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Magnetic resonance imaging of the cervix

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Abstract

Due to deficiencies of clinical staging, magnetic resonance (MR) imaging is being increasingly used in the pre-treatment work-up of cervical cancer. Lymph node status, as evaluated by advanced imaging modalities, is also being incorporated into management algorithms. Familiarity with MR imaging features will lead to more accurate staging of cervical cancer. Awareness of impact of staging on management will enable the radiologists to tailor the report to clinically and surgically relevant information. This article emphasizes the guidelines on the MR staging criteria, dependence of newer treatments on imaging staging and lymph node involvement, and MR imaging in post-treatment surveillance of cervical cancer.

Keywords: *Cervical cancer; MR imaging; staging.*

Introduction

Cancer of the cervix is the only gynecological cancer staged clinically, in accordance with the modified classification of the International Federation of Gynecology and Obstetrics (FIGO). Clinical staging (Table 1), however, has inherent deficiencies in evaluation of several parameters critical for treatment planning, including parametrial and pelvic side-wall invasion, and size of endocervical tumors[1]. It also disregards lymph node status, the most important prognostic factor in all stages[2–4]. These shortcomings, coupled with emergence of newer treatment options has encouraged the incorporation of cross-sectional imaging into evaluation and treatment planning of cervical cancer patients.

Imaging modalities

MR imaging is regarded as the most reliable modality for the pre-treatment work-up of cervical cancer. Although a large multicenter trial has shown helical computed tomography and MR imaging to have a comparable staging accuracy, helical CT had much greater interobserver variability when compared to MR imaging in the same patient population[5–7]. Due to its superior soft-tissue resolution and multiplanar capability, MR imaging provides a "one-stop" assessment of local disease extent[6,8]. MR should be performed as part of the pre-treatment evaluation for tumors larger than 2 cm, in endocervical lesions, and in obese or pregnant patients[9].

Staging

The T2 weighted image (T2WI) may be normal in micro-invasive (stage Ia) carcinomas.

Once abnormal increased signal is observed on axial scans, the tumor is usually at least a stage Ib, which is a clinically invasive tumor confined to the cervix without invasion of the vagina or parametrium. Stromal invasion of more than 5 mm is almost always detected on T2WI[10], and T1-dynamic imaging can detect stromal invasion of 3 mm or more with a 93% sensitivity[11]. At this stage, the most important determinant of surgical treatment is parametrial involvement and tumor size. Parametrial invasion can only be inferred from the appearance of the peripheral stromal hypointense rim.
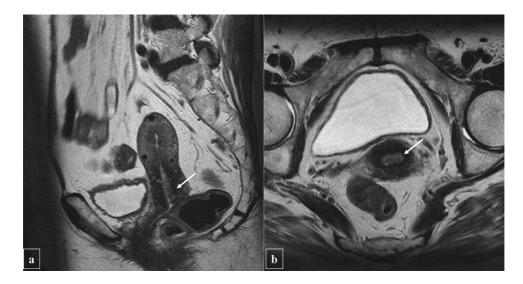
With partial stromal involvement, a rim of hypointensity surrounds the hyperintense tumor. When the thickness of this low signal intensity rim is greater than 3 mm, the "hypointense rim" sign is very specific (96–99%) for excluding parametrial invasion (Fig. 1), labeling the lesion as a "definitive Ib"[12–17]. Complete disruption of the low-signal stripe is a much less specific sign, with a positive predictive value of only 50%[12]. In tumors with such "full-thickness stromal invasion" but no parameterial mass, parametrial invasion is present in 40–73%. Dynamic MR imaging[18] and size criteria have been shown to improve the accuracy of parametrial invasion detection in this setting. A craniocaudal diameter of more than 3 cm for full-thickness tumors, measured on thin-section short-axis T2WI through the cervix[19], is 89% accurate for this purpose. Parametrial invasion is also favored with small tumor extensions beyond the cervical contour, tumor protrusion, irregular margins and abutment or encasement of periuterine vessels in supravaginal tumors. With tumors confined to the portio vaginalis, intact vaginal fornices argue against parametrial involvement. The accuracy of MRI ranges between 77 and 96% in detecting parametrial spread[13,14,20–23], although microscopic invasion always remains a possibility with full-thickness stromal involvement. The highest accuracy is seen in small tumors, in which preservation of an intact dark stromal ring has a negative predictive value of 94–100% in excluding parametrial invasion[13,14]. False positives can result from hemorrhage following biopsy. In larger tumors, peripheral edema might obscure the real boundary of the lesion and cervical stroma can be compressed into a thin margin, leading to over- or under-staging[24].

Once the tumor is assigned to stage Ib by exclusion of parametrial and vaginal involvement, tumor size needs to be taken into account as a crucial determinant of management. Clinical exam even under anesthesia is a poor estimate of the actual tumor size[25]. MR dimensions have been shown to be within 5 mm of surgical size in 70–90% of cases[17,26,27], with an overall accuracy of 93% in predicting tumor size[14]. In addition, clinical exam only provides dimensions in the axial plane, and not in the usual cranio-caudal orientation of the tumor axis. When using the cut-off value of 4 cm, the cranio-caudal diameter has been shown to be a more significant prognostic factor[28] than the axial size because of higher association with endometrial and lymph node involvement. MR can also be used to calculate the tumor volume as a prognostic factor, with 91% 5-year survival in tumors

Table 1   *FIGO clinical staging of cervical carcinoma*

0			Carcinoma in situ, intraepithelial
I			Carcinoma strictly confined to cervix
	IA		Preclinical tumors (i.e., diagnosed only with microscopy)
		IA1	Invasion ≤3 mm in depth, ≤7 mm horizontal
		IA2	Invasion >3 mm but ≤5 mm in depth, ≤7 mm horizontal
	IB		Confined to cervix or lesions greater than stage IA
		IB1	Clinical lesions ≤4 cm
		IB2	Clinical lesions >4 cm
II			Extension beyond the cervix but not to pelvic wall or lower third of vagina
	IIA		No obvious parametrial involvement
	IIB		Obvious parametrial involvement
III			Carcinoma extending to pelvic wall, lower third of vagina or causing hydronephrosis
	IIIA		Involvement of lower third of vagina, but not pelvic wall
	IIIB		Extension to pelvic wall or hydronephrosis
IV			Extension beyond true pelvis or involving mucosa of bladder or rectum
	IVA		Invasion of bladder or rectal mucosa
	IVB		Distant metastasis

Figure 1   **Stage Ib. (a) Sagittal and (b) axial T2WI demonstrate a predominantly hyperintense soft tissue mass (arrow) within the cervical canal. There is no disruption of the peripheral stromal hypointense rim.**

Figure 2   **Stage II-b. (a) Sagittal T2WI shows a hyperintense mass involving the posterior lip of the cervix. (b) On the short-axis T2WI, the fibrous stroma is completely disrupted posteriorly and towards the left, with tumor extension into the parametrium (arrow).**
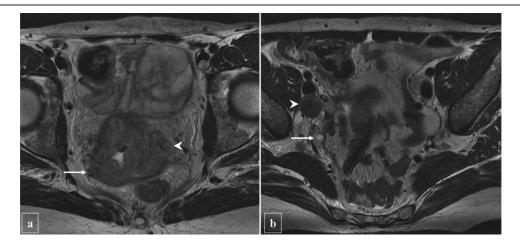

Figure 3   **Stage IIb. (a) Sagittal T2WI demonstrates a 4.5 cm cervical mass extending inferiorly to involve the upper two-thirds of the vagina. The posterior fat plane between the mass and the rectum, and the low signal intensity of the bladder wall remain intact. (b) On the axial T2WI image, parametrial invasion manifests as complete disruption of the fibrous stroma on the left with margin irregularity (arrow).**

smaller than $2.5 \, \text{cm}^3$ and 70% for tumors between $10 \, \text{cm}^3$ and $50 \, \text{cm}^{3}$[25].

In stage II, the tumor has grown beyond the uterus but still has not infiltrated the pelvic side wall or the lower third of the vagina. At stage IIa the tumor infiltrates the upper vagina without parametrial invasion. Parametrial infiltration classifies the tumor as stage IIb (Fig. 2). For supravaginal cervical tumors, the presence of an irregular margin or abutment or encasement of periuterine vessels suggest parametrial spread (Fig. 3). For tumors confined to the portio vaginalis, disruption of the vaginal wall is suggestive of parametrial spread[29]. Accuracy of MR imaging in detection of parametrial invasion falls to 74% in stage IIa and higher tumors, still

remaining superior to clinical examination (53% accuracy)[14].

MR imaging is highly sensitive (86–93%) in depiction of vaginal infiltration[14]. Large tumors may cause a diagnostic challenge by stretching the vaginal fornices and falsely suggesting invasion. MR imaging of vaginal involvement is less crucial as clinical examination accuracy has been shown to be very high[30].

Stage III carcinomas invade the lower third of the vagina, extend to the pelvic side wall, or involve the ureter to cause hydronephrosis. In stage IIIa, the tumor only involves the lower third of the vagina. Occasionally, disruption of the anterior vaginal wall leads to infiltration of the bladder wall, without mucosal involvement[31].

Figure 4   **Stage IIIb. (a) Axial T2WI demonstrates a bulky cervical mass, completely replacing the cervical fibrous stroma. There is parametrial invasion on the left, evidenced by indistinct tumor borders and soft tissue (arrowhead) extending into the parametrium. The right tumor boundary is more well defined and smooth, however, encasement of parametrial vessels (long thin arrow) indicates parametrial invasion. (b) A more cephalad image demonstrates an enlarged external iliac lymph node (arrowhead) and hydroureter (long thin arrow) due to lateral extension of tumor.**

In stage IIIb the pelvic side wall or the ureters are involved (Fig. 4), with obliteration of the entire cardinal ligament and extension to pelvic musculature or iliac vessels. Presence of tumor within 3 mm of the internal obturator, levator ani, and pyriform muscles or the iliac vessels[1,28] is suggestive of stage IIIb disease. Increased signal in pelvic muscles and fine strands of tissue between the tumor and pelvic muscles are additional features of stage IIIb lesions.

In stage IVa, the tumor invades the vesical or rectal mucosa. Bladder invasion is seen as segmental disruption of the hypointense vesical wall[16,17,32]. When bullous edema is present, it appears as a hyperintense band along the interior surface of the bladder wall[8]. MR imaging is highly accurate (99%) in detection of bladder invasion, with a sensitivity of 83% and specificity of 99%[33]. Findings suggestive of invasion are obliteration of the hypointense bladder wall, nodularity and irregularity of the wall, masses protruding into the lumen, high signal in the anterior part of the posterior wall, abnormal strands in the uterovesical space and vesicovaginal fistula. Preservation of hypointensity in the wall, sparing of perivesical fat and an intact vesicouterine ligament make bladder invasion unlikely. Again, due to the edema masquerading as the tumor, increased signal in these structures is a less reliable sign of tumoral involvement. Dynamic imaging has been used to improve the accuracy of bladder invasion in problematic cases[23].

As the pouch of Douglas separates the posterior fornix from the rectum, direct invasion of the rectum is uncommonly seen; uterosacral ligaments provide the preferred route for rectal invasion.

Stage IVb is characterized by distant para-aortic or inguinal lymph node metastases although the latter do not change the FIGO stage. Lymphangitic carcinomatosis of the lung or hepatic metastases can be seen in advanced disease, best evaluated by CT scan[30].

Lymph node assessment

Lymph node involvement is the most important prognostic factor in cervical cancer. Para-aortic node metastasis calls for extension of the radiation field to this region, which because of intestinal morbidity is not routinely included in the treatment field. It is also an important determinant of adjuvant radiotherapy after surgery. As this combined treatment generates complications with uncertain survival benefit, identification of nodal metastasis is crucial in proper selection of these patients for primary radiation therapy[34,35]. Risk of nodal metastasis increases with tumor size, depth of stromal invasion, lymphovascular invasion and parametrial disease[36–38].

The only generally accepted criterion for diagnosis of pelvic node metastasis is size. From a range of 6–15 mm, 10 mm is the most valid upper limit for short axis of normal nodes. For round nodes, 8 mm is typically used as a cut-off value[1,39–43]. However, CT and MR imaging fail to differentiate reactive enlargement (in bulky necrotic tumors) from malignant infiltration, and more importantly, they lack the resolution to detect micrometastases in normal sized nodes. Therefore, advanced techniques such as iron oxide-enhanced MRI lymphography or single and dual-phase positron emission tomography (PET) have been attempted to more accurately assess nodal status of cervical tumors.

Ultrasmall super-paramagnetic iron oxide (USPIO) increases the sensitivity of nodal metastasis detection by MR imaging, without loss of specificity: on a node-by-node basis, the sensitivity increases from 29% to 82–93%

and on a patient-by-patient basis, from 27% to 91–100%[44–46]. High specificity is maintained at 94% and 97% for nodal and patient based diagnoses, respectively. Microlesions are still missed due to inherent resolution limitations of MR imaging, as well as contrast–dose dependent susceptibility artifacts. Fluorodeoxyglucose (FDG)-PET has a sensitivity of 86–91% for detection of metastases in both pelvic and para-aortic nodes, compared to a sensitivity of 57% for CT[47] and 73% for MR imaging[48]. A strong correlation has been found between FDG-PET lymph node findings and patient survival[49,50]]. Overall, PET imaging seems to be increasingly incorporated into cervical cancer care, either in routine diagnostic evaluation[49] or as a supplemental investigation in high-risk patients with enlarged pelvic lymph nodes but no obviously enlarged para-aortic lymph nodes on CT or MR imaging[50].

Management

Pre-invasive lesions and stage 0 cancers are ablated or excised by loop electrosurgery, conization, or cryosurgery[51].

In stage Ia, the major determinants of treatment are fertility and lymphovascular invasion. For patients who have completed childbearing, the treatment of choice remains extrafascial hysterectomy without nodal dissection[53]. However, with higher detection of early invasive cervical cancer, increasing incidence of adenocarcinoma especially in younger women and the tendency for women to delay childbearing, the impact of cervical cancer on fertility is escalating. In stage Ia1, with invasion no deeper than 3 mm below the basement membrane, the rates of parametrial and pelvic lymph node involvement are negligible (less than 1%). With a favorable 95–98% survival rate, loss of fertility becomes the prime concern in this group of patients. In the absence of lymphovascular invasion, conization can be offered as a fertility-preserving treatment to these patients[54].

In stage Ia2 there is higher risk of lymph node metastasis (2–8%), and treatment must ensure the removal of all lymph node-bearing pelvic tissue through pelvic lymph node dissection and parametrectomy. If fertility is no longer desired, most experts would advise radical hysterectomy or radiotherapy as treatment[52]. When fertility is a concern, conization is no longer suitable as it leaves the parametrium in place, and radical trachelectomy is considered the best fertility-sparing option, also suitable for stage Ia1 lesions with lymphovascular invasion[55]. In trachelectomy candidates, the relationship of the proximal extent of the tumor to the internal os and lower uterine body becomes a critical determinant, best assessed by MR imaging[56]. MR imaging has a sensitivity of 86–100% and a specificity of 96–100%[14,55] in depicting the proximal relationship of tumor to the internal os, best seen in the sagittal plane.

Spread of the tumor to the body of the uterus, defined as extension of tumor across the internal os, expansion of the endometrial cavity or disruption of the normal uterine zonal anatomy will make the patient unsuitable for radical trachelectomy. During surgery, a tumor free margin of 8 mm on frozen section is considered safe without any need to remove additional cervical tissue. A "close" margin is defined as an upper free margin less than 5 mm. While these measurements have not been correlated with tumor clearance of internal os on MR imaging, a distance of at least 1 cm between the upper limit of tumor and the internal os can be considered as an MR imaging eligibility criteria for trachelectomy.
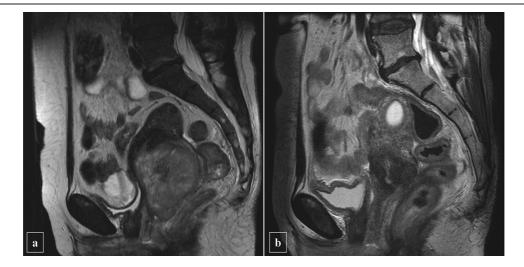
Stage Ib1 is still considered early-stage cervical cancer. Tumor size, depth of stromal invasion, lymphovascular invasion and the nodal status are now accepted as prognostic factors[35,57,58]. Radical hysterectomy with pelvic lymph node dissection is the standard operation for node-negative early-stage cervical cancer. Trachelectomy can be offered to patients with a tumor smaller than 2 cm and without lymphovascular invasion, as both size ≥2 cm and lymphovascular invasion are risk factors for recurrence.

In stage I tumors, primary radiotherapy offers cure rates equivalent to those with radical hysterectomy. Stage Ib2 tumors, the so-called bulky (>4 cm) or barrel shaped tumors, have higher rates of pelvic and para-aortic lymph node metastasis. They usually extend beyond the tumoricidal isodose curve of brachytherapy and areas of hypoxia render radiotherapy less effective. Chemoradiation therapy has been shown to improve survival in stage Ib2 and II disease and is the standard treatment for bulky (stage Ib2 to IVa) disease[59].

Patients with stage IVb disease are offered chemoradiation as a means of helping to control central disease, with radiotherapy for palliation of metastatic lesions. Pelvic exenteration is the standard treatment for pelvic recurrences after radiation therapy. It has a high morbidity rate and therefore is considered only if the cancer is deemed "curable", with no extra-pelvic disease and free margins[60]. Pelvic recurrence after surgery can be treated with radiotherapy if not given previously. Isolated pulmonary metastasis or isolated central recurrence may be considered potentially curable.

Post-treatment imaging and detection of recurrence

Early, non-invasive and accurate assessment of recurrence is crucial for proper selection of salvage treatment versus palliation, improved survival and quality of life, and optimized resource allocation. It is desirable to identify recurrences before symptoms develop, as survival decreases once they become symptomatic. However, clinical post-treatment surveillance of asymptomatic patients is problematic. Therefore patients are usually followed after primary treatment with CT or MR

Figure 5 **Post-radiation changes. (a) Pre-treatment sagittal T2WI shows a bulky exophytic cervical mass with upper vaginal invasion. (b) Two months after radiation therapy, there is complete reconstitution of the cervical stroma with homogenous low signal. Superiorly, hematometra has developed secondary to cervical stenosis. Bladder wall thickening represents post-radiation changes.**

imaging[61−66]. MR imaging is superior to CT in demonstrating pelvic recurrences[13,64,67−69].

The majority of recurrences occur within the pelvis. For detection of recurrent disease, T2WI is highly sensitive (90−91%)[70,71] but has a low specificity (22−38%). During the first few months, widening of the endocervical canal, high signal within the cervical stroma due to edema and inflammation[65,72] and early fibrosis with abundant granulation tissue could mimic residual or recurrent tumor[66,73]. Although serial imaging can help to confirm the stable or fading nature of inflammation or fibrosis[65], imaging-guided biopsies may be required in some cases for diagnosis. In patients in whom there is complete reconstitution of the low signal intensity stroma on MR imaging (Fig. 5), recurrent disease can be excluded with a greater than 95% negative predictive value[65].

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