Cohort Study

ANNALS OF MEDICINE & SURGERY

OPEN

Patient survival prediction in locally advanced cervical squamous cell carcinoma using MRI-based radiomics: retrospective cohort study

Anan Bseiso, MD[a], Muhammad Saqib, MBBS[b,*], Muhammad Sherdil Saigol, MBBS[c], Aribah Rehman, MBBS[d], Almatou Sare, MD[e], Ahmed Elmustafa Yagoub, MD[f], Hassan Mumtaz, MBBS, MRSPH, MSPH[g]

Abstract

Cervical cancer is a major health concern for women, ranking as the fourth most common cancer and a significant cause of cancer-related deaths worldwide. To enhance prognostic predictions for locally advanced cervical squamous cell carcinoma, we conducted a study utilizing radiomics features extracted from pretreatment magnetic resonance images. The goal was to predict patient survival and compare the predictive value of these features with clinical traits and the 2018 International Federation of Obstetrics and Gynecology (FIGO) staging system. In our retrospective cohort study, we included 500 patients with confirmed cervical squamous cell carcinoma ranging from FIGO stages IIB to IVA under the 2018 staging system. All patients underwent pelvic MRI with diffusion-weighted imaging before receiving definitive curative concurrent chemoradiotherapy. The results showed that the combination model, incorporating radiomics scores and clinical traits, demonstrated superior predictive accuracy compared to the widely used 2018 FIGO staging system for both progression-free and overall survival. Age was identified as a significant factor influencing survival outcomes. Additionally, primary tumour invasion stage, tumour maximal diameter, and the location of lymph node metastasis were found to be important predictors of progression-free survival, while primary tumour invasion stage and lymph node metastasis position individually affected overall survival. During the follow-up period, a portion of patients experienced disease-related deaths or tumour progression/recurrence in both sets. The radiomics-score significantly enhanced prediction ability, providing valuable insights for guiding personalized therapy approaches and stratifying patients into low-risk and high-risk categories for progression-free and overall survival. In conclusion, our study demonstrated the potential of radiomics features as a valuable addition to existing clinical tools like the FIGO staging system, offering promising advancements in managing locally advanced cervical squamous cell carcinoma.

Keywords: cervical cancer, FIGO stages, MRI, radiomics, survival prediction

Introduction

Cervical cancer is the fourth most common malignancy in women and the fourth leading cause of cancer-related death worldwide.

HIGHLIGHTS

- Cervical cancer is the fourth most common malignancy in women and the fourth leading cause of cancer death worldwide.
- We aimed to predict the progression-free and overall patient survival in locally advanced cervical squamous cell carcinoma using radiomics features from pretreatment magnetic resonance images and to compare the predictive value of these features to that of clinical traits and the new 2018 International Federation of Obstetrics and Gynecology (FIGO) staging system.
- The radiomics-score might significantly enhance prediction ability when compared to the widely used 2018 FIGO staging system and clinical features.
- The combined model's ability to stratify patients into low-risk and high-risk categories for progression-free survival and overall survival may give doctors fresh ideas for directing therapy approaches.

More than two-thirds of people diagnosed with cervical cancer have locally advanced cervical cancer (LACC)[1]. Unfortunately, a lack of screening programs contribute to a greater rate of

[a]Hebron University, Hebron, Palestine, [b]Khyber Medical College, Peshawar, [c]Services Hospital, Lahore, [d]Bahawal Victoria Hospital, Bahawalpur, [e]Health Services Academy, Islamabad, Pakistan, [f]Joseph Ki-Zerbo University, Ouagadougou, Burkina Faso and [g]Mayo General Hospital, Castlebar, Ireland

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

*Corresponding author. Address: Khyber Medical College, Peshawar, Khyber Pakhtunkhwa, Pakistan. E-mail: muhammadsaqib.drkmc@gmail.com (M. Saqib).

Annals of Medicine & Surgery (2023) 85:5328–5336

Received 22 July 2023; Accepted 31 August 2023

Supplemental Digital Content is available for this article. Direct URL citations are provided in the HTML and PDF versions of this article on the journal's website, www.lww.com/annals-of-medicine-and-surgery.

Published online 11 September 2023

http://dx.doi.org/10.1097/MS9.0000000000001288

invasive cervical cancer in nations where median incomes are lower than those in the industrialized nations. After the Papanicolaou smear test became widely used in industrialized nations, invasive cervical cancer rates fell towards a decreasing trend in those nations[2]. Chemoradiotherapy (CRT) combined with early brachytherapy is the current standard of care for this disease. Surgery is still a viable option for those who complete the treatment. The final decision on which surgery to perform is based on the evaluation of tumour remnants obtained from pelvic MRI. The FIGO method is used to classify cervical cancer into stages. Locally, cervical cancer may vary in stage from IB2 to IVA. The World Federation of Obstetrics and Gynecology defined stage IB2 or IIA2 as the condition. After histology confirms the diagnosis, the first step involves a variety of diagnostic procedures, including MRI, a clinical exam, PET, and surgical dissection. Multimodal treatment has improved results for LACC patients, although the overall recurrence rate is 35%, and median survival after recurrence is still only 10–12 months[3–5].

There have been a lot of studies that evaluate the efficacy of noninvasive imaging approaches for detecting lymph node metastases in cervical cancer patients. Radiological methods used include computed tomography (CT), MRI, PET with 2-[18F] fluoro-2-deoxy-D-glucose (FDG), and diffusion-weighted MRI. Lymph node (LN) metastases have often been discovered by MRI and CT based on size and/or morphologic assessments of nodes. PET or PET/CT, which combines the benefits of anatomical and functional imaging, can be used to pinpoint areas of increased FDG uptake with improved anatomic specificity[6].

Radiomics, on the other hand, have received more attention in recent years than have conventional PET/CT and MRI features. Radiomics is a method that uses artificial intelligence (AI) and machine learning (ML) to analyze a large quantity of high-dimensional data derived from a collection of medical images. The recovered features can be then used as surrogate markers for underlying patterns of gene expression that characterize biological aspects such as intratumor heterogeneity and tumour shape[7,8]. Recent progress in radiomics has shown that PET/CT and MRI can be of further prognostic and discriminatory use in assessing cervical cancer[9].

This study aims to generate radiomics features from pretreatment MRI images that predict progression-free survival (PFS) and overall survival (OS) in patients with locally advanced cervical squamous cell cancer treated with concurrent CRT (CCRT), and to compare the predictive value of these features to that of clinical traits and the new 2018 International Federation of Obstetrics and Gynecology (FIGO) staging system.

Methodology

A retrospective cohort study of patients with cervical cancer who were diagnosed and treated at our institution was conducted between January 2020 and September 2022. We used a sample size of 500 patients who fit the inclusion criteria of our study using a non-probability consecutive sampling technique. A total of 500 patients were randomly categorized into two separate groups that is control group ($n = 350$) and testing group ($n = 150$) at a ratio of 7:3, respectively, to test the efficacy of the prediction models as shown in Fig. 1. For a confidence level of 95%, the P value was set at 0.05. A recently published and related study[10] used a similar technique as well.

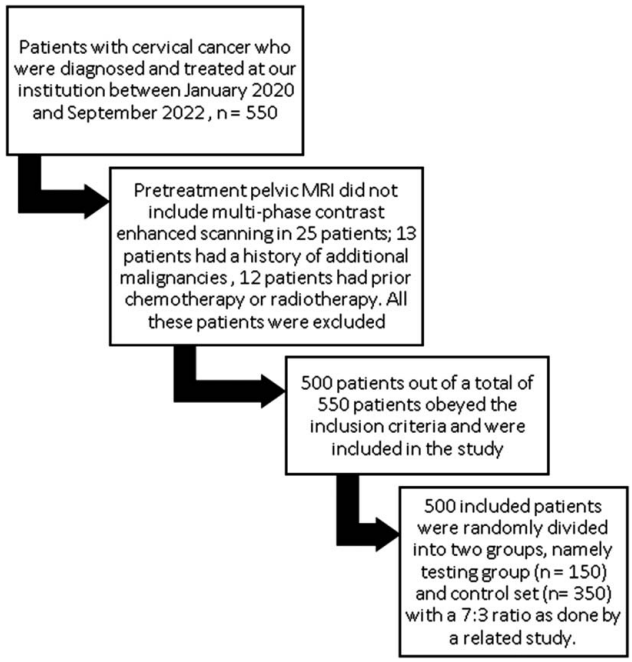

Figure 1. Methodology of patient selection for the study.

The standards set forth by STROCSS 2021[11] have been adhered to in our research. For your convenience, we have included a thorough STROCSS 2021 checklist in the supplementary file, Supplemental Digital Content 1, http://links.lww.com/MS9/A248. Each step of our research has been performed in compliance with the Declaration of Helsinki and other comparable guidelines wherever applicable.

Inclusion and exclusion criteria

Patients were included in our study if they met the following criteria: histologically confirmed cervical squamous cell carcinoma; FIGO stages IIB to IVA according to the 2018 staging method, pelvic MRI with diffusion-weighted imaging before treatment, and definitive curative CCRT. Curative CCRT was defined in our study as the patients showing complete cure with no histopathological, clinical and radiological signs of cancer after treatment with concurrent chemoradiotherapy.

Those patients who met any of the following criteria were excluded from our study: Their pretreatment pelvic MRI did not include multi-phase contrast-enhanced scanning; their radiographic images contained artefacts; patients who had a history of additional malignancies, patients who had prior chemotherapy or radiotherapy, and patients that had demonstrated a failure to complete treatment.

In order to test the efficacy of the prediction models, data from eligible patients were divided into a control set ($n = 350$) and a test set ($n = 150$) with a 7:3 ratio. Control set was used for background information of patients by constructing a hypothesis for doing experiment and analyze data by comparing to control group to draw a conclusion while a test sets was used for a medical procedure performed to detect, monitor diseases, disease method, susceptibility, or to regulate a development of treatment. Patients were categorized based on their age, BMI, presence or absence of squamous cell carcinoma antigen, tumour grade

(low-grade: well or moderately differentiated; high-grade: poorly differentiated), 2018 FIGO stage, primary tumour invasion stage, tumour's maximum diameter, and LN metastasis [number and position (pelvic/para-aortic)].

MRI acquisition strategy

We enroled patients who already underwent routine contrast-enhanced pelvic MRI before receiving CCRT. The machines used for acquisition of MRI images were two 3.0-T MR imaging units (Discovery MR 750 and Signa Excite HDx, GE Medical System) that used eight-element phased coils. Patients who were retrospectively enroled had multi-phase contrast-enhanced scanning done using liver acquisition with volume acceleration-extended volume sequence 15 s after an intravenous injection contrast agent (gadodiamide, 0.1 mmol/kg; Omniscan; GE Healthcare,) at a rate of 2.0 ml/s, per phase of 15 s with a total acquisition time of 105 s, followed by 20 ml of normal saline to flush the tubing off any material. We were able to this because MR imaging using such approach is routinely done at our institution for these patients.

Treatment strategy

On a thorough examination of treatments records, patients in our cohort had retrospectively received treatment with whole pelvic external pelvic beam radiation therapy or extended-field radiotherapy to the areas deemed to be cancerous on imaging. Subsequent high-dose-rate brachytherapy treatments were performed a week after the external beam radiation therapy.

Patients who have recurrent primary or secondary brain tumours tend to benefit from repeated radiation with doses up to 120 Gy2 EQD2 to the brain, doses under 100 Gy2 to the brainstem, and doses under 75 Gy2 EQD2 to the chiasm and optic nerves. The total dose that was reported ranged between 21 and 47 Gy at 5.6–8.6 Gy per fraction. Records showed that all patients received concurrent chemotherapy with weekly cisplatin or nedaplatin at a dose of 50 mg/m^2 for treatment of their cancer when diagnosed at our institution.

Strategy used for extraction of radiomics features

After attaining data regarding MR images of all patients that were retrospectively enroled in our study, we normalized every included patient's MR scan data with Z-scores. This was done in an attempt to get a standard distribution of the normal image intensities. We used PyRadiomics (https://pyradiomics.readthedocs.io) to extract a set of 100 normalized radiomics features from every image voxel of our interest. Radiomics features that were extracted were: (i) 14 shape features, (ii) 18 first-order features, (iii) 22 grey-level co-occurrence matrix (GLCM) features, (iv) 16 grey-level run length matrix (GLRLM) features, (v) 16 grey-level size zone matrix (GLSZM) features, and (vi) 14 grey-level dependence matrix (GLDM) features. These features were extracted from the MR image data that was provided to us by our institution for this study. Two radiologists that had more than 5 years of expertise in gynaecological tumours assessed the whole procedure and any disagreement between them was resolved by discussion. For the sake of obtaining uniform and factual data, an intraclass correlation coefficient was used. All radiomics features that had an intraclass correlation coefficient greater than 0.80 were included in our current study. A histogram of all grey values is shown in Fig. 2.

Selection of radiomics features and construction

Univariate Cox regression analysis was used to assess the predictive capability of each radiomic feature in predicting PFS and OS in the control group. Statistically significant features with a *P* value less than 0.05 were then determined to be significant features of prognostic value. These features were then selected as candidate features. In order to eliminate any redundancy, the correlation between the features was then calculated by Spearman or Pearson correlation analysis according to their distribution types; features with coefficient r greater than or equal to 0.8 were removed accordingly. The radiomics-score was then computed by adding significant radiomics features weighted based on their statistical coefficients.

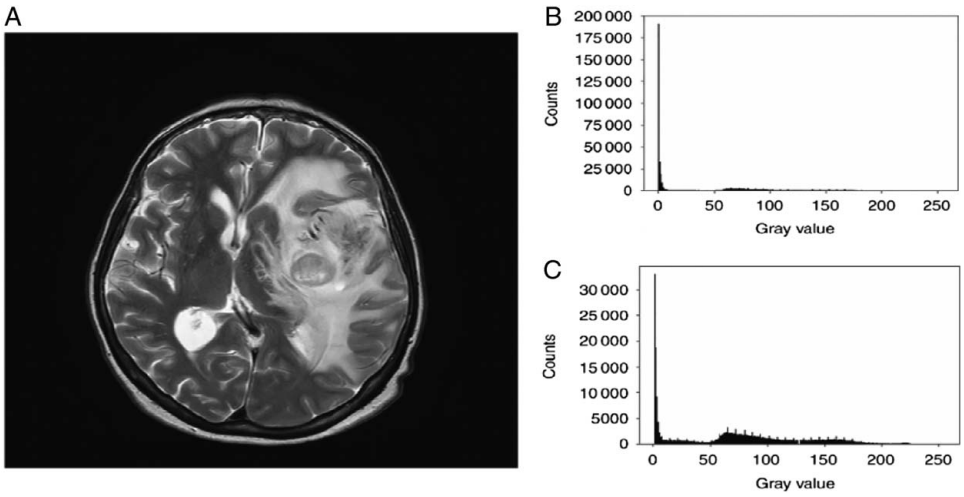

Figure 2. (A) An axial slice near the middle of the brain and its associated histograms. (B) A histogram of all grey-level values (0–255). (C) A histogram of all grey-level values but 0 (1–255).

Performance of the radiomics-score in PFS and OS prediction

A total of five radiomics features were selected for radiomics-score building for PFS estimation (Rad-PFS). Six radiomics features were selected for radiomics-score building for OS estimation (Rad-OS). The features selected for the radiomics-score computation along with their calculation formulas are presented in the supplementary file, Supplemental Digital Content 2, http://links.lww.com/MS9/A249.

Data analysis

Without knowing the final clinical outcomes of the patients or reporting the outcomes of any imaging tests, a radiologist with expertise in gynaecological imaging and an expert clinical pathologist with expertise in gynaecological tumours reclassified all patients using clinical data according to the most recent version of the FIGO staging system (2018 revision)[12]. Both clinicians also agreed on a primary tumour invasion stage diagnosis based on the TNM 9th edition[13]. Maximum tumour diameter was determined using the greatest diameter on T2-weighted MRI images (T2WI) in the sagittal or transverse axial planes. If the short axis diameter of a lymph node was greater than 1 cm, or if necrosis had set in, it was considered to be LN metastasis.

Tumour segmentation and image preprocessing

The ITK-SNAP software (Version 3.8.0, http://www.itksnap.org/) was used to automatically rigidly register T1WI images to the domain of T2WI images and divide the structures in the three-dimensional diagnostic image. On registration T2WI and T1WI pictures, a neuroradiologist with 10 years of expertise manually segmented the lesions of every participant. Then, a radiologist with 10 years of expertise divided 500 cases into 350 cases of pathologically confirmed brain abscesses. Additionally, each aspect of these 500 cases' intraclass correlation coefficient is determined. The following image preparation steps were taken. An picture with the highest cross-sectional area and its highest and lowest layers was selected as a three-channel image. The MR image was then cropped to include a square area of interest surrounding the tumour contour. The tumour patch was then adjusted to 224×224 in order to match the prepared CNN model's input size criteria. B-spline interpolation was used to resample all pictures to the same voxel size of $1 \times 1 \times 1$ mm^3 before the high contrast radiology characteristics were retrieved.

Patient follow-up

Patients were followed up every 3 months for the first year after treatment. After the first year, patients were followed up with every 6 months until the end of the second year, and then at the end of the study. CT scans, MRI, PET-CT, gynaecological examinations, and tumour marker testing all verified the presence of disease progression or recurrence.

Primary and secondary outcomes of interest

The primary outcome of interest was determined to be PFS. The secondary outcome of interest was determined to be OS. Disease progression, recurrence, death, or the end of follow-up were the endpoints used to calculate PFS. In order to determine the OS, we looked at how much time had elapsed since the patient's final treatment or last scheduled appointment for follow-up.

Criteria used to determine cancer recurrence and progression

Cancer progression or recurrence was confirmed using a detailed gynaecological examination along with tumour marker, CT, MRI, and PET-CT evaluation.

Discrepancies on continuous variables were analyzed using the *t*-test to determine the relative standing of the two groups. The χ^2 test was used to determine significance in categorical variables. The predictive value of the radiomics-score and clinical characteristics were assessed using a regression analysis. Harrell's C-index was used to evaluate the predictive power of the model. A value under 0.70 indicated poor accuracy, between 0.71 and 0.90 indicated sufficient accuracy, and over 0.90 indicated excellent accuracy. The combined radiomics-score and risk score cutoffs were calculated using the maximally selected test statistics. Results were determined to be significant if the *P* values were less than 0.05. All statistical analysis was performed using IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0 IBM Corp software.

Results

A total of 500 patients were randomly split into a control set ($n = 350$) and a test set ($n = 150$) with a 7:3 ratio. They were followed up for 60 months. The mean ages in the two groups were significantly different, with the control group having a mean age of 53.67 + 8.76 (mean + S.D.) and the test group averaging 49.64 + 7.21 (mean + S.D.).

The median amount of time for which participants in the control group were followed up was 36 months (range, 36–60 months). There were 29/350 (8.3%) deaths from chronic or recurring illness in the control set. 47/350 (13.4%) cases of tumour progression or recurrence (36.7%) were also observed in the control set by the end of the follow-up period.

After a median follow-up of 5 years (range, 1–5 years), 21/150 (14%) patients from the test set died from persistent or recurrent illness and, 129/150 (12%) patients from the test set had tumour progression or recurrence. In the control group, the majority of patients [295/350 patients (84.28%)] had tumours in the T2 stage, 35/350 (11.14%) patients had tumours in the T3 stage, and 20/350 (4.58%) patients had tumours in the T4 stage. The majority of patients in the test group [79/150 patients (52.66%)] had tumours in the T2 stage, whereas 39/150 (22.66%) patients had T3 tumours and 32/150 (24.68%) patients had tumours in the T4 stage. The tumour FIGO stages of the control group patients were as follows: 269/350 (76.85%) FIGO stage II, 52/350 (14.85%) and FIGO stage III. Among the testing group patients, the tumour FIGO stages were as follows: 67/150 (44.66%) FIGO stage II and 48/150 (32%) FIGO stage III. The clinical characteristics of the control and testing groups are shown in Table 1.

Performance of the combined model in PFS and OS prediction

The C-index values for the combination model with radiomics-score and clinical features were 0.746, 0.617, and 0.439 in the

Table 1

Comparison of clinical characteristics between control and testing groups

Parameters	Control group ($n=350$)	Test group ($n=150$)	*P*
Age (years, mean ± SD)	53.67 ± 8.76	49.64 ± 7.21	**0.04**
BMI (kg/m^2, mean ± SD)	24.80 ± 3.44	24.63 ± 3.78	0.57
Tumour grade, *n* (%)			
Low-grade (well/moderately differentiated)	268 (76.5)	95 (63.33)	0.79
High-grade (poorly differentiated)	82 (23.5)	55 (36.67)	**0.02**
Tumour staging, *n* (%)			
T2	295 (84.28)	79 (52.66)	0.63
T3	35 (11.14)	39 (22.66)	
T4	20 (4.58)	32 (24.68)	
2018 FIGO stage, *n* (%)			
II	269 (76.85)	67 (44.66)	0.97
III	52 (14.85)	48 (32)	
Tumour maximum diameter (cm, mean ± SD)	5.94 ± 1.31	4.32 ± 1.36	0.04
Lymph node metastases position, *n* (%)			
Negative	194 (55.42)	73 (48.66)	0.96
Pelvic lymph node metastasis	140 (40)	49 (32.66)	
Para-aortic lymph node metastasis	16 (4.58)	28 (18.68)	
Lymph node metastases number, *n* (%)			
0	174 (49.71)	93 (62)	0.73
≤ 2	145 (41.42)	43 (28.66)	
> 2	31 (8.87)	14 (9.34)	

Values in bold indicate statistically significant values.
P value 0.050 is considered to be significant.
FIGO, 2018 International Federation of Obstetrics and Gynecology.

Table 2

Prognostic prediction models for the outcomes of patients with locally advanced cervical squamous cell carcinoma

	Control group ($n=350$)			Test group ($n=150$)		
Prediction models	**Wald test**	***P***	**C-index**	**Wald test**	***P***	**C-index**
Progression-free survival						
2018 FIGO staging system	19.74	0.01	0.439	9.74	0.01	0.427
Clinical Model	33.46	0.00	0.617	23.46	0.00	0.602
Radiomics-PFS model	39.62	0.00	0.746	29.41	0.01	0.724
Combined model	49.34	0.01	0.791	38.64	0.00	0.731
Overall survival						
2018 FIGO staging system	11.51	0.00	0.564	4.52	0.00	0.557
Clinical Model	21.61	0.01	0.780	14.74	0.02	0.767
Radiomics-PFS	22.74	0.00	0.734	13.78	0.00	0.714
Combined model	30.69	0.01	0.823	21.94	0.01	0.809

FIGO, 2018 International Federation of Obstetrics and Gynecology.

control group and 0.724, 0.602, and 0.427 in the testing group, respectively. This model was the most accurate in predicting PFS and OS. The combined model beat the individual radiomics-PFS model, clinical-predicting model, and 2018 FIGO staging system. These numbers topped those obtained by the individual radiomics-PFS model ($P=0.00$ in control, $P=0.00$ in testing), the clinical characteristics model ($P=0.00$ in control, $P=0.00$ in testing), and the FIGO staging system ($P=0.00$ in control, $P=0.00$ in testing). In addition, multivariate Cox regression found that the combined model was superior than the single radiomics-OS model, with C-index values of 0.734 in the control group and 0.809 in the testing group with *P* values of 0.00 in both the test and control groups. In terms of discrimination performance, the clinically predictive model had C-index values of 0.780 in the control group and combined model had C-index values of 0.809 in test group (with *P* values of 0.01 in the control and 0.01 in the test groups). The 2018 FIGO staging system had C-index values of 0.564 in the control and 0.557 in the test groups (control and testing *P* value = 0.00), as shown in Table 2. A predictive Rad-score was developed using the Cox regression model. The training set consisted of six T2WI predictors with high potential. Finally, the Rad-score was developed using the aforementioned six characteristics, using the following formula for its computation: Rad-score = − 0.253 × T2WI_MinIntensity + 0.210 × T2WI_ClusterShade + 0.076 × T2WI_GLCM-IDM + 0.201 × T2WI_RLM-LongRunEmphasis × T2WI_RLM-LongRunHighGreyLevelEmphasis + 0.391 × T2WI_LowIntensityLargeAreaEmphasis + 0.198.

Kaplan–Meier plots for overall and progression-free survival predicted using combined model in the control and test groups are shown in Figs. 3 and 4.

Table 3 displays the results of a regression analysis of PFS and OS. Multivariate analysis showed that tumour stage, tumour maximal diameter, and the location of lymph node metastasis were all significant predictors of PFS, whereas tumour stage and lymph node metastases position were individually significant predictors of OS. Clinical prediction algorithms were developed using the results. Kaplan–Meier plots for overall and progression-free survival predicted using radiomics-model in the control and test groups are shown in Fig. 5.

Age was found to have a hazard ratio of 0.943 in relation to PFS in a univariate analysis is (95% CI 0.923–0.961, $P=0.030$). The hazard ratio for tumour stage in relation to PFS in a univariate analysis is 2.975 (95% CI 1.962–4.413, $P=0.001$). Maximum tumour diameter has a hazard ratio of 1.567(95% CI 1.167–1.940, $P=0.003$) in a univariate analysis in relation to PFS. The hazard ratio for death due to any cause is 0.994 (95% CI: 0.950–1.041, $P=0.09$) for people of any age, while the hazard ratio for death (95% CI 0.847–1.154, $P=0.72$). Tumour stage has a hazard ratio of 3.342 (95% CI 1.837–5.569, $P=0.001$) for overall survival in a univariate analysis.

Discussion

The International Federation of Gynecology and Obstetrics (FIGO) staging method is universally recognized as the gold standard method for the diagnosis and treatment of cervical cancer. Although not included in FIGO clinical staging, the presence or absence of metastases to the pelvic and para-aortic lymph nodes is a major prognostic indication for cervical cancer patients[14,15]. Many of the invasive and time-consuming imaging techniques recommended by FIGO for cervical cancer staging are no longer used in clinical practice. More precise and cost-effective staging decisions can be made for cervical cancer, thanks to cross-sectional imaging (CT, MRI, PET-CT). Due to its widespread availability, CT is often the method of choice for the evaluation of oncologic patients, as

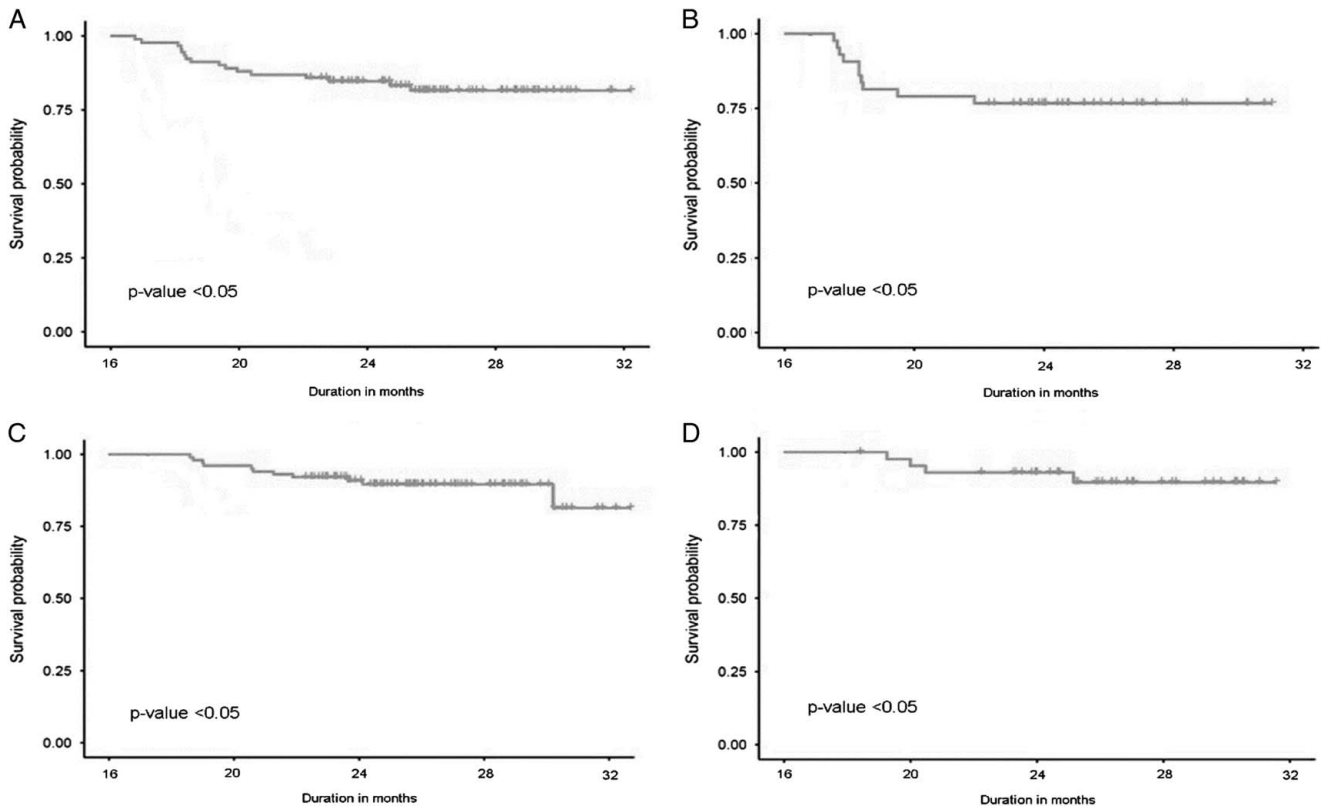

Figure 3. Combined model—Kaplan–Meier plots for: (A) progression-free survival in control group; (B) progression-free survival in test group; (C) overall survival in control group; (D) overall survival in test group.

many doctors have found[16]. CT's claimed accuracy for overall cervical cancer staging is between 32% and 80%. However, CT has a low positive predictive value for early parametrial invasion because it cannot differentiate between normal cervical stroma and malignant tissue[17]. Because of its superior contrast resolution, MRI is the preferred imaging method for assessing the regional spread of cervical cancer[18].

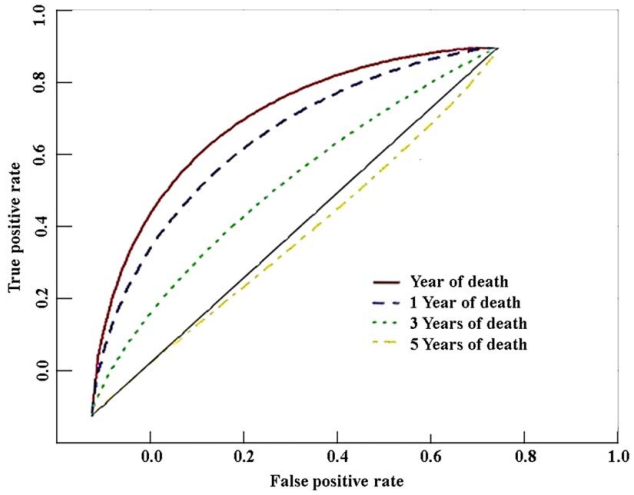

Figure 4. Time-dependent receiver operating characteristic curve of patients.

This study synthesized and then validated radiomics-score for determining prognosis in locally advanced cervical squamous cell carcinoma patients who had received treatment using chemoradiotherapy. Upon analysis, the radiomics-score which was computed using features obtained from voxels of interest in MR images demonstrated significant accuracy for predicting PFS and OS. The radiomics-score was so accurate that is beat the 2018 FIGO staging system and clinical models currently utilized for this purpose. Our analysis clearly demonstrated that a combined model that used both the radiomics-score as well as clinical characteristics into account best predicted the most accurate durations of PFS and OS. We observed that the radiomics approach helped us extract the most significant imaging features necessary for purposes of diagnosis, treatment as well as prognosis of locally advanced cervical squamous cell carcinoma[19].

Over eighty percent (80%) of cervical malignancies are squamous cell carcinomas[20]. The prognosis of invasive cervical cancer is strongly affected by the cancer's stage at the time of detection. Among women with invasive cervical cancer, nearly half have their disease diagnosed at a localized stage, where it has a good 5-year survival rate (up to 91.5%). Survival rates drop to 57.4% and 16.5%, respectively, after 5 years if regional lymph nodes or distant metastases are present[21].

According to the results of this research, the visual distinction between PFS and OS in the 2018 FIGO staging method is still subpar. Patients with lymph node metastases, especially paraaortic lymph node metastasis, exhibited lower PFS and OS, as shown by our research. Furthermore, we found that a higher

Table 3

Clinical characteristics analysis for progression-free survival and overall survival.

	Progression-free survival (PFS)				Overall survival (OS)			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
Characteristics	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Age	**0.943 (0.923–0.961)**	**0.030**			**0.994 (0.950–0.998)**	**0.040**		
Body mass index	0.937 (0.871–1.038)	0.650			1.004 (0.847–1.154)	0.690		
Squamous cell carcinoma	1.004 (0.960–1.013)	0.750			1.005 (0.945–1.031)	0.641		
Tumour grade	1.341 (0.704–2.371)	0.370			2.280 (1.017–4.827)	0.682		
Tumour stage	**2.975 (1.962–4.413)**	**0.001**	**1.627 (1.125–3.041)**	**0.016**	**3.342 (1.837–5.569)**	**0.001**	**2.473 (1.164–5.032)**	**0.017**
Tumour maximum diameter	**1.567 (1.167–1.940)**	**0.003**	**1.204 (0.914–1.526)**	**0.001**	**1.640 (1.151–2.314**	**0.002**		
Lymph node metastasis position	**2.471 (1.662–3.643)**	**0.002**	**1.645 (1.049–2.684)**	**0.024**	**2.606 (1.534–4.366)**	**0.001**	**1.520 (1.378–3.023)**	**0.038**
Lymph node metastasis number	**1.910 (1.377–2.658)**	**0.001**			**2.064 (1.278–3.282)**	**0.002**		

Values in bold indicate statistically significant values.
P value 0.050 is considered to be significant.
HR, hazard ratio.

tumour stage predicted a shorter PFS and OS. Matsuo K and colleagues and Tomizawa K and colleagues found very comparable outcomes in their respective studies[22,23]. Similar to our findings, Mu *et al.*[24] found that the clinical prediction model integrating tumour stage and lymph node metastasis for PFS and OS had a significantly higher C-index compared to the 2018 FIGO staging approach[24]. However, factors that influence tissue microstructure are not accounted for in the clinical prediction model. Currently, it is known that intertumoral heterogeneity has significant effects on tumour prognosis[25]. Laliscia *et al.*[26], reported in their study that radiomics features from T2WI were of great use in the prediction of locally advanced cervical carcinoma prediction[26]. To add to this, a retrospective study from China[27] that enroled 248 stage IB–IIA cervical cancer patients investigated the prognostic value of the pretreatment MRI (T2WI and contrast-enhanced T1WI) based radiomics-score for estimation of disease-free survival. They extracted 18 such radiomics features that were significantly predictive of disease-free survival. These features consisted of 10 features that were extracted from T1WI that were contrast-enhanced while the remaining 8 features were

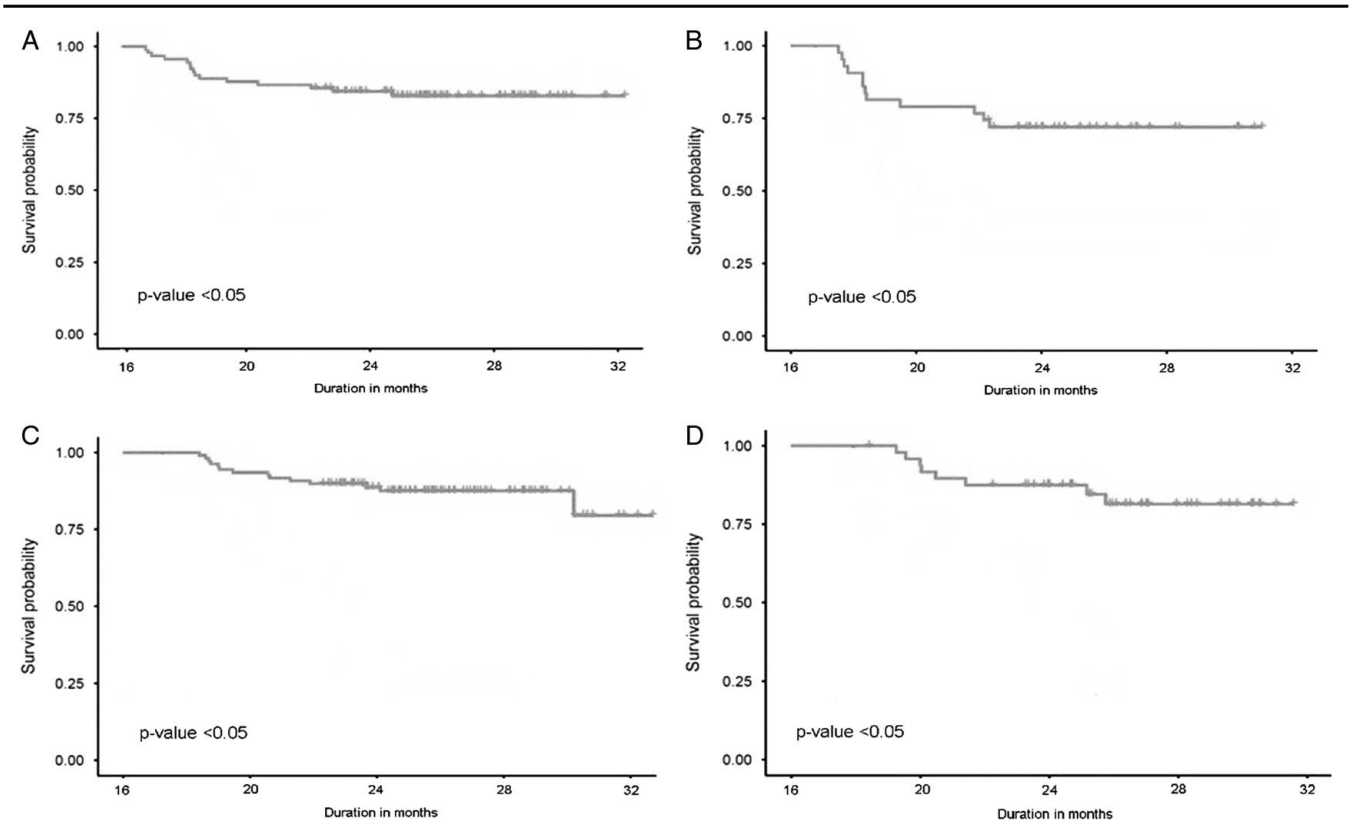

Figure 5. Radiomics model—Kaplan–Meier plots for: (A) progression-free survival in control group; (B) progression-free survival in test group; (C) overall survival in control group; (D) overall survival in test group.

extracted from T2WI. In their analysis, the radiomics-score yielded a C-index of 0.753 for predicting disease-free survival. These findings point to the fact that contrast-enhanced T1WI probably contain an added prognostic data when compared to T2WI alone. It also suggests that radiomics-score derived from MRI can be of significant prognostic utility as a biomarker for patients that have early-stage cervical carcinoma[27].

We also used multi-phase contrast-enhanced MRI in addition to T2WI. Tumour aggressiveness, cellularity, and vascularization were only few of the tumour characteristics that had an increased chance of being altered by changing the imaging sequence in which they develop. Most locally advanced cervical malignancies have a high degree of phenotypic heterogeneity in terms of proliferation, vascularity, metabolism, oxygenation and other factors. We were able to determine tumour density using T2WI, whereas intertumoral heterogeneity and architecture as well as changes in the tumour's blood supply were attainable using multi-phase contrast-enhanced MRI. These factors were strong predictors of tumour resistance to treatment and portended a poor prognosis. Similar findings are also reported by other studies[28–30].

The National Comprehensive Cancer Network clinical guidelines state that CCRT is still the best course of treatment for cervical cancer in stages IB3 and IIA2 ahead of radical hysterectomy plus pelvic lymphadenectomy[31]. CCRT is the only treatment available for cervical cancer in stage IIB. However, radiotherapy can affect young women' ovarian function and vaginal suppleness, which lowers the quality of their sexual life. Recent studies have indicated that radical surgery performed after neoadjuvant chemotherapy may be a significant treatment option for individuals with LACC and may perform better than CCRT, particularly in patients who are relatively early in the disease process[32].

A number of limitations exist in our study, despite the promising findings from MRI-based radiomics. To begin, this was a single-centre, retrospective investigation. In any case, the prediction model needs to be tested further, preferably with larger cohorts and at more facilities. The current lymph node metastasis selection criteria, however, may lead to the omission of people with lower lymph node metastasis or a false positive of the lymph node metastasis, tumour volume, vascular infiltration and uterine involvement. may be included. Because of how short the follow-up was, further longitudinal study is needed to determine the long-term predictive utility of MRI-based radiomics analysis in locally advanced cervical squamous cell carcinoma. How to combine genetic traits, radiomics signatures, and clinical traits will be a key factor in future research.

Conclusion

Our study demonstrated that MRI-based radiomics-score was able to accurately predict the outcome of locally advanced cervical squamous cell carcinoma treated with concurrent chemoradiotherapy with appropriate statistical significance. The radiomics-score might significantly enhance prediction ability when compared to the widely used 2018 FIGO staging system and clinical features. The best prediction performance was demonstrated by the combination model, which included the radiomics-score and clinically characteristic features. Utilization and adoption of such models may give doctors fresh ideas for directing therapy approaches to this cohort of cancer patients and individualize their follow-up as per their individual risks computed using such combined models.

Ethics declarations

Ethical approval was given by ethics committee. The informed consent was waived by the Ethics Committee. The study was approved on 1st of January, 2020 by the Ethics Committee of Liaquat University of Medical & Health Sciences, Jamshoro, Pakistan under reference no: ERC/16-XA/01/20.

Consent

Measures were taken to protect the confidentiality and privacy of participants, by deidentification of data. The study was conducted in accordance with the Declaration of Helsinki and relevant international ethical guidelines.

Sources of funding

The study received no funding from any source.

Author contributions

A.B.: Conceptualization, methodology, formal analysis, investigation, writing—original draft preparation; M.S.S.: conceptualization, methodology, formal analysis, investigation, writing—review and editing; A.R., A.S., A.E.Y., H.M.: conceptualization, methodology, writing—review & editing; M.S.: conceptualization, methodology, formal analysis, writing—review and editing. All authors reviewed the final version of the manuscript and approved it for submission.

Conflicts of interest disclosure

The authors declare that they have no competing interests.

Research registration unique identifying number (UIN)

1. Our study's unique identifier (UIN) is researchregistry8427, and it may be found on the website of Research Registry.
2. https://www.researchregistry.com/browse-the-registry#home/registrationdetails/63564ac11918d00023555e9a/.

Guarantor

Hassan Mumtaz.

Data availability statement

Data are available upon reasonable request.

Provenance and peer review

Not commissioned, externally peer-reviewed.

References

[1] Arbyn M, Weiderpass E, Bruni L, *et al*. Estimates of incidence and mortality of cervical cancer in 2018: a worldwide analysis. Lancet Glob Health 2020;8:e191–203.

[2] Macgregor JE, Campbell MK, Mann EM, *et al*. Screening for cervical intraepithelial neoplasia in north east Scotland shows fall in incidence and mortality from invasive cancer with concomitant rise in preinvasive disease. BMJ (Clinical research ed) 1994;308:1407–11.

[3] Cibula D, Pötter R, Planchamp F, *et al*. The European Society of Gynaecological Oncology/European Society for Radiotherapy and Oncology/European Society of Pathology Guidelines for the Management of Patients with Cervical Cancer. Virchows Arch 2018;472:919–36.

[4] Magné N, Chargari C, Vicenzi L, *et al*. New trends in the evaluation and treatment of cervix cancer: the role of FDG-PET. Cancer Treat Rev 2008; 34:671–81.

[5] Marth C, Landoni F, Mahner S, *et al*. Cervical cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2017;28(suppl_4):iv72–83.

[6] Yeh LS, Hung YC, Shen YY, *et al*. Detecting para-aortic lymph nodal metastasis by positron emission tomography of 18F-fluorodeoxyglucose in advanced cervical cancer with negative magnetic resonance imaging findings. Oncol Rep 2002;9:1289–92.

[7] Lambin P, Rios-Velazquez E, Leijenaar R, *et al*. Radiomics: extracting more information from medical images using advanced feature analysis. Eur J Cancer (Oxford, England : 1990) 2012;48:441–6.

[8] Tomaszewski MR, Gillies RJ. The biological meaning of radiomic features 2021;298:505–16.

[9] 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.

[10] 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;22:35.

[11] Mathew G, Agha R. STROCSS 2021: Strengthening the reporting of cohort, cross-sectional and case-control studies in surgery. Int J Surg (London, England) 2021;96:106165.

[12] Bhatla N, Berek JS, Cuello Fredes M, *et al*. Revised FIGO staging for carcinoma of the cervix uteri. Int J Gynaecol Obstetr 2019;145:129–35.

[13] Olawaiye AB, Baker TP, Washington MK, *et al*. The new (Version 9) American Joint Committee on Cancer tumor, node, metastasis staging for cervical cancer. CA Cancer J Clin 2021;71:287–98.

[14] Chung HH, Park NH, Kim JW, *et al*. Role of integrated PET-CT in pelvic lymph node staging of cervical cancer before radical hysterectomy. Gynecol Obstetr Investig 2009;67:61–6.

[15] Reinhardt MJ, Ehritt-Braun C, Vogelgesang D, *et al*. Metastatic lymph nodes in patients with cervical cancer: detection with MR imaging and FDG PET. Radiology 2001;218:776–82.

[16] Thomeer MG, Gerestein C, Spronk S, *et al*. Clinical examination versus magnetic resonance imaging in the pretreatment staging of cervical carcinoma: systematic review and meta-analysis. Eur Radiol 2013;23:2005–18.

[17] Ho CM, Chien TY, Jeng CM, *et al*. Staging of cervical cancer: comparison between magnetic resonance imaging, computed tomography and pelvic examination under anesthesia. J Formosan Med Assoc 1992;91:982–90.

[18] Sala E, Rockall AG, Freeman SJ, *et al*. The added role of MR imaging in treatment stratification of patients with gynecologic malignancies: what the radiologist needs to know. Radiology 2013;266:717–40.

[19] Gillies RJ, Kinahan PE, Hricak H. Radiomics: images are more than pictures, they are data. Radiology 2016;278:563–77.

[20] International Collaboration of Epidemiological Studies of Cervical Cancer. Comparison of risk factors for invasive squamous cell carcinoma and adenocarcinoma of the cervix: collaborative reanalysis of individual data on 8,097 women with squamous cell carcinoma and 1,374 women with adenocarcinoma from 12 epidemiological studies. Int J Cancer 2007;120:885–91.

[21] Bourgioti C, Chatoupis K, Moulopoulos LA. Current imaging strategies for the evaluation of uterine cervical cancer. World J Radiol 2016;8: 342–54.

[22] Matsuo K, Machida H, Mandelbaum RS, *et al*. Validation of the 2018 FIGO cervical cancer staging system. Gynecol Oncol 2019;152:87–93.

[23] Tomizawa K, Kaminuma T, Murata K, *et al*. FIGO 2018 staging for cervical cancer: influence on stage distribution and outcomes in the 3D-image-guided brachytherapy era. Cancers 2020;12:1770.

[24] 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 intel 2020;2:e190218. doi:10.1148/ryai.20 20190218

[25] Ramón YCS, Sesé M, Capdevila C, *et al*. Clinical implications of intratumor heterogeneity: challenges and opportunities. J Mol Med 2020;98: 161–77.

[26] 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.

[27] 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.

[28] Zhang B, Tian J, Dong D, *et al*. Radiomics features of multiparametric MRI as novel prognostic factors in advanced nasopharyngeal carcinoma. Clin Cancer Res 2017;23:4259–69.

[29] Pinho DF, King B, Xi Y, *et al*. Value of intratumoral metabolic heterogeneity and quantitative (18)F-FDG PET/CT parameters in predicting prognosis for patients with cervical cancer. Am J Roentgenol 2020;214: 908–16.

[30] Yang F, Young L, Grigsby P. Predictive value of standardized intratumoral metabolic heterogeneity in locally advanced cervical cancer treated with chemoradiation. Int J Gynecol Cancer 2016;26:777–84.

[31] 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.

[32] Hu K, Wang W, Liu X, *et al*. Comparison of treatment outcomes between squamous cell carcinoma and adenocarcinoma of cervix after definitive radiotherapy or concurrent chemoradiotherapy. Radiat Oncol 2018;13:249 .