

# Evaluation of Cervical Cancer Staging Based on Magnetic Resonance Imaging

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**Abstract** Cancer of the cervix uteri (CCU) ranks third in the incidence of malignancies in women. The choice of CCU treatment mainly depends on the extent of the tumor process, i.e. the stage of the disease. Determining the stage of CCU is based on the clinical classification of the International Federation of Gynecology and Obstetrics (FIGO) (2009) and has a number of substantial limitations in evaluating parametrial invasion, tumor spread to the pelvic wall, and involvement of regional lymph nodes and in determining the true tumor sizes. Magnetic resonance imaging (MRI) is now the method of choice in staging invasive CCU. Multiparameter MRI will be able to enhance the efficiency of diagnosing microinvasive CCU as well (FIGO 2009), to plan surgical and/or chemoradiation treatment, to evaluate its efficiency, and to diagnose locally recurrent CCU.

**Keywords** Cancer of the cervix uteri, International Federation of Gynecology and Obstetrics, Magnetic resonance imaging, Diffusion-weighted magnetic resonance images, Measured diffusion coefficient, Dynamic contrast-enhanced magnetic resonance imaging, Positron emission tomography

## 1. Introduction

Cervical cancer (CC) is a socially significant disease that poses a serious problem for modern medicine [1]. CC ranks third in the incidence of malignant neoplasms in women, according to A. Jemal et al.; in 2013, 12,340 new cases and 4,030 deaths were registered worldwide [2]. The average age of patients with CC was 48 years. Its widespread prevalence is noted in developing countries, which account for 78% of all cases, and in general, the share of CC reaches 15% of all malignant neoplasms in women (in developed countries - 4.4%) [3], and more often these are advanced, technically inoperable cases. In Russia in 2010, 14.7 thousand patients with CC were registered. Among all malignant neoplasms in women, the highest incidence rates of cervical cancer are observed in the age group of 15–39 years – 22.4%, in the age group of 40–54 years it is 9.4% (2nd place after breast cancer). Mortality from cervical cancer in Russia on average in 2010 was 5.2 per 100 thousand of the female population, which was 2.8 times lower than the incidence rate – 14.3 per 100 thousand of the female population. In the age group of 15–40 years, cervical cancer is the main cause of death in women among all malignant neoplasms (19.5% of cases), in patients aged 40–54 years it shifts to 2nd place (9.7%). The distribution of newly diagnosed patients with cervical cancer

in Russia by stage of the process in 2010 was as follows: I–II stage – 59.8%, III stage – 29.0%, IV stage – 9.1%, stage not established – 2.1%. In 2011, 13,807 new cases of invasive cervical cancer and 7,161 deaths from it were registered in Russia [1]. The main risk factors for the development of cervical cancer are considered to be early onset of sexual activity, frequent change of sexual partners, refusal of barrier methods of contraception, early first birth and decreased immunity in HIV infection; additional factors may include hypovitaminosis and smoking [4]. The main etiopathogenetic factor in the development of cervical cancer is the DNA-containing virus of the papovavirus family, the human papillomavirus (HPV). The most vulnerable area is the transition zone of multilayer squamous epithelium to cylindrical. Modern methods of HPV detection allow to detect it in tumor cells in 35-100% of cases. More than 100 types of HPV are known, 34 of which affect the genitals [5]: at least 13 types of HPV are considered oncogenic, and 7 non-oncogenic types of HPV are also known. The overwhelming majority of neoplasms caused by HPV are localized in the cervix (CM) and anal canal, and up to 94% of such malignant tumors occur in women. Comprehensive clinical and morphological studies have shown that cervical cancer almost never occurs on intact epithelium [6]. As a rule, cervical cancer is preceded by a number of changes, among which the main ones are dysplastic processes of the stratified squamous epithelium of varying severity, with disturbances in normal differentiation and stratification due to hyperplasia of basal and parabasal cells, followed by disturbances in the entire process of differentiation of these cells, an increase in the

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nuclear-cytoplasmic ratio, nuclear polymorphism, the occurrence of mitoses in the middle layers of the epithelium, and aneuploidy [7]. The more pronounced the dysplasia, the higher the probability of preservation and progression of changes and the development of invasive cancer, although individual cases of the occurrence of invasive cervical cancer *de novo* have been described. A more thorough analysis showed that in 95% of patients the absence of changes in cervical smears performed earlier was due to false-negative results of a cytological study (A. Ostor *et al.*). The commonality of morphological changes occurring in the cervical epithelium in dysplasia and early forms of cervical cancer allows us to classify them as cervical intraepithelial neoplasia (CIN) of varying severity: mild, moderate, severe. According to R.J. Kurman *et al.* (1994), the entire spectrum of cytological changes in dysplastic processes of the cervical epithelium fits into four cytological types according to the Bethesda system [8]: I - atypia of an indeterminate type, not related to oncological pathology; II - low degree of intraepithelial changes - epithelial dysplasia with koilocytic atypia; III - high degree of intraepithelial changes (severe dysplasia); IV - squamous cell cervical cancer. The average period of development of changes of type CIN I–II is 1.6 years, CIN II–III — 2.2 years, CIN III (carcinoma in situ) — 4.5 years. After the development of cancer in situ, the process often stabilizes for a long time, but it is impossible to predict the rate of disease progression. Invasive cervical cancer can develop against the background of CIN II and even CIN I, bypassing CIN III. According to E. Sala *et al.* for 2007, the widespread use of the Pap test in screening programs and the effectiveness of cancer in situ treatment have led to a significant decrease in the risk of death from cervical cancer in developed countries.

## 2. Objective of the Study

To analyze the literature data on the use of radiomics and image texture analysis in the diagnosis and prediction of the aggressiveness of oncogynecological diseases, including cervical cancer.

## 3. Materials and Methods

A systematic literature search was conducted in the PubMed/MEDLINE databases using the search strings “Radiomics” [All Fields], “digital image texture analysis” [All Fields], and “Cervical cancer” [All Fields], in eLibrary – “radiomics” and “digital image texture analysis”, Scopus (collections of scientific monographs and articles), in the resources of the National Comprehensive Cancer Network (NCCN), the European Society of Urogenital Radiology (ESUR), and the American College of Radiology (ACR); the search interval was 2016–2023.

All published papers on the use of radiomics and image texture analysis in the diagnosis and prognosis of oncological

diseases were reviewed. Full-text sources and literature reviews on the topic under study were included in the study. Duplicate publications were excluded. decompression using an ultrasound probe, which is applied to the skin, creating an compression at a depth of 2-5 mm. To ensure proper execution, a control scale - either a Strain Graph or a Pressure Graph - provided by the manufacturer was used. Each equipment manufacturer has its own control scale. On this particular device, correct procedure execution is confirmed when all cells on the scale turn green.

## 4. Results

Examination of patients with gynecological pathology includes a whole range of clinical and diagnostic procedures, including ultrasound examination (US), computed tomography and magnetic resonance imaging (CT and MRI), radioisotope diagnostic methods (scintigraphy, single-photon emission computed tomography (SPECT) and positron emission tomography (PET)) and hybrid technologies (SPECT-CT, PET-CT, PET-MRI). Each of these methods plays a certain role in assessing the prevalence of the tumor process, its staging and further monitoring during treatment. It is possible to obtain the maximum amount of information for the detection and staging of cervical cancer, and prognosis of the disease using a range of different visualization methods. In the diagnosis and monitoring of patients with cervical cancer, the main problems with ultrasound are the existence of “blind” zones of the small pelvis that are inaccessible to it and the dependence on the manual skills of the specialist conducting the examination. However, ultrasound has been and remains the “gold standard” of the primary diagnostic stage in gynecology.

The use of contrast-enhanced CT during the primary examination is effective in detecting cervical cancer and its relapses, establishing the stage of the tumor process only in the case of massive cervical lesions. In reality, CT is highly effective only in searching for areas of blood accumulation.

The use of MRI allows visualizing the details of the structure of focal changes in the cervix with high relative contrast and spatial resolution. The development of MRI has made it possible to combine the capabilities of other visualization methods in assessing the main prognostic factors of tumor damage, as well as to obtain unique information about tumor invasion into the parametrium and disruption of the zonal structure, which is a decisive factor in choosing surgical tactics [9].

The capabilities of PET (including the hybrid technologies PET-CT, PET-MRI) are limited to searching for distant metastases and assessing the involvement of lymph nodes, and do not allow reliable assessment of the depth of invasion, the degree of infiltration of adjacent tissues and structures. In addition, PET effectively detects only lesions larger than 1.0 cm [9].

When comparing various imaging methods in terms of

tumor detection efficiency and determining the most significant prognostic factors for cervical cancer, in fact, the stage of the disease, according to the literature, MRI has an absolute advantage in diagnosing cervical cancer (Table 1).

**Table 1.** Possibilities of visualization methods in diagnosing cervical cancer according to literature data [9]

Sign/prognostic factor	Ultrasound	CT	MRI	PET
Tumor size	+	+	+	+
Depth of invasion			+	
Spread to parametria		+	+	
Spread to vaginal walls		+	+	+
Spread to bladder/rectum		+	+	
Lymph node involvement		+	+	+
Distant metastases		+	+	+

This is the only method that allows for a comprehensive assessment of both the local status of the tumor process and the presence of distant metastases. For dynamic monitoring of the patient's condition, it is important that MRI does not use ionizing radiation [9]. The cervix is up to 3–4 cm long: the upper 2/3 are its supravaginal part, the lower third is the vaginal part. In the center is the cervical canal, opening into the uterine cavity internally, and into the vagina – the external cervical os. The edges of the os form the anterior and posterior lips of the cervix, and its intussusception into the vagina – the vaginal vaults. From the outside, the uterus is covered with the serous membrane of the peritoneum. Between its leaves around the cervix is the loose connective tissue of the parauterine tissue – the parametrium. Inside from it is the myometrium, the thickest layer of the uterine wall. The mucosa forms the inner layer of the cervix. The vaginal part of the cervix is lined with stratified squamous epithelium, the cervical canal is lined with columnar epithelium, the area of transition from one to the other is called the transition zone, in which squamous cell cervical cancer most often develops. Most cervical tumors are localized in the ectocervix, have exophytic growth and tend to spread to the vaginal vaults. Endophytic growth of tumors, often involving the cervical canal, is rarer. Tumors with a mixed type of growth are common. Squamous cell carcinoma is detected in 70–80% of patients with invasive cervical cancer, adenocarcinoma in 10–20%, and poorly differentiated cancer in 10%. The incidence of other malignant cervical tumors does not exceed 1% [5]. Due to the tendency for cervical cancer to spread along the ligaments, their anatomy should also be taken into account. The anatomy of the uterus is best visualized on T2-weighted images (T2WI), which clearly differentiate three separate layers in the body and cervix in young women [4]. The functional layer of the endometrium, the mucous membrane of the cervical canal, has the highest MR signal intensity. The transitional junctional zone is formed by the basal layer of the endocervix, fibrous connective tissue of the cervical stroma, and the vascular component. In fact, its largest part belongs to the inner layer of the

myometrium, adjacent to a thin lamina of the basal layer of the endometrium, with a developed vascular network (interlayer) between them (equivalent to the hypoechoic layer of the myometrium located under the endometrium in ultrasound) [10]. The boundaries between these histological structures cannot be distinguished even with ultra-high resolution MRI.

The transitional junctional zone has a low MR signal on T2-weighted images, but its intensity can change due to continuous movements of the myometrium, which is assessed as uterine tone on ultrasound. The frequency, amplitude, and direction of the contraction wave depend on the phase of the menstrual cycle and average 2–3 cycles per minute: the direction is most often from the cervix to its fundus in the middle of the cycle and the opposite during menstruation. These contractions of the inner layer of the myometrium are minimal during the luteal phase to facilitate embryo implantation. The frequency of myometrial contractions almost doubles in women with endometriosis or infertility [11]. Fine wave-like movements of the inner layer of the myometrium create a “diffuse” summative dynamic blur on T2-weighted images, which does not allow the layers of the transitional junctional zone to be differentiated separately [4]. The outer muscular layer of the cervix (which has a looser structure and is thinner than the myometrium of the uterine body) has a higher MR signal relative to the transitional junctional zone [4,12].

The mucous membrane of the cervix often intensively accumulates MR contrast agent (MRCA) and is more clearly differentiated from the hypointense stroma in MRI with contrast enhancement. The outer part of the cervical stroma at the border with the myometrium also more actively accumulates MRCA [4].

On T1-weighted images (T1-WI) without contrast enhancement, the cervix has the appearance of a homogeneous cylindrical structure of isointense signal without differentiation of individual layers. T1-WI is usually used to search for lesions of the lymph nodes (LN), they also allow the detection of the presence of hemoglobin biodegradation products in hemorrhages [4]. Mucus or fluid in the cervical canal on T2-WI are visible as linear structures of higher intensity compared to the functional layer of the endometrium, and gas has a very low MR signal on both T1-WI and T2-WI [11]. The choice of treatment method for cervical cancer depends on the prevalence of the tumor process, that is, on the stage of the disease, which is determined according to the clinical classification of the International Federation of Obstetricians and Gynecologists FIGO (2009) [13] (Table 2). However, it does not include gradations of the degrees of tumor invasion into the parametrium, tumor spread to the pelvic walls, and damage to regional lymph nodes. As a result, this classification in 22–75% of cases does not require determination of the true size of the tumor, although the dependence of the tumor volume and the clinical prognosis of cervical cancer is obvious.

Table 2

Stage I	The carcinoma is strictly confined to the cervix (extension to the corpus should be disregarded)
IA	Invasive carcinoma that can be diagnosed only by microscopy with a maximum depth of invasion $\leq 5$ mm <sup>a</sup>
IA1	Measured stromal invasion $\leq 3$ mm in depth
IA2	Measured stromal invasion $>3$ mm and $\leq 5$ mm in depth
IB	Invasive carcinoma with measured deepest invasion $>5$ mm (greater than Stage IA); lesion limited to the cervix uteri with size measured by maximum tumour diameter <sup>b</sup>
IB1	Invasive carcinoma $>5$ mm depth of stromal invasion and $\leq 2$ cm in greatest dimension
IB2	Invasive carcinoma $>2$ cm and $\leq 4$ cm in greatest dimension
IB3	Invasive carcinoma $>4$ cm in greatest dimension
Stage II	The cervical carcinoma invades beyond the uterus, but has not extended onto the lower third of the vagina or to the pelvic wall
IIA	Involvement limited to the upper two-thirds of the vagina without parametrial invasion
IIA1	Invasive carcinoma $\leq 4$ cm in greatest dimension
IIA2	Invasive carcinoma $>4$ cm in greatest dimension
IIB	With parametrial invasion but not up to the pelvic wall
Stage III	The carcinoma involves the lower third of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or non-functioning kidney and/or involves pelvic and/or paraaortic lymph nodes
IIIA	Carcinoma involves lower third of the vagina, with no extension to the pelvic wall
IIIB	Extension to the pelvic wall and/or hydronephrosis or non-functioning kidney (unless known to be due to another cause)
IIIC	Involvement of pelvic and/or paraaortic lymph nodes (including micrometastases) <sup>c</sup> , irrespective of tumour size and extent (with r and p notations) <sup>d</sup>
IIIC1	Pelvic lymph node metastasis only
IIIC2	Paraaortic lymph node metastasis
Stage IV	The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. A bullous oedema, as such, does not permit a case to be allotted to Stage IV
IVA	Spread of the growth to adjacent organs
IVB	Spread to distant organs

Source: Reproduced with permission from Ref 65. <sup>a</sup>Imaging and pathology can be used, when available, to supplement clinical findings with respect to tumour size and extent, in all stages, pathological findings supercede imaging and clinical findings; <sup>b</sup>The involvement of vascular/lymphatic spaces should not change the staging. The lateral extent of the lesion is no longer considered; <sup>c</sup>Isolated tumour cells do not change the stage, but their presence should be recorded. <sup>d</sup>Adding notation of r (imaging) and p (pathology) to indicate the findings used to allocate the case to stage IIIC.

Determination of the prevalence of the disease based only on clinical examination data in stage I–II cervical cancer leads to errors in 32%, in stage III–IV – in 65–90% of cases [14]. Therefore, the accuracy of determining the size and prevalence of the tumor process is of fundamental importance for radiation diagnostic methods [15]. Lymphogenous and hematogenous metastasis variants have been described for

cervical cancer. The presence of lympho-regional spread is prognostically unfavorable. Four stages of lymphogenous metastasis of cervical cancer are distinguished: Stage I – parametrial, paracervical, external, internal iliac and obturator lymph nodes; Stage II – common iliac and sacral lymph nodes; Stage III – lumbar lymph nodes; Stage IV – mediastinal and cervical lymph nodes. Frequency of metastasis to lymph nodes in stage IA1 cervical cancer. – 1%, stage IA2 – 5–8%, stage IB – 15–18%, stage II – 25–30%, stage III – 50–60%. That is, the volume of lymphogenous metastasis correlates with the stage of cervical cancer according to FIGO (2009). In case of metastases of pelvic lymph nodes, retrograde involvement of inguinal lymph nodes can be observed.

#### Local spread

Cervical cancer leads to hematogenous metastasis, which is most often observed in the lungs, liver and bones. Hematogenous metastases of cervical cancer without lymph node involvement are rare.

Cervical cancer is the only gynecological malignant neoplasm, the stage of which is still determined by clinical data, although the FIGO classification has undergone many revisions since its creation in 1985. After its revision and addition in 2012, CT and MRI were recognized as necessary methods for determining the stage of the disease.

The sensitivity and specificity of MRI in staging cervical cancer exceed other clinical and radiation diagnostic methods and amount to 90.9 and 79.0%, respectively. These 9.1% of cervical cancer cases, not detected by MRI, belonged to stage I–II of the disease, were asymptomatic and were not diagnosed during clinical examination either. At present, MRI capabilities do not always allow visualization of cervical cancer stage IA1–IA2.

Currently, MRI staging is recommended for all patients with invasive, morphologically verified cervical cancer stage IB1–IV [18]. Analysis of MRI data allows us to suspect and more reliably detect the involvement of other structures and organs of the small pelvis in the process, for example, minimal invasion of the bladder wall.

On T2-WI, cervical cancer is often characterized by a moderately hyperintense signal in relation to the hypointense cervical stroma. In young women, the cervical stroma on T2-WI may have an MR signal with a moderate decrease in intensity, which may complicate the distinction between healthy tissue and tissue affected by cancer. The relationship between the MRI picture and the stages of cervical cancer according to FIGO (2009) is given in Table 2.

The diagnostic accuracy of MRI in determining the stage of invasive cervical cancer is 77–90%. In the postoperative period, MRI is capable of determining the size of the cervical tumor within 55 mm from the resection edge with an accuracy of 70–90%. MRI also has a high sensitivity in diagnosing the spread of cervical cancer to the vaginal vaults (stage IIA) – 86–93%. Large tumors can cause additional diagnostic difficulties due to intussusception of the affected cervix into the vagina, which is erroneously interpreted as invasion into its vaults. In 50–60% of patients with stage

IIB cervical cancer, the clinical stage of the disease is overestimated due to difficulties in differential diagnosis of the tumor and inflammatory changes in the parameters. At the present stage, MRI copes with this problem, but the wide range of values for assessing the effectiveness of the method is noteworthy: the diagnostic accuracy of MRI in identifying parametrium invasion, according to some data, is 88–97%, while according to others, it is 77–96%, sensitivity is 44–100%, specificity is 80–97%, and negative predictive value is 94–100% [13,15], while assessing the degree of parametrium damage is fundamental when selecting patients for radical surgical treatment.

An attempt to use the MRI method in isolation does not solve the problem of diagnosing cervical cancer recurrence: the negative prognostic value based on the analysis of T2-WI alone reaches 95%. Recurrence of cervical cancer is more reliably indicated by: 1) a moderately or hyperintense signal on T2-WI against the background of hypointense fibrous tissue; 2) a high MR signal on DWI with a high b-factor value and a low ADC value [14]. Adding MRI-DCU to this complex will allow an assessment of the state of tumor angiogenesis in the treatment area and, presumably, an assessment of the degree of hypoxia.

## 5. Conclusions

Thus, among the safe non-ionizing methods of radiation diagnostics of cervical cancer, MRI with simultaneous complex use of high-resolution T2-WI, DWI with construction of ICD maps and MRI-DCU (in studies of prostate cancer, these methods are usually called multiparametric MRI) [15] may improve the diagnostic efficiency of both the primary detection of cervical cancer and the progression of the disease after therapy, with timely correction of the treatment process, as well as more accurately predict the possible results of the manipulations performed.

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