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Imaging and Staging of Cervical Cancer

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Cervical carcinoma remains a common gynecologic malignancy. Physical examination has historically served as the predominant tool for staging and assessment, in part due to lack of availability of additional diagnostic resources in many parts of the world. Cross-sectional imaging in the evaluation of cervical cancer has become standard of care in developed countries, and has recently been incorporated into the official staging classification of the International Federation of Gynecology and Obstetrics. This article will describe the use of computed tomography, magnetic resonance imaging, and positron emission tomography/computed tomography and positron emission tomography/magnetic resonance imaging in cervical cancer patients, review optimal techniques for MR evaluation of the cervix, and describe key aspects of staging and management of cervical carcinoma.
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Introduction

Cervical carcinoma remains the fourth most common cancer in females worldwide, following breast, colorectal, and lung cancer, and is the second most common cancer in females in underdeveloped countries.[1] Cervical cancer was previously a major cause of death among women of childbearing age in the United States, but the incidence and death rates of cervical cancer decreased dramatically following the development of the Papanicolaou smear in the 1950s. Between 1955 and 1992, U.S. cervical cancer incidence and death rates declined by more than 60%.[2] In 2018, the estimated number of new cases of cervical carcinoma in the United States was 13,240 and the estimated number of deaths was 4170.[3]

Squamous cell carcinoma (SCC) accounts for 85% of all cervical cancers. Nonsquamous histologies (adenocarcinoma, adenosquamous, undifferentiated) are less common (15%) and are usually associated with a poorer prognosis. The main risk factor for developing cervical cancer is infection by the human papillomavirus (HPV). Additional risk factors include low socioeconomic background, early sexual life, multiple partners, immunosuppression, and smoking.[4]

The vast majority of cases of cervical cancer are caused by persistent infection of the lower genital tract by the HPV, which is sexually transmitted. Of the many strains of HPV, 2 subtypes, HPV-16 and HPV-18, cause 70% of cervical cancers worldwide. Several vaccines have been approved to prevent persistent infections with HPV and are recommended by major health organizations around the world for all children prior to coitarche.[5]

Anatomy

The cervix is a 2-3 cm long cylindrical structure composed of stroma and epithelium. The endocervical canal connects the uterine cavity and the lumen of the vagina via the internal cervical os and external os, respectively. The lower part of the cervix, the ectocervix, is covered by stratified squamous epithelium as a continuation of the vaginal epithelium. The endocervical canal is lined by columnar epithelium that secretes mucus. The junction between the squamous epithelium in the ectocervix and the columnar epithelium in the endocervical canal is the squamocolumnar junction. Metaplasia at this junction results in SCCs. The location of the squamocolumnar junction varies with age and hormonal status. The squamocolumnar junction is located near the external os in young women, but recedes superiorly into the endocervix with advancing age. This movement accounts for a typical pattern of exophytic tumors in young women and endocervical tumors in older women.[6] A thick layer of fibrous stroma underlies both types of epithelium. T2 weighted MR imaging demonstrates the distinct zones of the cervix: hyperintense mucus located centrally in the canal, hyperintense endocervical mucosa, and hypointense fibrous stroma forming the outer layer (Fig. 1).

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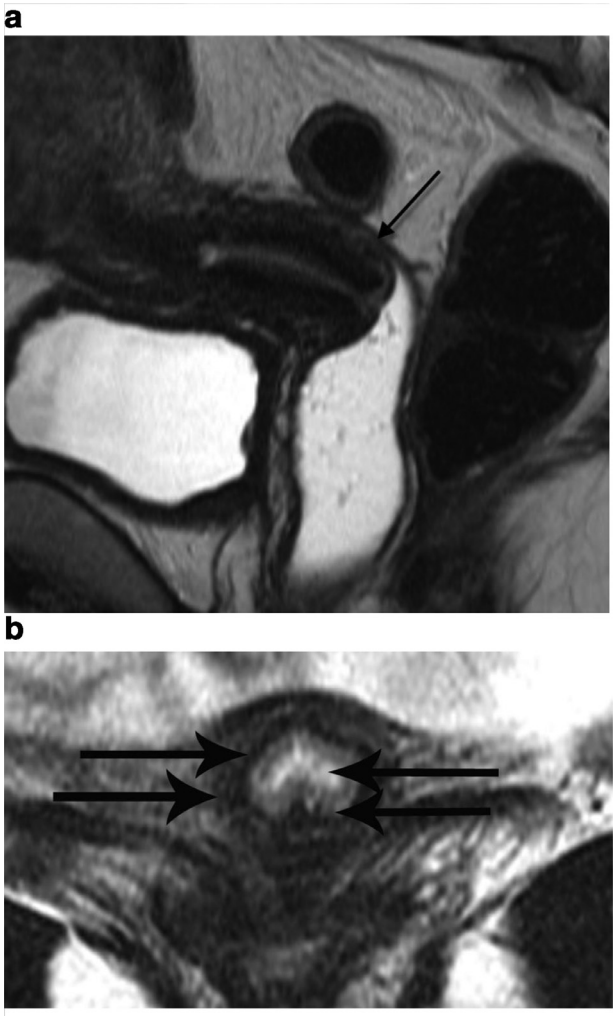

Figure 1 Normal cervix. (a) sagittal T2 weighted MRI of the pelvis with vaginal gel reveals normal cervix (arrow) (b) axial T2 weighted MRI of the normal cervix demonstrates normal zonal anatomy (in order from the center): high T2 signal intensity in fluid/mucus in the endocervical canal, intermediate high T2 signal intensity in columnar epithelium in the endocervix, low T2 signal intensity cervical stroma, and low-intermediate T2 signal intensity in the outer cervical stroma.

Histopathology

SCC accounts for the vast majority of cases of cervical cancer. Nonsquamous cell cancers account for a much smaller number of cases and include andenocarcinoma, adenosquamous carcinoma, adenocystic carcinoma, small-cell carcinoma, and lymphoma.[7] Adenoma malignum is a rare subtype of cervical adenocarcinoma which carries a very poor prognosis, and has a characteristic feature of copious watery vaginal discharge. It is a multicystic lesion which may be indistinguishable from multiple Nabothian cysts on MRI. The presence of a solid component and a deep location of the cysts favor malignancy, but this exceedingly rare entity should not be diagnosed based on imaging findings alone.[8]

Patterns of Spread

Cervical cancer most commonly spreads via direct local extension into the parametrium, vagina, uterus, leading to invasion of adjacent organs, the bladder, and rectum. It also spreads via lymphatic dissemination to pelvic and para-aortic lymph nodes; and less commonly, hematogenous spread to the lungs and bones.[9]

Federation of Gynecology and Obstetrics Staging

Historically, Federation of Gynecology and Obstetrics (FIGO) staging was based mainly on clinical examination in consideration of the prevalence of cervical cancer in low-income populations with limited access to advanced technology. In 2018, this practice was revised by the FIGO Gynecologic Oncology Committee to allow imaging and pathologic findings, where available, to assign the stage. The revised staging is shown in Table 1 (presented at the FIGO XXII World Congress of Gynecology and Obstetrics).[10]

Treatment and Prognosis

The standard treatment for early-stage cervical cancer is radical hysterectomy with pelvic lymphadenectomy. Radical trachelectomy, which removes the cervix, but leaves the uterine body intact, is an accepted fertility-preserving option for patients with early-stage cervical cancer who desire future fertility.[11]

Computed Tomography

Computed tomography (CT) provides some information about the overall size of the cervix, but is inferior to MRI in staging of the primary cervical tumor due to its limited soft-tissue resolution.[12] CT is very useful in diagnosing hydronephrosis, a sign of stage III or higher disease, and detecting distant metastases. Overall, CT has an accuracy of 65% for staging cervical cancer and an accuracy of 86% for detecting metastatic lymph node involvement (Fig. 2).[13]

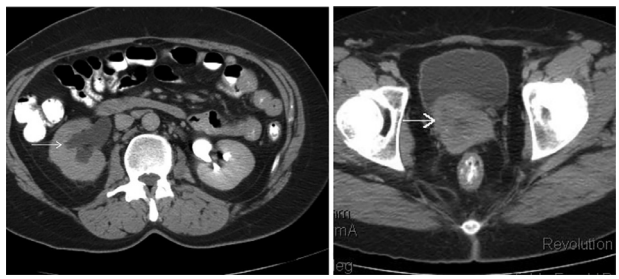

Figure 2 CT images reveal right hydronephrosis due to obstruction of the distal right ureter by a large cervical mass.

Table 1 FIGO Staging of Cancer of the Cervix Uteri (2018)

Stage	Description
I	The carcinoma is strictly confined to the cervix (extension to the uterine corpus should be disregarded)
IA	Invasive carcinoma that can be diagnosed only by microscopy, with maximum depth of invasion <5 mm*
IA1	Measured stromal invasion <3 mm in depth
IA2	Measured stromal invasion ≥3 mm and <5 mm in depth
IB	Invasive carcinoma with measured deepest invasion ≥5 mm (greater than Stage IA), lesion limited to the cervix uteri†
IB1	Invasive carcinoma ≥5 mm depth of stromal invasion, and <2 cm in greatest dimension
IB2	Invasive carcinoma ≥2 cm and <4 cm in greatest dimension
IB3	Invasive carcinoma ≥4 cm in greatest dimension
II	The 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 involvement
IIA1	Invasive carcinoma <4 cm in greatest dimension
IIA2	Invasive carcinoma ≥4 cm in greatest dimension
IIB	With parametrial involvement but not up to the pelvic wall
III	The carcinoma involves the lower third of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or nonfunctioning kidney and/or involves pelvic and/or para−aortic lymph nodes‡
IIIA	The carcinoma involves the lower third of the vagina, with no extension to the pelvic wall
IIIB	Extension to the pelvic wall and/or hydronephrosis or nonfunctioning kidney (unless known to be due to another cause)
IIIC	Involvement of pelvic and/or para−aortic lymph nodes, irrespective of tumor size and extent (with r and p notations)c
IIIC1	Pelvic lymph node metastasis only
IIIC2	Para−aortic lymph node metastasis
IV	The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. (A bullous edema, as such, does not permit a case to be allotted to Stage IV)
IVA	Spread to adjacent pelvic organs
IVB	Spread to distant organs

When in doubt, the lower staging should be assigned.
*Imaging and pathology can be used, where available, to supplement clinical findings with respect to tumor size and extent, in all stages.
†The involvement of vascular/lymphatic spaces does not change the staging. The lateral extent of the lesion is no longer considered.
‡Adding notation of r (imaging) and p (pathology) to indicate the findings that are used to allocate the case to Stage IIIC. Example: If imaging indicates pelvic lymph node metastasis, the stage allocation would be Stage IIIC1r, and if confirmed by pathologic findings, it would be Stage IIIC1p. The type of imaging modality or pathology technique used should always be documented.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is the most sensitive and specific imaging modality for initial staging and follow-up of cervical cancer.[12] MRI is highly accurate in evaluating the extent of disease in the cervix and tumor extension in the pelvis, thus impacting management and treatment options. In particular, MRI is essential to screen candidates desiring fertility preservation for radical trachelectomy given its high accuracy in determining the size of the tumor, length of the cervix, and distance from the tumor to the internal cervical os.[14] Following brachytherapy and chemoradiation therapy, MRI is used to assess response and detect tumor recurrence.

MRI Technique

Proper patient preparation is essential in obtaining high quality MR images. The patient should be instructed to fast for 4 hours prior to the study to reduce bowl motion artifact. An antiperistaltic agent, such as 1 mg of glucagon intramuscularly, is helpful to further minimize bowl motion. The bladder should be moderately full, but not uncomfortably full, in order to displace loops of bowel out of the pelvis. The patient should be imaged on a high field magnet (1.5 Tesla or higher). A very useful addition to the imaging protocol is the use of vaginal gel. Approximately 20-30 cc of warm ultrasound gel instilled into the vagina via a catheter creates excellent contrast on the T2 weighted sequences, highlighting the contour of the vaginal portion of the cervix.

The T2-weighted sequences are the mainstay of cervical cancer imaging, namely sagittal and axial oblique thin section; small field of view, high-resolution T2 weighted sequences. The axial oblique images should be obtained perpendicular to the long axis of the cervix. Dynamic gadolinium-enhanced T1-weighted imaging is useful in the detection of small cervical tumors and the evaluation of depth of stromal invasion and bladder wall invasion.

Additional sequences may include an axial T1-weighted sequence with a large field of view to evaluate the entire pelvis and lower abdomen for lymphadenopathy and bone marrow abnormalities, a large field of view SSFSE T2 weighted sequence to include the kidneys, and diffusion weighted images (Table 2).

Table 2 Typical MRI Sequences

Sequence	Scanning Plane	Purpose
T2	Coronal (large FOV)	Assess for hydronephrosis, overview of lower abdomen and pelvis
T2	Axial	Assess lymph nodes Overview of pelvis Assess ovaries
T1	Axial (large FOV)	Overview of pelvis Evaluate nodes, bone marrow Assess for hematometra or other collections
T2	Sagittal thin section (3 mm), small FOV (20-22 cm)	Measure primary tumor size Assess tumor extent Assess extension into uterus, vagina, bladder, rectum
T2	Axial oblique (perpendicular to the long axis of the cervix), thin section (3 mm), small FOV (20-22 cm)	Measure primary tumor size Assess parametrial invasion
DWI	Axial (large FOV)	Highlight neoplastic tissue, localize very small tumors Evaluate response to therapy
Dynamic contrast enhanced T1	Sagittal, small field of view	Evaluate extent of cervical involvement, distance between tumor and internal os

Abbreviations: DWI, diffusion weighted imaging; FOV, field of view.

Tumor Size

The earliest detectable stage on imaging is Stage IB, which is seen as focal T2 hyperintense signal within the cervix, distinguishable from the normal T2-hypointense signal of the fibromuscular stroma. The tumor usually cannot be distinguished on T1-weighted images. Diffusion-weighted images can be helpful to localize very small tumors. Cervical carcinoma is hyperintense on diffusion-weighted images with corresponding low signal intensity on the apparent diffusion coefficient map. Very small (< 1 cm) cervical tumors are difficult to detect, but may be detected as a focus of early enhancement on dynamic contrast-enhanced images.[15]

Tumors should be measured in all 3 planes, and accurate measurement of macroscopic primary tumors is possible, with MRI coming within 5 mm of pathologic measurements of surgical specimens with 83%-93% accuracy.[16] Tumor size affects treatment decisions and has prognostic implications. In early-stage cervical carcinoma ($\leq$ IB1 and distance of >5 mm from the internal os) treatment with trachelectomy (which removes the cervix, but leaves the uterine body intact) can be considered to preserve fertility. Involvement of the internal os is a contraindication to such treatment. Tumor involvement of the internal os is best evaluated on sagittal T2-weighed images, with reported sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of 91%, 97%, 81%, 98%, and 96%, respectively (Figs. 3 and 4).[17]

Larger tumors are associated with an increased incidence of extrauterine spread and lymph node involvement. Patients with large tumors ($\geq$ 4 cm, FIGO IB2-IIA) are not candidates for fertility sparing surgery, and may undergo chemoradiation rather than radical surgery. In large tumors, peritumoral edema may be mistaken for tumor. In these cases, diffusion weighted imaging (DWI) may be helpful, since edema lacks molecular restriction (Fig. 5).[18]

Parametrial Involvement

Cervical cancer most commonly spreads via direct local extension into the parametrium.[9] Parametrial invasion (FIGO IIB) is an essential determination as it precludes surgical treatment. The accuracy of MRI for parametrial extension ranges from 88% to 97%, significantly higher compared to clinical examination.[19]

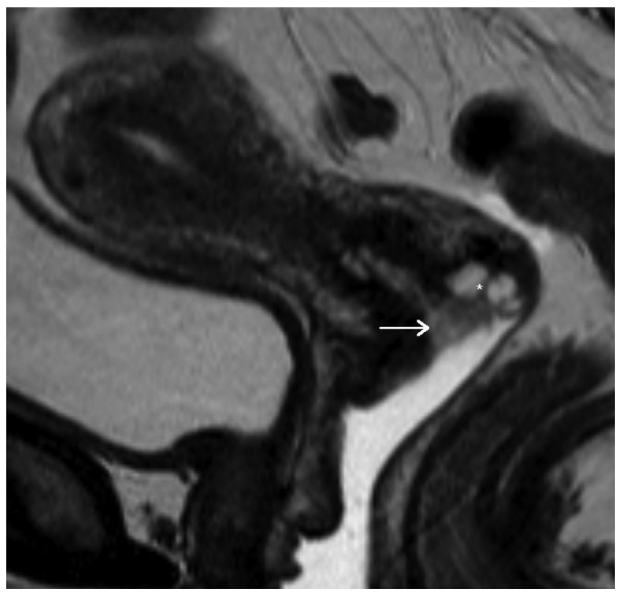

Figure 3 The earliest detectable stage on imaging is Stage IB, which is seen as focal T2 hyperintense signal within the cervix, distinguishable from the normal T2-hypointense signal of the fibromuscular stroma. MRI demontrates a 1 cm cervical mass (arrow) remote from the internal os. Stage 1B1. Nabothian cysts are noted within the cervix (asterisk).

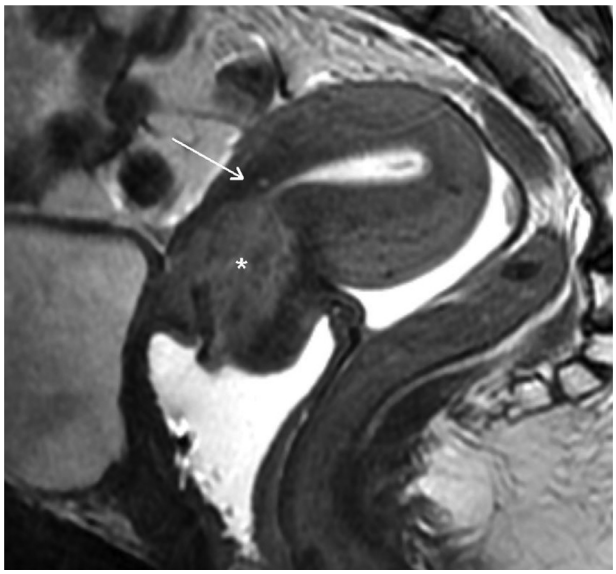

Figure 4 Stage IB2 squamous cell carcinoma of the cervix (asterisk) with involvement of the internal os (arrow).

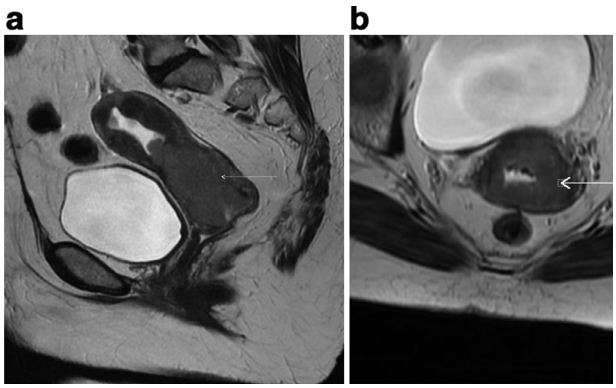

Figure 5 Stage IB3 cervical carcinoma. (a) sagittal T2W image of large cervical mass. (b) axial T2W image reveals no parametrial extension.

Once the tumor breaches the cervical stroma and extends into the parametrium, it is classified as IIB. The stromal ring should be evaluated using axial oblique T2 weighted images perpendicular to the long axis of the cervix. The presence of an intact cervical stromal ring excludes parametrial extension with a negative predictive value of 94%-100%.[20]

Early parametrial extension is seen as irregularity and spiculation at the interface between the cervix and the parametrium. More advanced parametrial extension can be a frank mass in the parametrial fat (Fig. 6).

Pelvic Wall and Adjacent organ Involvement

More advanced cervical tumors can progressively involve the vagina and uterus, and invade the bladder and rectum. Pelvic sidewall involvement (stage IIIB) is diagnosed when tumor is present within 3 mm from the internal obturator, levator ani or pyriformis muscles, or if the iliac vessels are encased by

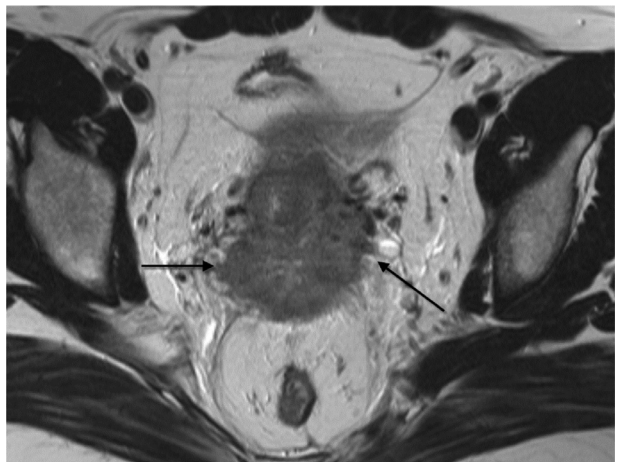

Figure 6 A key determination is the presence or absence of parametrial invasion. Abnormal signal intensity disrupting the cervical stroma is a reliable indicator of parametrial invasion. Axial T2-weighted MRI reveals a large cervical tumor with parametrial extension, Stage IIB (arrows).

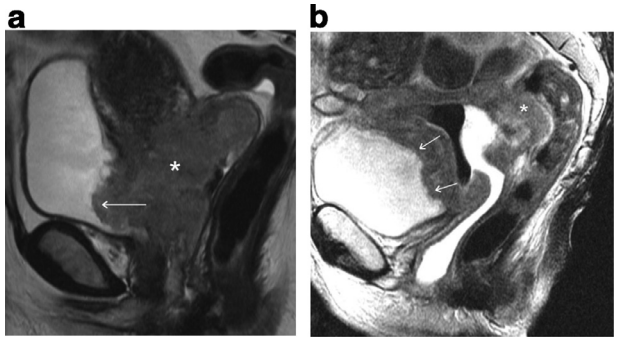

Figure 7 Stage IV Invasion of adjacent organs. (a) Sagittal T2 weighted MRI of the pelvis reveals a large cervical tumor (asterisk) with bladder invasion. (b) Sagittal T2 weighted MRI of the pelvis with vaginal gel demonstrates a large tumor with invasion of the posterior bladder wall (arrows) and rectal involvement (asterisk).

tumor. Involvement of the ureters resulting in hydronephrosis is automatically stage IIIB disease. Wide field of view coronal T2-weighted images including the kidneys provide a quick, reliable evaluation of urinary tract.

Invasion of the bladder or rectum classifies the tumor as stage IVA, and can be seen as disruption of the T2-hypointense wall, presence of an intraluminal mass, or demonstration of a vesicovaginal or rectovaginal fistula. A pitfall in assessing rectal and bladder invasion is bullous edema. Uniform thickening and hyperintensity of the bladder or rectal wall on T2-weighted images is more suggestive of bullous edema than tumor invasion. An intact fat plane between the cervical tumor and the urinary bladder or rectum on MRI is highly accurate in excluding bladder or rectal invasion (Fig. 7).[15]

Lymph Node Assessment

Nodal involvement is one of the most important prognostic factors in cervical cancer. Survival rates decline from

85%-90% to 30%-60% if nodal metastases are present at the time of surgery. If metastatic pelvic nodes are found at surgery, adjuvant chemoradiation is required.[9]

Normal lymph nodes are ovoid and homogeneous with intermediate signal intensity on T2-weighted sequences, low signal intensity on T1-weighted sequences and high signal intensity on DWI. Normal nodes enhance homogeneously after intravenous contrast. MRI determination of metastatic lymph nodes is primarily based on size criteria, with a short-axis diameter of 1 cm or more indicating metastatic involvement. This assessment has obvious limitations, as enlarged lymph nodes may be reactive, and small nodes may contain microscopic foci of disease. Other nodal features suggestive of metastases include a round shape, irregular margins, and internal heterogeneity. Central necrosis is highly indicative of nodal metastases.[16]

The initial lymphatic drainage from the cervix leads to parametrial nodes. From this point, the lymphatic drainage proceeds laterally to external iliac nodes, inferiorly to internal iliac nodes, or posteriorly along sacral nodes. These routes then lead in an orderly progression to the common iliac nodes and the para-aortic nodes.[20] Rarely there are direct metastases to para-aortic nodes.[21]

Distant Metastases

A very small percentage of patients with cervical carcinoma present with distant metastases. Only 1%-2% of patients present with lung metastases, although up to 35% will eventually develop pulmonary metastases.[22] Hematogenous spread in cervical cancer is more common in patients who initially presented with an advanced stage of disease. In patients who develop distant metastases, the most frequent sites are lung, para-aortic nodes, abdominal cavity, supraclavicular nodes, bone, and liver.[23]

FDG-PET/CT and PET/MR

Fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT is useful in staging, treatment planning, and in evaluating response to therapy. PET/CT is frequently used in combination with MRI staging, either routinely or as a problem solving modality if for example, indeterminate nodes are found on MRI. PET/CT has the highest diagnostic performance for detecting nodal metastases in cervical cancer patients, although its accuracy decreases for very small nodes.[24]

FDG PET/MRI combines the advantages of MRI and PET and has excellent initial results in assessing the primary tumor and performing nodal staging. PET/MR is an emerging diagnostic tool, but is not yet widely available (Fig. 8).[25]

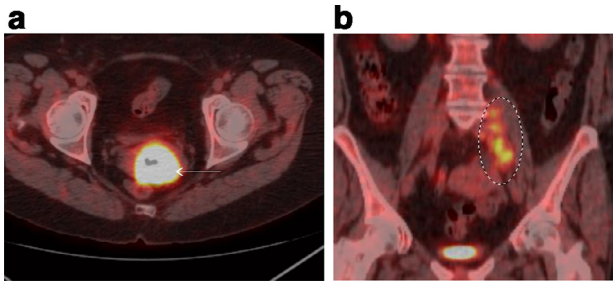

Figure 8 (a) FDG-PET/CT of cervical tumor. (b) PET/CT revealed left iliac lymphadenopathy.

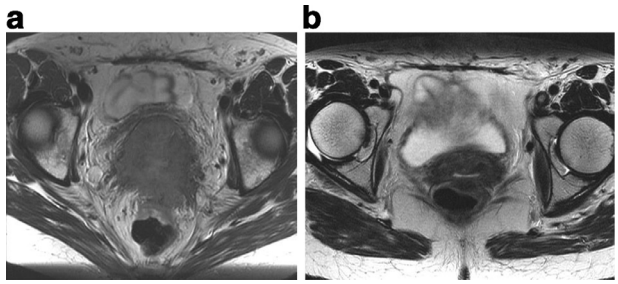

Figure 9 Stage IV tumor in the same patient pre (a) and post (b) treatment.

Follow-up

Chemoradiation followed by brachytherapy is the standard treatment for patients with locally advanced cervical carcinoma. Tumor response is determined by clinical examination and MRI. The MR criteria for a complete response include resolution of the cervical mass, homogenous hypointense cervical stroma, and uniform delayed enhancement of the cervix postcontrast. Comparison to pretreatment images is essential.[26] In postsurgical cases, imaging follow-up varies by institution and is often guided by clinical suspicion. Post-trachelectomy patients should be followed more closely with an MRI at 6 months and 1 year at the minimum due to their higher risk of recurrence (Fig. 9).[27]

Conclusion

The latest FIGO system encourages the use of imaging as a complement to clinical assessment. Radiologists should be familiar with the FIGO staging system and understand how the imaging findings affect FIGO staging and thus patient management. MRI is the imaging modality of choice for initial staging and follow-up of cervical tumors. CT, PET/CT, and PET/MRI also have roles in the assessment of cervical cancer patients.

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