

# Revised FIGO Staging for Cervical Cancer – A New Role for MRI

## Staging des Zervixkarzinoms – die neue Rolle der MRT-Bildgebung

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### ABSTRACT

Cervical cancer is still the fourth most common malignancy in women worldwide and has a high mortality rate. The prognosis as well as the therapy depends largely on the extent of the tumor at the time of initial diagnosis. This shows the importance of correct staging of cervical cancer. In order to promote a globally uniform approach, staging of cervical cancer in the past was based on widespread examinations such as exam under anesthesia, histology from cervical conization or biopsy, systematic lymphadenectomy, cystoscopy, proctoscopy, i. v.-pyelogram and chest X-ray. However, as the primary tumor stage was often underestimated, the 2018 revised FIGO classification now permits cross-sectional imaging techniques and pathological findings to be incorporated into disease staging or an already existing stage to be adapted based on radiological findings. Thanks to its excellent soft tissue contrast, magnetic resonance imaging (MRI) is the method of choice for local-regional staging of cervical cancer, evaluating the response to treatment, detecting tumor recurrence

and for follow-up examinations. It is important that radiologists interpreting pelvic MRI in case of suspected cervical cancer are familiar with the current FIGO staging system. This is the only way to determine the tumor stage as precisely as possible and thus lay the foundation for the success of therapy for patients. The aim of this review is to present the changes of the revised FIGO classification as well as to show the importance of MRI as the method of choice for local-regional tumor staging as a complement to clinical examination.

### Key Points:

- Cervical cancer is still the world's fourth most common female cancer and has a high mortality rate.
- The FIGO classification for staging cervical cancer in the past was based on clinical and widespread examinations.
- The primary tumor stage has often been underestimated with the FIGO staging system since 2018.
- Since 2018, cross-sectional imaging techniques have been incorporated into disease staging.
- MRI is the method of choice for local-regional tumor staging, evaluation of the response to treatment, detection of tumor recurrence and possible complications.

### Citation Format

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### ZUSAMMENFASSUNG

Das Zervixkarzinom ist weltweit noch immer das vierthäufigste Malignom der Frau und hat eine hohe Mortalitätsrate. Die Prognose sowie die Therapie hängen maßgeblich von der Tumorausdehnung bei Erstdiagnose ab. Daraus wird ersichtlich, welchen Stellenwert das Staging des Zervixkarzinoms hat. Um ein weltweit einheitliches Vorgehen zu ermöglichen, beruhte das Staging des Zervixkarzinoms bis 2018 auf flächendeckend verfügbaren Untersuchungen wie der Narkoseuntersuchung, der histologischen Sicherung mittels Konisation oder Zervixbiopsie, der systematischen pelvinen und gegebenenfalls retroperitonealen Lymphonodektomie sowie der Zystoskopie und Proktoskopie, dem i. v.-Pyelogramm und dem Röntgen-Thorax. Da jedoch das primäre Tumorstadium häufig unterschätzt wurde, berücksichtigt die 2018 überarbeitete FIGO-Klassifikation nun erstmals Schnittbildverfahren zur Festlegung des initialen Tumorstadiums. Außerdem darf ein bereits festgelegtes Tumorstadium auf Grundlage radiologischer Befunde angepasst werden. Die Magnetresonanztomographie

mografie (MRT) ist dank ihres hervorragenden Weichgewebekontrastes die Methode der Wahl für das lokale Tumorstaging, ebenso wie für die Evaluation des Therapieerfolgs, die Detektion von Tumorrezidiven sowie für Nachsorgeuntersuchungen. Radiologen, die eine Becken-MRT bei Verdacht auf Zervixkarzinom interpretieren, müssen also vertraut sein mit dem aktuellen Staging-System nach FIGO. Denn nur so

gelingt es, das Tumorstadium möglichst exakt festzulegen und damit den Grundstein für den Therapieerfolg für die Patientinnen zu legen. Ziel dieser Übersichtsarbeit ist es, die Neuerungen der überarbeiteten FIGO-Klassifikation darzustellen sowie den Stellenwert der MRT als Methode der Wahl für das lokale Tumorstaging als Ergänzung zu der klinischen Untersuchung aufzuzeigen.

## Introduction

The “Fédération Internationale de Gynécologie et d’Obstétrique” (FIGO) classification for staging cervical cancer was introduced in 1958 and has since been revised multiple times, most recently in 2018. The recently revised FIGO classification takes into account for the first time the use of cross-sectional imaging techniques of the pelvis to determine the primary tumor stage [1]. Results from studies, reviews and the S3 guidelines “Diagnosis, treatment, and follow up of patients with cervical cancer” serve as the basis for this article. PubMed was used for the literature search.

## Cervical cancer

The most common histological types of cervical cancer are keratinized squamous cell carcinoma and non-keratinized squamous cell carcinoma, adenocarcinoma, and adenosquamous carcinoma [2]. In most cases cervical cancer is caused by an infection with high-risk human papilloma virus (HPV) with the carcinogenesis being multifactorial. There are only a few cases of HPV-negative cervical cancer (typically adenocarcinoma). The prognosis in these cases is less favorable [3]. Among high-risk HPV subtypes, especially subtypes 16 and 18 play a central role since an infection of this type is responsible for approx. 70 % of cervical cancer cases [4].

On average, patients with cervical cancer are between 40 and 59 years of age at the time of initial diagnosis [2]. In recent decades in Germany the ranking of invasive cervical cancer among the most common malignancies in women has dropped from no. 1 (1971) to no. 13 [5]. One reason for this is the cancer early detection program introduced in 1971 including the performance of regular pap smears during preventive care examinations. Improved genital hygiene also plays a decisive role in this drop [2]. A further reduction of the incidence of cervical cancer in Germany is expected in the coming years since the HPV vaccine for girls has been approved in Germany since 2006 [6, 7] and has been included in the recommendations of the Standing Committee on Vaccination since 2007 [8]. Since 2018, the Standing Committee on Vaccination has also recommended the HPV vaccine for boys [9]. However, with 570 000 new cases and 311 000 deaths globally in 2018, cervical cancer is still the fourth most common cancer in women and is even in second place after breast cancer in developing countries with respect to incidence and mortality [10].

In contrast to endometrial cancer or ovarian cancer, the local extent of cervical cancer was still determined preoperatively pri-

marily on the basis of clinical examinations until 2018. The reason for this is the high prevalence of cervical cancer particularly in developing countries where the availability of cross-sectional imaging methods is greatly limited as well as the relatively good ability to evaluate local findings by means of clinical examination. In order to promote a globally uniform approach, the staging of cervical cancer was consequently based only on methods with widespread availability [11]. This includes examinations under anesthesia, histological confirmation via conization or cervical biopsy, systematic pelvic and if applicable also retroperitoneal lymphadenectomy to rule out lymph node metastases, cystoscopy and proctoscopy, IV pyelogram and chest X-ray [12]. The use of additional imaging like computed tomography (CT), magnetic resonance imaging (MRI) or positron emission tomography (PET) for staging local findings was considered desirable but not mandatory and the acquired findings were not taken into consideration when determining the tumor stage. However, clinical examinations are highly examiner-dependent, resulting in an underestimation of the tumor stage in many cases [13]. However, since the initial tumor stage is the deciding prognostic factor for patients, primary staging and precise determination of the tumor extent are extremely important. For this reason, the FIGO classification revised in 2018 takes into account for the first time cross-sectional imaging methods for visualizing local findings when determining the primary stage. Moreover, an already determined tumor stage can be adjusted based on imaging [1].

## MRI – method of choice

Thanks to its excellent soft tissue contrast, MRI is an excellent imaging method for the local staging of cervical cancer as well during follow-up for the evaluation of treatment success [12]. Particularly compared to CT, MRI is superior regarding the evaluation of stromal invasion and the infiltration of adjacent structures and neighboring organs. In relation to infiltration of the parametria, MRI has a sensitivity of over 90 %, while CT has a sensitivity of only 55 %. MRI is also superior with respect to the evaluation of bladder infiltration (specificity of 88–91 % (MRI) compared to 73 % (CT)) [14, 15]. In relation to local staging, PET/MRI hybrid imaging is not significantly more accurate with respect to assigning the tumor to a FIGO stage but is significantly less available than MRI [16]. The sensitivity of MRI is still inferior to whole-body hybrid imaging, e. g., FDG-PET/CT, only with respect to identifying pelvic and/or retroperitoneal lymph node metastases or distant metastases (► **Table 1**) [17].

► **Table 1** Reported diagnostic performance of pelvic imaging methods for the assessment of parametrial invasion, infiltration of the urinary bladder and metastatic lymph nodes in cervical cancer.

	parametrial invasion			infiltration of the urinary bladder			lymph node metastasis			reference
	sens.	spec.	acc.	sens.	spec.	acc.	sens.	spec.	acc.	
CT	14–55 %	77–100 %	74–82 %	64 %	73 %	NR	31–57 %	92–97 %	NR	[14, 16, 17, 19, 38, 39]
MRI	40–92 %	77–99 %	65–98 %	71–100 %	88–97 %	NR	37–76 %	83–93 %	77 %	[13–16, 19, 38–40]
PET/CT	NR	NR	NR	NR	NR	NR	34–82 %	93–100 %	NR	[17, 19, 38]
PET/MRI	90 %	94 %	NR	100 %	100 %	NR	83–91 %	90–94 %	87 %	[16, 19, 41]

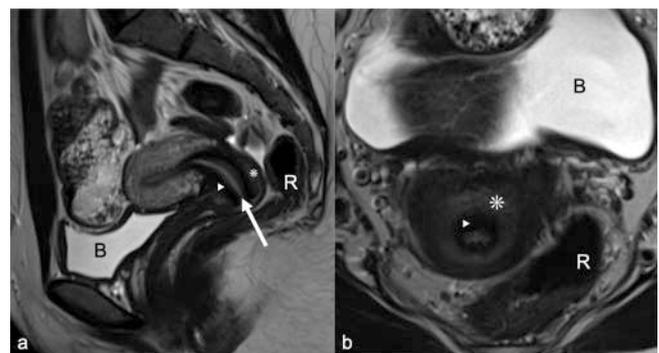
NR = not reported, Sens. = Sensitivity, Spec. = Specificity, Acc. = Accuracy.

## Examination technique

MRI examinations as part of primary staging can be performed at a field strength of 1.5 Tesla (T) as well as 3 T. Although better image quality can usually be achieved at 3 T due among other things to the significantly better signal-to-noise ratio, no major differences regarding diagnostic accuracy between 1.5 T and 3 T can be identified [18]. To further improve the diagnostic significance of MRI examinations, the vagina can be filled prior to the examination and, in the case of primary staging, the rectum can also be filled (e. g. with ultrasound gel). The IV administration of butylscopolamine (Buscopan®) minimizes intestinal peristalsis thereby further improving image quality [19, 20].

The examination protocol for primary staging should include high-resolution T2-weighted sequences on three planes. In these sequences the healthy cervix exhibits characteristic wall stratification: highly hyperintense signaling of the mucosa of the cervical canal and highly hypointense signaling of the inner fibromuscular stroma. In contrast, the outer fibromuscular stroma has a slightly higher T2 signal and an inhomogeneous, less compact structure (► **Fig. 1**) [12]. Intermediate signal intensity between the inner and the outer fibromuscular stroma is a characteristic finding in cervical cancer (► **Fig. 2**). T2-weighted sequences are therefore best suited for differentiating tumor tissue from healthy cervical stroma and are essential for the evaluation of tumor extent [12, 21]. The extent of the tumor in the corpus uteri and in the vagina can be precisely evaluated on the sagittal plane, while the axial plane is particularly suitable for evaluating stromal invasion and infiltration of the parametria [19]. Strictly orthogonal (paraaxial) angulation of the axial plane with respect to the course of the cervix is helpful here. The fibromuscular stroma of the cervix is thus visualized as a hypointense ring. If this ring is intact and continuous on MRI, the examination has a high negative predictive value regarding parametrial infiltration (► **Fig. 1**) [12, 22].

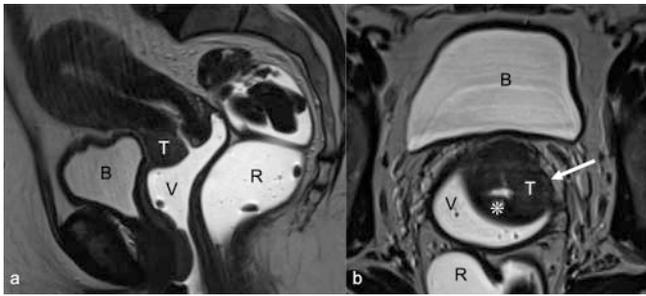
However, reactive tissue changes, e. g. peritumoral edema, which also cause a signal increase in T2-weighted sequences, can result in overstaging of the cervical cancer because of the resulting overestimation of the tumor size. Since cervical cancers like almost all gynecological tumors have a diffusion restriction, diffusion-weighted sequences can help to determine the exact tumor size/extent thus minimizing the risk of overstaging as a result of



► **Fig. 1** Normal findings. In the sagittal plane the characteristic appearance of the cervix can be easily assessed: hyperintense signaling of the mucosa (white arrow), hypointense signaling of the inner fibromuscular stroma (white arrowhead) and intermediate to hyperintense signaling of the outer fibromuscular stroma (\*). Urinary bladder (B) and rectum (R) are partially depicted.

better differentiation between tumor tissue and reactive changes [13]. Moreover, diffusion-weighted sequences play a decisive role in restaging for the evaluation of treatment success or when diagnosing recurrence.

The additional use of intravenously administered gadolinium-containing contrast agent is a topic of controversy in the literature. There is no clear consensus among experts [13]. However, it has been shown that the contrast between tumor tissue and healthy cervical stroma can be increased with the intravenous administration of contrast agent, which can be helpful particularly for detecting very small tumors [21]. The use of dynamic sequences after the administration of contrast agent (DCE) can also facilitate evaluation of the infiltration of the bladder and/or rectum [21]. Moreover, dynamic contrast-enhanced sequences play a decisive role in the differentiation between post-radiogenic fibrosis and residual tumor tissue or tissue suspicious for recurrence during treatment monitoring [23]. Studies were also able to show that DCE sequences can be used to predict response to radiotherapy: Tumors with a high pretreatment  $K^{trans}$  (volume transfer constant – describes the efflux rate of gadolinium from blood plasma into the extravascular extracellular space of a tumor) had a significantly better response to treatment [24].



► **Fig. 2** Cervical carcinoma FIGO stage 1b. **a** The sagittal plane shows a T2w intermediate tumor (T) limited to the cervix **b** without evidence of infiltration of the parametria in the axial plane (white arrow). Dorsal: Evidence of healthy hypointense cervical stroma (\*). Distended vagina (V) and rectum (R) with sonographic gel for better assessment. Urinary bladder (B) partially depicted.

► **Table 2** shows a possible examination protocol for primary staging or restaging in cervical cancer.

## Changes to the revised FIGO classification

The following changes to the FIGO classification were implemented in 2018 by the FIGO committee for gynecology oncology [1]:

1. Imaging methods can be used as a supplement to histology and clinical examination for determining tumor stage.
2. In stage I: Adaptation of the definition of microscopic pathological findings and size designations to allow evaluation of cervical cancer by means of cross-sectional imaging methods.
3. In stages I to III: Lymph nodes can be evaluated based on imaging and histopathological findings. If they are classified as suspicious for metastasis, the case is categorized as stage IIIC regardless of the size and extent of the tumor (with specification of the method being used).
4. To date, there is no recommendation for the routine use of imaging methods for the local staging of cervical cancer. They can be performed in a supplementary capacity on the basis of clinical findings.

## Staging according to the new FIGO classification

### Stage 1

The tumor is limited to the cervix.

#### Stage 1A

Microinvasive carcinoma limited to the cervix that is only microscopically visible. The maximum invasion depth is <5 mm.

- 1A1 stromal invasion <3 mm
- 1A2 stromal invasion ≥3 mm and ≤5 mm

► **Table 2** Possible MRI protocol for staging of cervical carcinoma.

sequences	plane	slice thickness
T2w TSE (high-resolution)	sagittal	3 mm
	coronary to the uterine cervix	3 mm
	axial to the uterine cervix	3 mm
T1w TSE	axial, pelvis and abdomen to the renal hilum for evaluation of the lymph nodes	5 mm
DWI (b-values 50, 400, 800, 1000 s/mm <sup>2</sup> )	axial	3 mm
optional: dynamic T1w TSE fs post contrast (T1w TSE fs post contrast)	axial	3–5 mm

### Stage 1B

Invasive carcinoma limited to the cervix with stromal invasion of ≥5 mm or a clinically visible tumor. Starting in this stage, MRI can be performed for local staging (► **Fig. 2**).

- 1B1 clinically visible tumor <2 cm or microscopically visible lesion with an invasion depth of ≥5 mm
- 1B2 invasive carcinoma with a diameter of ≥2 cm and ≤4 cm
- 1B3 invasive carcinoma with a diameter of ≥4 cm

### Stage 2

The tumor is not limited to the cervix and infiltrates the upper 2/3 of the vagina or the parametria.

#### Stage 2A

Infiltration of the upper 2/3 of the vagina (► **Fig. 3**).

- 2A1 maximum diameter is <4 cm
- 2A2 maximum diameter is ≥4 cm

#### Stage 2B

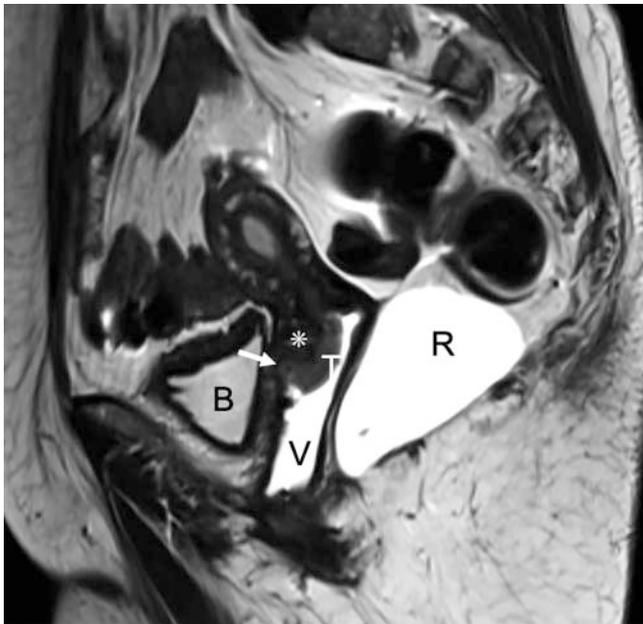
Infiltration of the parametria but the pelvic wall is not affected (► **Fig. 4**).

### Stage 3

Infiltration of the lower 1/3 of the vagina or the pelvic wall. Cervical cancers with locoregional lymph node metastases identified either histopathologically or by means of imaging methods are classified as FIGO stage 3C since the FIGO update in 2018.

#### Stage 3A

Tumor extends to the lower 1/3 of the vagina but does not reach the pelvic wall.



► **Fig. 3** Cervical carcinoma FIGO stage 2a. The sagittal plane shows a T2w intermediate tumor (T) with infiltration of the upper vagina (white arrow). Healthy cervical stroma adjacent (\*). Distended vagina (V) and rectum (R) with sonographic gel for better assessment. Urinary bladder (B) partially depicted.

### Stage 3B

Infiltration of the pelvic wall or the ureters resulting in hydronephrosis (► **Fig. 5**). Per definition, pelvic wall infiltration is present when the iliac vessels, the obturator internus muscle, the piriformis muscle, or the levator ani muscle is infiltrated.

### Stage 3C

Pelvic and/or retroperitoneal lymph node metastases, regardless of tumor size or extent.

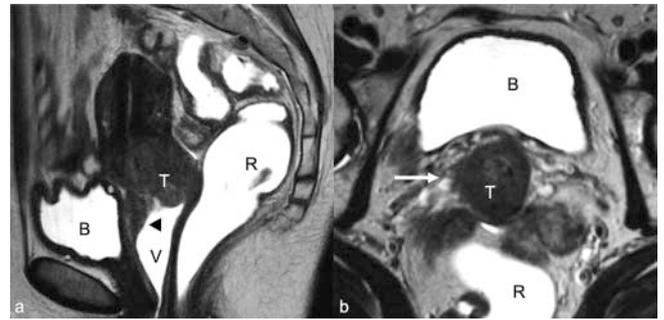
- 3C1 pelvic lymph node metastases
- 3C2 retroperitoneal lymph node metastases In the TNM classification, involvement of retroperitoneal lymph nodes is categorized as distant metastasis (M1).

### Stage 4

Detection of infiltration of the bladder and/or rectum or extension of the tumor beyond the borders of the small pelvis. To be classified as stage IV, the tumor tissue must infiltrate the wall layers of the bladder and/or rectum to the mucosa (infiltration of mesorectal fat tissue is not stage IV per definition). MRI has a very high negative predictive value (up to 100%) for ruling out infiltration of the bladder or rectum so that the FIGO classification does not specify the use of cystoscopy or endoscopy if infiltration of the bladder or rectum has been ruled out by MRI [25].

### Stage 4A

Infiltration of the bladder and/or rectum to the mucosa (► **Fig. 6**).



► **Fig. 4** Cervical carcinoma FIGO stage 2b. **a** The sagittal plane shows a T2w intermediate tumor (T) with infiltration of the upper vagina (black arrowhead) and the corpus uteri. **b** In the axial plane evidence of parametrial infiltration on the right (white arrow). Distended vagina (V) and rectum (R) with sonographic gel for better assessment. Urinary bladder (B) partially depicted.



► **Fig. 5** Cervical carcinoma FIGO stage IIIb. **a** The sagittal plane shows a large T2w intermediate tumor (T) with infiltration of the upper 2/3 of the vagina (black arrowhead) and the uterine corpus. **b** In the coronal plane, evidence of infiltration of the left ureter (U) with consecutive urinary retention (white arrow). Distended vagina (V) and rectum (R) with sonographic gel for better assessment. Partially depicted urinary bladder (B).

### Stage 4B

Presence of distant metastases.

## Treatment of cervical cancer

Treatment of cervical cancer is based on the primary tumor stage, the patient's comorbidities, and a possible desire to have children [26]. In addition to staging, MRI can be used to identify additional prognostic factors that can determine or influence treatment method selection. Therefore, for example, diffusion-weighted sequences can be used to predict response to radiochemotherapy [27, 28].

Surgery and radio(chemo)therapy are available as primary treatment options [2]. A combination of the two treatment options should be avoided due to side effects. In Germany, surgical therapy is the primary treatment up to tumor stage FIGO ≤ 2A. Simple hysterectomy is performed in stage 1A and radical hysterectomy per laparotomy starting in stage 1B. Adenocarcinomas are treated with bilateral salpingo-oophorectomy or radical trachelectomy as a fertility-preserving method in young patients

with a desire to have children. Beginning in tumor stage FIGO  $\geq 2B$ , primary radiotherapy with percutaneous radiation as well as local brachytherapy and cisplatin as a radiosensitizer is the first-line method [2]. Ovariopexy to move the adnexa out of the radiation field should be performed in premenopausal women during staging lymphadenectomy in order to prevent radiation-induced early menopause.

The prognosis for cervical cancer is highly dependent on the initial tumor stage and the presence of lymph node involvement. In patients without lymph node involvement, the 5-year survival rate is almost 100% in stage 1A but only 5–15% in stage 4 [29]. The presence of lymph node metastases in a patient in stage 1A lowers the 5-year survival rate to approx. 50% [30].

## Evaluation of treatment success

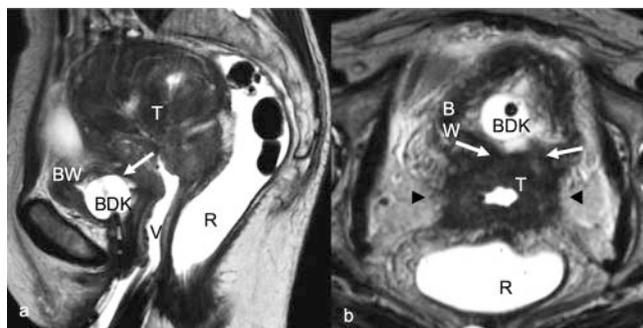
As previously mentioned, MRI in addition to clinical examination is not only a suitable method for primary staging prior to treatment but also plays a central role in follow-up, e. g. for the evaluation of treatment success after radiochemotherapy. T2-weighted sequences visualizing tumor tissue with an intermediate to hyperintense signal are decisive for the identification of residual tumor tissue. However, a significant T2w signal loss indicates post-treatment fibrosis of the cervix as a result of radio(chemo)therapy (► Fig. 7) [31]. Diffusion-weighted sequences can also help to evaluate treatment success since an increasing signal loss particularly in the high b-values as well as a decrease in contrast uptake in contrast-enhanced sequences indicates regression of vital tumor tissue (► Fig. 7). Moreover, some studies were able to show that diffusion-weighted sequences are also useful biomarkers for predicting response to radiochemotherapy or for treatment monitoring during radiochemotherapy [32, 33].

## Diagnosing recurrence

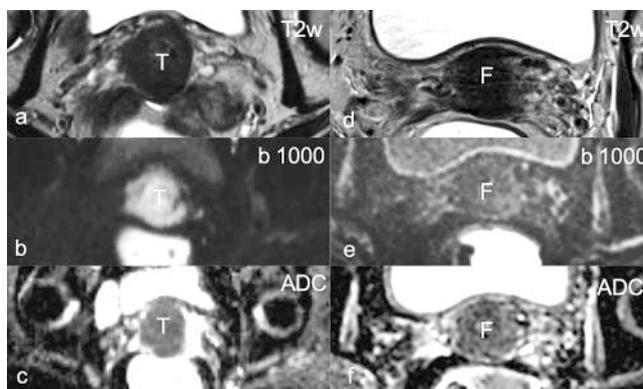
On average, the recurrence of cervical cancer (local recurrence or distant metastases) occurs within 7 to 36 months after initial diagnosis. The rate of recurrence depends on the FIGO stage and is approx. 8–26% [34]. Risk factors for local recurrence include an advanced tumor stage, lymph node involvement, and histology. Adenocarcinoma has a higher risk in this regard than squamous cell carcinoma [2, 35].

Treatment of recurrence depends on the primary therapy and the comorbidities of the patient and ranges from resection to radio(chemo)therapy [2]. However, the prognosis for patients with recurrence is very poor. The average survival time is only 7 to 17 months after the diagnosis of recurrence [34].

Local recurrence typically occurs in the region of the vaginal stump (e. g. after hysterectomy (► Fig. 8)) or in the region of the pelvic wall. In the case of clinical suspicion of local tumor recurrence, MRI is a suitable diagnostic imaging method. In particular, contrast-enhanced sequences are useful for detecting local tumor recurrence [36]. Diffusion-weighted sequences can help to differentiate between recurrence with diffusion restriction and postradiogenic changes. Moreover, it may be possible to predict a possi-



► Fig. 6 Cervical carcinoma FIGO stage IVa. In the sagittal **a** and axial **b** plane evidence of a large tumor formation (T) with infiltration of the corpus uteri, the entire vagina, the parametria on both sides (black arrowheads) as well as the bladder wall (BW) up to the mucosa (white arrows). Permanent bladder catheter (BDK) located in the urinary bladder. Distended vagina (V) and rectum (R) with sonographic gel for better assessment.

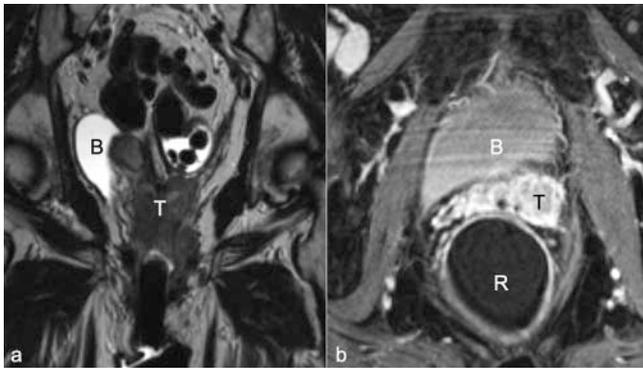


► Fig. 7 Left side: Cervical carcinoma FIGO stage 2b (T) with infiltration of the parametria on the right **a** and evidence of a diffusion restriction with hyperintense signal in the high b-values **b** and reduction of the ADC-value **c**. Right side: After radiochemotherapy posttreatment fibrosis (F) of the cervix with signal loss in the T2w **d** and regressive diffusion restriction **e, f**.

ble early recurrence based on DWI: A study from the year 2016 showed significant differences in ADC values between patients with tumor recurrence and patients without recurrence during radiochemotherapy treatment. A lower increase in ADC values during treatment was seen in patients with recurrence compared to patients without recurrence [37].

## Conclusion

In addition to clinical examination, imaging now plays a central role in primary diagnosis in the case of suspicion of a locally advanced cervical carcinoma with respect to precisely evaluating tumor extent and the possible presence of metastases and selecting the proper treatment. The FIGO classification revised in 2018 now takes into account for the first time cross-sectional imaging methods for tumor staging. Moreover, an already defined tumor stage can be revised based on the radiological findings. Therefore, a revision of currently valid national and international guidelines is



► **Fig. 8** Recurrence of cervical carcinoma after radical hysterectomy. **a** In the coronary plane evidence of a T2w intermediate tumor formation (T) with a blurred border and with inhomogeneous enhancement in the axial plane **b**. Distended rectum with sonographic gel (R) for better assessment. Urinary bladder (B) partially depicted.

necessary since they do not yet take the new FIGO classification into consideration.

Thanks to its excellent soft tissue contrast, MRI is the method of choice for local tumor staging, treatment response evaluation, and detection of tumor recurrence and possible complications. MRI examination for cervical cancer staging should include at least triplanar high-resolution T2-weighted sequences, a T1-weighted sequence, and a diffusion-weighted sequence. Optionally, a simple or dynamic T1-weighted fat-saturated sequence can be additionally performed after intravenous contrast administration to be able to better detect any small tumors or the infiltration of adjacent organs or to evaluate a possible treatment response. Post-treatment changes can be evaluated with the help of T2-weighted and diffusion-weighted sequences. Primarily contrast-enhanced and diffusion-weighted sequences play a decisive role in the diagnosis of recurrence. The latter can even be a useful biomarker for the prediction of early recurrence after radiochemotherapy.

### Conflict of Interest

The authors declare that they have no conflict of interest.

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