maquilan GM, Thomas K, *et al*. Quantitative PET imaging and clinical parameters as predictive factors for patients with cervical carcinoma: implications of a prediction model generated using multi-objective support vector machine learning. *Technol Cancer Res Treat* 2020;19:153303382098380.
49 Yusufaly TI, Zou J, Nelson TJ, *et al*. Improved prognosis of treatment failure in cervical cancer with nontumor PET/CT Radiomics. *J Nucl Med* 2022;63:1087–93.
50 Laliscia C, Gadducci A, Mattioni R, *et al*. MRI-based radiomics: promise for locally advanced cervical cancer treated with a tailored integrated therapeutic approach. *Tumori* 2022;108:376–85.
51 Nakajo M, Jinguji M, Tani A, *et al*. Machine learning based evaluation of clinical and pretreatment ^{18}F-FDG-PET/CT radiomic features to predict prognosis of cervical cancer patients. *Abdom Radiol (NY)* 2022;47:838–47.
52 Liu B, Sun Z, Xu Z-L, *et al*. Predicting disease-free survival with multiparametric MRI-derived radiomic signature in cervical cancer patients underwent CCRT. *Front Oncol* 2022;11:812993.
53 Li H, Zhu M, Jian L, *et al*. Radiomic score as a potential imaging biomarker for predicting survival in patients with cervical cancer. *Front Oncol* 2021;11:706043.
54 Ferreira M, Lovinfosse P, Hermesse J, *et al*. [18F]FDG PET radiomics to predict disease-free survival in cervical cancer: a multi-scanner/center study with external validation. *Eur J Nucl Med Mol Imaging* 2021;48:3745–6.
55 Zhang Y, Zhang K, Jia H, *et al*. IVIM-DWI and MRI-based radiomics in cervical cancer: prediction of concurrent chemoradiotherapy sensitivity in combination with clinical prognostic factors. *Magnetic Resonance Imaging* 2022;91:37–44.
56 Zhang X, Zhang Q, Xie L, *et al*. The value of whole-tumor texture analysis of ADC in predicting the early recurrence of locally advanced Cervical squamous cell cancer treated with concurrent chemoradiotherapy. *Front Oncol* 2022;12:852308.
57 Wei G, Jiang P, Tang Z, *et al*. MRI radiomics in overall survival prediction of local advanced cervical cancer patients tread by adjuvant chemotherapy following concurrent chemoradiotherapy or concurrent chemoradiotherapy alone. *Magn Reson Imaging* 2022;91:81–90.
58 Ikushima H, Haga A, Ando K, *et al*. Prediction of out-of-field recurrence after chemoradiotherapy for cervical cancer using a combination model of clinical parameters and magnetic resonance imaging radiomics: a multi-institutional study of the Japanese radiation oncology study group. *J Radiat Res* 2022;63:98–106.
59 Zhang X, Zhang Q, Guo J, *et al*. Added-value of texture analysis of ADC in predicting the survival of patients with 2018 FIGO stage Iiicr cervical cancer treated by concurrent chemoradiotherapy. *Eur J Radiol* 2022;150:110272.
60 Pedraza S, Seiffert AP, Sarandeses P, *et al*. The value of metabolic parameters and Textural analysis in predicting prognosis in locally advanced cervical cancer treated with chemoradiotherapy. *Strahlenther Onkol* 2022;198:792–801.
61 Zhang X, Zhao J, Zhang Q, *et al*. MRI-based radiomics value for predicting the survival of patients with locally advanced cervical squamous cell cancer treated with concurrent chemoradiotherapy. *Cancer Imaging* 2022;22.
62 Zhang Y, Liu L, Zhang K, *et al*. Nomograms combining clinical and imaging parameters to predict recurrence and disease-free survival after concurrent chemoradiotherapy in patients with locally advanced cervical cancer. *Acad Radiol* 2023;30:499–508.
63 Zhang X, Zhang Q, Chen Y, *et al*. MRI-based radiomics for pretreatment prediction of response to concurrent chemoradiotherapy in locally advanced cervical squamous cell cancer. *Abdom Radiol (NY)* 2023;48:367–76.
64 Cai M, Yao F, Ding J, *et al*. MRI radiomic features: a potential biomarker for progression-free survival prediction of patients with locally advanced cervical cancer undergoing surgery. *Front Oncol* 2021;11:749114.
65 Sun C, Tian X, Liu Z, *et al*. Radiomic analysis for pretreatment prediction of response to neoadjuvant chemotherapy in locally advanced Cervical cancer: a multicentre study. *EBioMedicine* 2019;46:160–9.
66 Tian X, Sun C, Liu Z, *et al*. Prediction of response to preoperative neoadjuvant chemotherapy in locally advanced cervical cancer using multicenter CT-based radiomic analysis. *Front Oncol* 2020;10:77.
67 McCague C, Ramlee S, Reinius M, *et al*. Introduction to radiomics for a clinical audience. *Clin Radiol* 2023;78:83–98.
68 Lambin P, Leijenaar RTH, Deist TM, *et al*. Radiomics: the bridge between medical imaging and personalized medicine. *Nat Rev Clin Oncol* 2017;14:749–62.
69 Shaikh F, Franc B, Mulero F. Radiomics as applied in precision medicine. In: *Clinical nuclear medicine*. Cham: Springer, 2020.
70 De Maria Marchiano R, Di Sante G, Piro G, *et al*. Translational research in the era of precision medicine: where we are and where we will go. *J Pers Med* 2021;11:216.
71 Liu B, Gao S, Li S. A comprehensive comparison of CT, MRI, positron emission tomography or positron emission tomography/CT, and diffusion weighted imaging-MRI for detecting the lymph nodes metastases in patients with cervical cancer: a meta-analysis based on 67 studies. *Gynecol Obstet Invest* 2017;82:209–22.
72 Li L, Zhang J, Zhe X, *et al*. A meta-analysis of MRI-based radiomic features for predicting lymph node metastasis in patients with cervical cancer. *Eur J Radiol* 2022;151:110243.
73 Ren J, Li Y, Liu X-Y, *et al*. Diagnostic performance of ADC values and MRI-based radiomics analysis for detecting lymph node metastasis in patients with Cervical cancer: a systematic review and meta-analysis. *Eur J Radiol* 2022;156:110504.
74 Surov A, Meyer HJ, Wienke A. Correlation between apparent diffusion coefficient (ADC) and cellularity is different in several tumors: a meta-analysis. *Oncotarget* 2017;8:59492–9.
75 Winfield JM, Tunariu N, Rata M, *et al*. Extracranial soft-tissue tumors: Repeatability of apparent diffusion coefficient estimates from diffusion-weighted MR imaging. *Radiology* 2017;284:88–99.
76 Bizzarri N, Boldrini L, Ferrandina G, *et al*. Radiomic models for lymph node metastasis prediction in cervical cancer: can we think beyond sentinel lymph node *Transl Oncol* 2021;14:101185:101185.:.
77 Jin X, Ai Y, Zhang J, *et al*. Noninvasive prediction of lymph node status for patients with early-stage cervical cancer based on radiomics features from ultrasound images. *Eur Radiol* 2020;30:4117–24.
78 Jin J, Zhu H, Teng Y, *et al*. The accuracy and radiomics feature effects of multiple U-Net-based automatic segmentation models for transvaginal ultrasound images of cervical cancer. *J Digit Imaging* 2022;35:983–92.
79 Cibula D, Raspollini MR, Planchamp F, *et al*. ESGO/ESTRO/ESP guidelines for the management of patients with cervical cancer - update 2023. *Int J Gynecol Cancer* 2023;33:649–66.
80 Li Y, Ren J, Yang J-J, *et al*. MRI-derived radiomics analysis improves the noninvasive pretreatment identification of multimodality therapy candidates with early-stage cervical cancer. *Eur Radiol* 2022;32:3985–95.
81 Abu-Rustum NR, Yashar CM, Bean S, *et al*. NCCN guidelines insights: cervical cancer, version 1.2020. *J Natl Compr Canc Netw* 2020;18:660–6.
82 Gui B, Autorino R, Miccò M, *et al*. Pretreatment MRI radiomics based response prediction model in locally advanced cervical cancer. *Diagnostics (Basel)* 2021;11:631.
83 Le Z, Wu D, Chen X, *et al*. A radiomics approach for predicting acute hematologic toxicity in patients with cervical or endometrial cancer undergoing external-beam radiotherapy. *Radiother Oncol* 2023;182:109489.
84 Ren K, Shen L, Qiu J, *et al*. Treatment planning computed tomography Radiomics for predicting treatment outcomes and haematological toxicities in locally advanced Cervical cancer treated with radiotherapy: A retrospective cohort study. *BJOG* 2023;130:222–30.
85 Lucia F, Bourbonne V, Visvikis D, *et al*. Radiomics analysis of 3d dose distributions to predict toxicity of radiotherapy for cervical cancer. *J Pers Med* 2021;11:398.
86 Albano D, Benenati M, Bruno A, *et al*. Imaging side effects and complications of chemotherapy and radiation therapy: a pictorial review from head to toe. *Insights Imaging* 2021;12:76.
87 Jiang X, Song J, Duan S, *et al*. MRI radiomics combined with clinicopathologic features to predict disease-free survival in patients with early-stage cervical cancer. *Br J Radiol* 2022;95:20211229.
88 Falconer H, Palsdottir K, Stalberg K, *et al*. Robot-assisted approach to cervical cancer (RACC): an international multi-center, open-label randomized controlled trial. *Int J Gynecol Cancer* 2019;29:1072–6.
89 Feng L, Liu Z, Li C, *et al*. Development and validation of a radiopathomics model to predict pathological complete response to neoadjuvant chemoradiotherapy in locally advanced rectal cancer: a multicentre observational study. *Lancet Digit Health* 2022;4:e8–17.