ROLE OF MRI DIFFUSION IN DIAGNOSIS OF UTERINE CERVICAL CARCINOMA

Essay

Submitted for fulfilment of Master degree in Radio-diagnosis.

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<tr>
<td>ADC</td>
<td>Apparent diffusion coefficient</td>
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<tr>
<td>CIN</td>
<td>Cervical intraepithelial neoplasia</td>
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<tr>
<td>CIS</td>
<td>Cervical carcinoma insitu</td>
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<tr>
<td>CTV</td>
<td>Clinical target volume</td>
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<tr>
<td>DVI</td>
<td>Direct visual inspection</td>
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<tr>
<td>DWI</td>
<td>Diffusion weighted image</td>
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<tr>
<td>FDG</td>
<td>^(^{18})F-fluoro-(^{18}))-deoxy-D-glucose</td>
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<td>FIGO</td>
<td>International federation of gynecology and obstetrics</td>
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<tr>
<td>Gd-DTPA</td>
<td>Gadolinium diethylene triamine penta-acetic acid</td>
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<tr>
<td>GTV</td>
<td>Gross target volume</td>
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<td>HPV</td>
<td>Human papilloma virus</td>
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<td>IV</td>
<td>Intra venous</td>
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<td>LEEP</td>
<td>Loop electrosurgical excision procedure</td>
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<td>LN</td>
<td>Lymph node</td>
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<td>MRI</td>
<td>Magnetic resonance imaging</td>
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<tr>
<td>PAP</td>
<td>Papanicolaou</td>
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<td>RH</td>
<td>Radical hysterectomy</td>
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<tr>
<td>RT</td>
<td>Radiotherapy</td>
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<tr>
<td>SCJ</td>
<td>Squamocolumnar junction</td>
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<tr>
<td>USPIO</td>
<td>Ultra small particles of iron oxide</td>
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INTRODUCTION

Cervical cancer is the third most common malignancy in women worldwide. The frequency varies considerably between developed and developing countries, however: Cervical cancer is the second most common cancer in developing countries (Jemal A, et al., 1100).

Conventional magnetic resonance (MR) imaging has an established role in gynecologic imaging. However, increasing clinical demand for improved lesion characterization and disease mapping to optimize patient management has resulted in the incorporation of newer sequences, such as diffusion-weighted (DW) imaging (Malayeri AA, et al., 1100).

DW imaging is a potentially useful adjunct to conventional MR imaging for evaluation of gynecologic tumors, thus improving overall diagnostic accuracy, tumor staging, prediction of response to therapy, and treatment follow up (Freeman SJ et al., 1101).

In cervical carcinoma, in the vast majority of cases the diagnosis is known before the patient arrives in the MR imaging suite. The critical clinical question we are asked to address is the stage of the disease, particularly when the tumor involves the parametrium. The clinician can assess the degree of vaginal involvement. Treatment options depend on our morphologic assessment of the cervical cancer, with the critical management decisions based on the size of the mass and the presence of parametrial (stage 2B) disease. We must carefully assess the stromal ring of the cervix, and our ability to include or exclude parametrial involvement will determine whether the patient will undergo a
hysterectomy or chemotherapy–radiation therapy as the first line of therapy (FollenM, et al., 1112).

The value of diffusion-weighted imaging lies on the localization of pelvic lymphadenopathy. Certainly, we know that lymph node size is a poor predictor of metastatic disease, and a modality that could help discriminate between malignant and nonmalignant lymph nodes would be very beneficial in staging. As stated by Whittaker et al, diffusion-weighted imaging shows promise in differentiating lymphoma from carcinoma (Sumi M, et al., 1112).
AIM OF THE WORK

The aim of this study is to evaluate the role of MRI diffusion in diagnosis of uterine cervical carcinoma.
Anatomy of the uterine cervix

Embryogenesis and normal development of the uterus and cervix:

The paramesonephric or müllerian ducts, which are formed in the mesonephrons by invagination of the coelomic epithelium, are responsible for the genesis of the uterus and the upper 2/3 of the vagina. Uterine epithelium is formed from the urogenital sinus. The uterine walls are formed by the splanchnic mesenchyme. The cervix may be of paramesonephric origin (Skandalakis et al., 2004).

Topography:

The cervix is approx. 3 to 4 cm in length and consists of a vaginal portion, and supravaginal portion, which is very important to the endopelvic fascial support system of the cervix and upper vagina. The anterior area of the supravaginal part is related closely to the base of the urinary bladder and is not covered by peritoneum. Its posterior area is covered by peritoneum which forms the recto uterine pouch of Douglas above and posterior vaginal fornix below. The pouch of Douglas separates the rectum from the uterus (Fig. 1 & 2) (Skandalakis et al., 2004).

The wall of the cervix is primarily made up of firm connective tissue. In contrast to the uterine corpus, the muscular portion accounts for less than 10% of the cervical wall and primarily consists of smooth muscle cells in circular arrangement. The cervical canal is coated with mucus-producing columnar epithelium and contains numerous gland-like units; the crypts. The squamocolumnar junction is the transition from the columnar epithelium of the endocervix to the non-keratinizing
squamous epithelium of the ectocervix and is situated at the level of the external os (Klüner and Ham, 2002).

Fig. (1): Anatomic sketch of coronal view showing the uterine cervix (Klüner and Hamm, 2002).

Fig. (2): Diagram of the peritoneum of the female pelvis in paramedian section (Skandalakis et al., 2002).
Lymphatic drainage of the cervix:

There are three lymphatic pathways of drainage for the cervix through which tumor can spread (Fig. 3):

1. The lateral route is along the external iliac vessels,
2. The hypogastric route is along the internal iliac vessels,
3. The presacral route is along the uterosacral ligament.

All three routes lead to the common iliac nodes, from where tumor can involve the paraaortic nodes (Pannu et al., 2001).

Fig. 3: Diagram of the lymphatic drainage of the uterine cervix (Pannu et al., 2001).
**Uterine Ligaments:**

A total of eight ligaments contribute to the support of the uterus. Diagnostically, which primarily pertains to the evaluation of the local extent of cervical cancer, the vesicouterine and the sacrouterine ligaments are most important (*Klüner and Ham, *).

The supravaginal cervix is suspended from the lateral pelvic side wall by the cardinal ligaments (for Mackenrodt) (Fig. 4), which pass from the cervix to the side wall and merge with the connective tissue surrounding the internal iliac vessels. The ureters pass through the middle of these ligaments. Interestingly, the ligaments may be pulled down in uterine prolapse and leads to kinking and obstruction of the ureters.

Anteriorly, the supravaginal cervix is suspended from the posterior aspects of the pubic bone by the pubocervical ligament. This ligament also surrounds the internal urethral sphincter.

Posteriorly, the cervix is connected to the sacrum at (S2-4) by the uterosacral ligaments, one on either side of the rectum. These are common sites of tumor spread from the cervix. All of these ligaments unite to form a continuous sheet of connective tissue across the pelvic floor (*Tempany and Fielding, *).
The peritoneum travels downwards to the pelvic cavity after covering anterior and posterior uterine surfaces. Two spaces are formed: the deep rectouterine space of Douglas and the shallow vesicouterine space (Skandalakis et al., 200).

**Parametrium:**

The Parametrium is the connective tissue between the leaves of the broad ligament. Medially, it abuts the uterus, cervix, and proximal vagina. Laterally, it extends to the pelvic side wall. Inferiorly, it is contiguous with the cardinal ligament. The Parametrium consists primarily of fat, especially in their lateral portions near the pelvic sidewall through which run uterine vessels, nerves, fibrous tissues, and lymphatic vessels.

The distal ureters are in the Parametrium as they pass from the pelvic side wall to the bladder crossing the uterine arteries.
approximately \( \approx \) cm lateral to the margin of the cervix (Pannu et al., 2001).

**Blood supply of the uterus and cervix: (Fig. 5)**

- **Arteries** – the main supply to the uterus is through the uterine branch of the internal iliac artery on each side; a branch supplies the cervix and the main vessel supplies the body and fallopian tubes.

- **Veins** – the uterine veins drain following the route of the artery to the internal iliac vein (Gray, 2001).

![Blood supply of the uterus](image)

Fig. (5): Blood supply of the uterus. Anterior view with left side of the uterus partially sectioned (Tortora & Grabowski, 2000).
Pathology of Uterine Cervical Carcinoma

Cervical carcinoma is the third most common gynecologic malignancy, with an average patient age at onset of 45 years (Nicolet et al., 2000).

Cervical carcinoma is also the second most common cause of gynecological malignancy death following ovarian carcinoma (Rubin et al., 2002).

Egypt has a population of 87,542 million women, ages 81 years and older who are at risk of developing cervical cancer. Current estimates indicate that every year, 17,742 women are diagnosed with cervical cancer and 47,187 die from the disease. Cervical cancer ranks as the second most frequent cancer among women in Egypt. About 7,11% of women in the general population are estimated to harbor cervical human papilloma virus (HPV) infection at a given time (World Health Organization and Institut Catala d'Oncologia, 2002).

One of the methods to improve this situation is to perform prophylactic physical examination to find the least advanced stages using Papanicolaou (pap) smears which do affect the health awareness of the potential patients (Mierzwa et al., 2002).

Pathogenesis and risk factors:

According to Rubin and colleagues (2002), invasive cervical carcinoma is thought to develop overtime from non-invasive precursor lesions referred to as cervical intraepithelial neoplasia (CIN) which is nearly always a disease of the metaplastic squamous epithelium in the transformation zone of the endocervix, which begins with minimal atypia.
And progresses through stages of more marked intraepithelial abnormalities to *invasive squamous cell carcinoma*.

The grades of *cervical intraepithelial neoplasia (CIN)* are as follows:

. CIN-¹: mild dysplasia.

. CIN-²: moderate dysplasia.

. CIN-³: severe dysplasia and carcinoma in situ. *(Howard et al., ²⁰⁸)*

In CIN-¹, the most pronounced changes are seen in the basal third of the epithelium. However, abnormal cells are present throughout the entire thickness of the epithelium. Substantial cytoplasmic differentiation proceeds as the abnormal cells migrate through the upper two-thirds of the epithelium, but the nuclei in the upper levels are still morphologically abnormal. In CIN-³, most of the cellular abnormalities are in the lower and middle thirds of the epithelium. Cytodifferentiations occur in cells in the upper third, but it is less than CIN-¹. CIN-³ is synonymous with severe dysplasia and carcinoma insitu (CIS). In severe dysplasia, the cells in the superficial (upper) epithelium disclose some, albeit minimal, differentiation, whereas CIS shows none at all *(Howard et al., ²⁰⁸)*.

The mean age distribution of early invasive cancers is the late third and early fourth decade. Late invasive cancer is seen in slightly higher age group. Known risk factores for cervical carcinoma, as stated by *Baay and his colleagues* in ²⁰⁸ include:

- "Intercourse at an early age.
- "Multiple sexual partners.
- "Large number of pregnancies.
- "Smoking (the mechanism is obscure)."
Human papilloma virus infection (HPV) is associated with increased risk of developing CIN. Thus CIN is a sexually transmitted disease. It is important to notice that prevalence of HPV in women with high-grade squamous intraepithelial lesions is higher than in cervical adenocarcinoma patients (Gudleviciene et al., 2007).

Virtually all squamous cell carcinomas and the overwhelming majority of adenocarcinomas of the cervix are HPV positive. HPV is essential for the onset of cervical carcinogenesis, but is probably not sufficient for progression to invasive cervical cancers. It is likely that several cofactors, such as environmental, viral and host-related factors, are necessary for the development of cervical cancer (Tjalma et al., 2007).

Clinical picture:

Cervical carcinomas are more common in grand multiparous women and major early presenting complaints are abnormal vaginal bleeding, watery discharge and postcoital bleeding (Olatunji and Sule-Odu, 2007).

With more advanced tumors, the symptoms are referable to the route and degree of spread (Rubin et al., 2007).

Cervical cancer is a preventable disease. Measures to reduce the incidence and morbidity would include mass education of the sexually active women to have cervical smear regularly and also to report symptoms early so as to diagnose the invasive disease in the early stages (Olatunji and Sule-Odu, 2007).
Histological varieties and prognosis of cervical carcinoma:

Squamous carcinoma accounts for $\approx 35\%$ of cervical cancers and adenocarcinoma for $\approx 17\%$. Several uncommon tumors such as adenoid cystic, small cell, adenosquamous carcinoma, and lymphoma, may also affect the cervix (*Kaur et al.*, 2003).

Squamous cells cover the epithelial surface of the portio continuing from the vagina. With age, they grow back to cover the columnar cells of the endocervical gland. This transitional area is called the squamocolumnar junction (SCJ). Carcinoma of the cervix develops almost exclusively within the transformation zone that extends between the original SCJ and the physiologic SCJ (Fig.3) (*Okamoto et al.*, 2003).

![Drawing of the uterus, cervix and vagina. The cervix consists of two different types of epithelium: squamous epithelium and glandular epithelium. Squamous cells cover the epithelial surface of the portio continuing from the vagina, and columnar cells cover the glandular epithelium of the endocervical gland, which produces mucin. With age, squamous cells grow back to cover the columnar cells. This transitional area is the SCJ (arrow) (*Okamoto et al.*, 2003).](image-url)
Invasive squamous carcinomas and adenocarcinomas are preceded by cervical intra-epithelial neoplasia and cervical glandular intra-epithelial neoplasia, respectively. Each is graded into low and high grade (Tiltman, 2009).

Other less frequent types include, neuro-endocrine tumors (Schmidt et al., 2009), adenosquamous carcinoma (Yasuda et al., 2009), cervical carcinomas (Iida et al., 2009) and cervical lymphomas (Gonzalez-Cejudo et al., 2009).

In a research work done by Yasuda and colleagues in 2009, that included 21 females with cervical carcinoma, the overall 5-year survival rates of cases histologically presented with adenosquamous carcinoma, adenocarcinoma, and squamous cell carcinoma were 44%, 44% and 40%, respectively, suggesting poor prognosis of the former type.

**Indicators of poor prognosis as stated by (Chargui et al., 2009) include:**

- Age more than 50 years.
- Pelvic lymphadenopathy.
- Tumor diameter larger than 4 cm.
- Depth of stromal invasion greater than 5 mm.
- Tumor grade.
- Advanced stage at presentation.
- Lymph-vascular space involvement.

Pelvic lymph node metastasis is an important prognostic factor of cervical carcinoma. Deep muscularis involvement of vaginal portion of
the cervix, uterine ligaments involvement, especially advanced stage and deep muscularis involvement of the cervical canal are risk factors of pelvic lymph nodes metastasis of cervical carcinoma (Feng et al., 2013).

**Squamous Cell Carcinoma:**

Squamous cell carcinoma is by far the most common type of cervical cancer. It often manifests in its early stages as a poorly defined, granular, eroded lesion or as a nodular and exophytic mass (Fig. 7). If it is predominantly within the endocervical canal, it may appear as an endophytic mass, infiltrating the stroma and causing diffuse enlargement and hardening of the cervix (barrel-shaped cervix). On microscopic examination, most tumors display a nonkeratinizing pattern that is characterized by solid nests of large malignant squamous cells, with no more than individual cell keratinisation. Most of the remaining cancers exhibit nests of keratinized cells organized in concentric whorls, so-called keratin pearls (Rubin et al., 2013).

**Fig.(V):** Cervical carcinoma with exophytic growth in a 44-year-old woman. The pathologic stage was Ib- 1. Photograph of the cut surface of the resected specimen shows a white mass that expands into the fornix (arrows). The tumor on photomicrograph is composed of atypical squamous epithelium with cancer "pearls" (Okamoto et al., 2013).

**Cervical Adenocarcinoma:**
Most of the tumors are of the endocervical cell (mucinous) type, but the various subtypes have little importance for overall survival. Adenocarcinoma shares epidemiological factors with squamous cell carcinoma of the cervix and spreads similarly. The tumors are often associated with adenocarcinoma in situ and are frequently infected with HPV (Rubin et al., 200).

This tumor typically manifests as a fungating polypoid or papillary mass. Microscopically, exophytic tumors often have a papillary pattern, whereas endophytic ones display tubular or glandular pattern. Poorly differentiated tumors are predominantly composed of solid sheets of cells (Hamm et al., 200).

Diagnostic challenge may be posed by an incidental finding of metastatic cervical adenocarcinoma in the presence of an asymptomatic primary tumor. Carcinoma metastatic to the uterine cervix is very rare, however when it does occur the most frequent nongenital primary sites are the stomach and colon (Sozen et al., 200).

Adenocarcinoma of the uterine cervix with nongestational choriocarcinoma presenting in the form of choriocarcinomatous metastasis is an extremely rare condition (Pavelka et al., 200).

**Adenosquamous carcinoma:**

Adenosquamous carcinomas range between 5-10% of cervical cancers and are composed by an admixture of malignant squamous and glandular elements. Adenosquamous cervical carcinomas occur at a similar age with squamous cervical carcinomas. A similar degree of differentiation of the two components would be expected, however registrations revealed a degree of variability in grading of the two components, with a tendency of squamous component towards poorly
differentiated aspect and a slightly dominant aspect of well differentiated glandular pattern \textit{(Amalinei et al., \textcopyright 200\textperiodcentered).}

**Neuro-endocrine tumors of the cervix:**

Neuroendocrine carcinomas of the cervix are rare. They cover a wide age range occurring in young adult women and very old women. Two types are distinguished: small cell carcinoma (oat cell) and large cell neuroendocrine carcinomas. They either occur in pure form or in combination with adenocarcinoma or squamous cell carcinoma. Typically, there is an association with a high risk HPV infection. The prognosis is still poor with early metastases to regional lymph nodes and distant sites such as lung, liver, bone, and brain \textit{(Schmidt et al., \textcopyright 200\textperiodcentered).}

**Cervical Lymphoma:**

Malignant lymphomas in the female genital tract are rare, and those arising from this tissue system are extremely uncommon. The most frequent type of lymphoma proved to be diffuse large B-cell lymphoma, closely followed by follicular lymphoma, including all grades of malignancy. Burkitt lymphoma showed a rather similar frequency. Marginal zone lymphoma occurred exclusively as primary lesions in the uterine mucosa. Lymphoplasmacytic lymphoma was restricted to the vulvo-vaginal area and occurred in women over 60 years of age \textit{(Kosari et al., \textcopyright 200\textperiodcentered).}
Staging and Management of uterine cervical carcinoma:

Cervical carcinoma is the third most common gynecologic malignancy. Although patients now survive longer due to radiation therapy and more effective chemotherapy, cervical carcinoma is also one of the most frequent causes of death in women. The staging system of the International Federation of Gynecology and Obstetrics (FIGO) is widely used for treatment planning, however, according to Jeong et al. (2003) there are significant inaccuracies in the FIGO staging system.

Detection and management of cervical intraepithelial neoplasia:

A study performed by Sigurdsson and Sigvaldason (2002) confirmed the effectiveness of the screening program and supported the recommendation that screening should commence below age 50 with a maximum of 3-year initial screening intervals. The interval can then be extended after age 5 and stopped after age 65.

Direct visual inspection (DVI) with acetic acid is a new screening test for early detection of cervical carcinoma in the Ain-Shams University, Maternity Hospital in Cairo, Egypt. Women, whose smear report showed abnormal cells suggestive of squamous intraepithelial lesion or HPV infection or those who showed abnormalities or acetowhite areas on DVI subsequently, were referred for colposcopy and biopsy when appropriate. Colposcopy also was performed for women with negative DVI and negative smears if they had contact bleeding or chronic per vaginal discharge. Direct visual inspection is feasible and had superior sensitivity compared with cervical cytological analysis in detecting premalignant lesions of the cervix. It can be used as a primary screening tool with
satisfactory low biopsy rate in low-resource settings or where cytological services are suboptimal (El-Shalakany et al., 2004).

When CIN is discovered, colposcopic examination in combination with a Schiller test is important to delineate the extent of the disease and to indicate the areas to be biopsied. Diagnostic endocervical curettage is also useful for determining the extent of endocervical involvement. Women with CIN-1 are often followed conservatively (i.e. repeated PAP smears plus close follow-up), although some gynecologists now advocate local ablative treatment. High-grade lesions are treated according to the extent of disease. LEEP (loop electrosurgical excision procedure), which can be performed on an outpatient basis, is commonly used. In certain situations, cervical conization (removal of a cone of tissue around the external os), cryosurgery, and (rarely) hysterectomy are performed. Follow-up smears and clinical examinations should continue for life, since vaginal or vulvar squamous cancer may develop later (Rubin et al., 2005).

Wang and coworkers (2005), had stated that several test modalities (cytological, molecular, and visual), may be used for cervical cancer screening, and follow-up, as no currently available single test for cervical neoplasia can detect disease with both high sensitivity and specificity, therefore combinations of available tests allow for improved risk prediction. They have evaluated the combination of liquid-based cytology, human papillomavirus (HPV) DNA testing, and visual inspection (cervicography), taken at a single point in time, to predict risk of subsequent cervical intraepithelial neoplasia 3 (CIN3) or cancer developing within 3 years in a triage population of 0.605 women referred for equivocal or mildly abnormal cytology. The concurrent administration
of all three test modalities showed that combinations of these test modalities permitted clear and distinct risk stratification.

Finally, a vaccine against HPV has been developed and its prophylactic potential is under clinical evaluation (Zaspel and Hamm, 2007).

**Detection and management of cervical carcinoma**

**Clinical staging:**

International Federation of Gynecology and Obstetrics (FIGO) classification is a clinical staging system based on findings from clinical assessment or examination of patients under anesthesia, which may be supplemented by chest radiography, excretory urography, cystoscopy, and proctoscopy (Table 1) (Fig.A). Cross-sectional imaging is not included as a part of the initial staging because access to this technology is not universally available (Kaur et al., 2003).

**Fig.(A):** Drawings of different stages of cancer cervix (a) & (b) Coronal drawing of the uterus shows tumor (arrow) confined to the cervix, and extending into the myometrium. Stage I; (c) Coronal drawing of the uterus shows extension of the cervical cancer into the upper one-third of the vagina (arrow). Stage IIa; (d) Axial drawing of the pelvis shows tumor encasing the right ureter, a sign of parametrial invasion. Stage IIb; (e) Axial drawing of the pelvis shows tumor involving the muscles of the right pelvic side wall, stage IIIb; (f) Axial drawing shows tumor involving the bladder and rectum, stage IVa. (Pannu et al., 2008)
Table (\( \text{T} \)): Revised FIGO staging of cervical carcinoma (Kaur et al., 2003)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Revised FIGO staging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>Carcinoma in situ, intraepithelial carcinoma</td>
</tr>
<tr>
<td>Stage I:</td>
<td>Carcinoma strictly confined to cervix (extension to the corpus should be</td>
</tr>
<tr>
<td>Ia</td>
<td>Preclinical carcinoma of cervix (microinvasive)</td>
</tr>
<tr>
<td>Ia^</td>
<td>Invasion of stroma &lt; ( \sqrt[3]{7} ) mm in depth and &lt; ( \sqrt[3]{7} ) mm in width</td>
</tr>
<tr>
<td>Ia^_</td>
<td>Lesions confined to cervix or preclinical lesions greater than stage IA</td>
</tr>
<tr>
<td>Ia^__</td>
<td>Clinical lesions ( \leq ) cm or smaller</td>
</tr>
<tr>
<td>Stage II:</td>
<td>Carcinoma extending beyond the cervix but not to the pelvic wall; carcinoma involves the upper two third of the vagina</td>
</tr>
<tr>
<td></td>
<td>No obvious parametrial involvement</td>
</tr>
<tr>
<td>Stage III:</td>
<td>Carcinoma extending to pelvic wall; on rectal examination, there is no cancer-free space between tumor and pelvic wall, and tumor involves lower third of vagina (all cases with hydronephrosis or nonfunctioning kidney should be</td>
</tr>
<tr>
<td></td>
<td>Involvement of lower third of vagina</td>
</tr>
<tr>
<td>Stage IV:</td>
<td>Carcinoma extending beyond true pelvis or involving bladder or rectum</td>
</tr>
<tr>
<td></td>
<td>Spread to adjacent organs</td>
</tr>
</tbody>
</table>

The significance of tumor size is reflected by a decline in the 5-year survival rate from \( \frac{4}{5} \) to \( \frac{3}{5} \) in tumors larger than \( \sqrt[3]{3} \) cm in diameter. In \( \text{Kaur et al., 2003} \), FIGO addressed the issue of tumor size by subdividing stage IB into Ib\^\_ (\( \leq \) cm or smaller) and Ib\^\_\_ (larger than \( \leq \) cm) (Creasman, \( \text{1991} \)).

Since the FIGO classification remains a clinical staging system, nodal status has still not been included. Given the limitations of clinical staging, "extended" clinical staging is frequently used when the technology is available. This staging system incorporates the results of cross-sectional...
imaging into therapeutic planning for most tumors more advanced than stage Ia (Kaur et al., ۲۰۰۳).

**Tumor spread:**

Cervical cancer spreads by direct extension and through lymphatic vessels, rarely by the haematogenous route. Local extension into surrounding tissues (parametrium) results in ureteral compression (Stage IIIb); the corresponding clinical complications are hydroureter, hydronephrosis and renal failure, the last being the most common cause of death. Bladder and rectal involvement (stage IVa) may lead to fistula formation. Metastases to regional lymph nodes involve the paracervical, hypogastric, and external iliac nodes. Overall, the cancer’s growth and spread are relatively slow, since the average age of patients with stage ۰ tumor (CIN-III) is ۵۳-۰۴ years; for stage Ia, ۷۴ years; and for stage IV, ۷۵ years (Rubin et al., ۲۰۰۳).

**Detection of cervical carcinoma**

Imaging modalities used to evaluate the extent of cervical cancer include excretory urography, barium enema, lymphangiography, sonography, CT, MR imaging, and positron emission tomography (PET). An important issue in the staging of cervical cancer is distinguishing early disease (stages Ia and Ib) that can be treated with less invasive measures from more advanced disease. Recent years have seen a decline in the use of excretory urography, barium enema, and lymphangiography and an increase in cross-sectional imaging, particularly CT. MR imaging, in spite of its proven superiority over other techniques for staging and detection of recurrent disease, remains underused (Kaur et al., ۲۰۰۳).
Chapter (۲) Staging and Management of Uterine Cervical Carcinoma

Sentinel lymph node mapping in combination with surgical biopsy is an emerging feasible and useful technique in the early stages of cervical cancer, being based on lymphoscintigraphy and blue dye to avoid lymph node dissection in these early stages. It has a high negative predictive value, which can be incorporated into clinical routine (laparoscopy or open surgery) (Roca et al., ۵۰۰۰).

After primary treatment, patients are usually followed up with CT or MR imaging (Table ۲). Because additional radiation therapy or chemotherapy can improve the prognosis, early detection of recurrent cervical carcinoma is important (Jeong et al., ۲۰۰۳).

In the coming chapters, detailed information on the various imaging modalities, now used in the assessment of cervical cancer, will be discussed.

Table (۲): Imaging modality of choice in respect to treatment/outcome variants (Jeong et al., ۲۰۰۳)

<table>
<thead>
<tr>
<th>Treatment or outcome</th>
<th>Imaging modality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total abdominal hysterectomy</td>
<td>CT or MR imaging</td>
</tr>
<tr>
<td>Pelvic irradiation</td>
<td>MR imaging</td>
</tr>
<tr>
<td>Complication</td>
<td></td>
</tr>
<tr>
<td>Pelvic recurrence</td>
<td>CT</td>
</tr>
<tr>
<td>Lymph node recurrence</td>
<td></td>
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</tbody>
</table>

Management of cervical carcinoma:

Carcinoma of the uterine cervix remains the most common form of cancer to affect women worldwide despite effective screening
techniques. Advances in treatment, particularly systemic therapies, have improved outcomes for cervical cancer (Thigpen, 2003).

Treatment of cervical cancer is individualized to the patient’s disease stage, and the therapeutic scheme may also depend on the gynecologic and radiation oncology institution (Zaspel and Hamm, 2007).

Management of cervical carcinoma starts by detection and management of CIN aided by abnormal smear result. The ability to detect and treat premalignant lesions on the cervix reversed the natural history of cervical cancer. Methods of conservative treatment that evolved over decades have been proven safe and effective, allowing retention of fertility (Lindeque, 200).

**Surgical therapy:**

Cone biopsy and/or hysterectomy can pick-up the various categories of cervical lesions including invasive carcinoma. For this reason, in the absence of colposcopy as occurs in many parts of the developing world, cone biopsy may be adequate treatment and should be offered first to women with moderately to severely abnormal Pap smears (Onah and Iyoke, 200).

Fertility preservation in early cervical cancer by radical trachelectomy is gaining acceptance as time passes. Controversies regarding technique and patient management are beginning to emerge as the procedure moves from being a new surgery to a part of standard of care and the effectiveness of radical trachelectomy for treating selected early-stage cancers continues to gain support. The survival of selected patients appears to be no different than that of similar patients treated with radical hysterectomy (Burnett, 200).
Table (*): Treatment strategies for different stages of cancer cervix

(Zaspel and Hamm, \( ^{2007} \))

<table>
<thead>
<tr>
<th>Stage</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \bullet ) (CIN I)</td>
<td>-Cytological follow up</td>
</tr>
<tr>
<td>( \bullet ) (CIS)</td>
<td>-Conization</td>
</tr>
<tr>
<td>Stage Ia</td>
<td>-Conization</td>
</tr>
<tr>
<td></td>
<td>-Simple hysterectomy</td>
</tr>
<tr>
<td></td>
<td>-Radical trachelectomy (only in patients wishing to preserve their fertility)</td>
</tr>
<tr>
<td>Stage Ib, IIa</td>
<td>-Radical hysterectomy with lymph node dissection</td>
</tr>
<tr>
<td></td>
<td>-Radical trachelectomy with lymph node dissection (only in patients wishing to preserve their fertility)</td>
</tr>
<tr>
<td></td>
<td>-Primary, neoadjuvant radiochemotherapy</td>
</tr>
<tr>
<td></td>
<td>-Adjuvant radiochemotherapy</td>
</tr>
<tr>
<td>Stage IIb, III, IVa</td>
<td>-Primary, neoadjuvant radiochemotherapy</td>
</tr>
<tr>
<td></td>
<td>-Radical hysterectomy with lymph node dissection</td>
</tr>
<tr>
<td></td>
<td>-Adjuvant radiochemotherapy</td>
</tr>
<tr>
<td></td>
<td>-Exenteration</td>
</tr>
<tr>
<td>Stage IVb</td>
<td>-Primary radiochemotherapy</td>
</tr>
</tbody>
</table>

Follow-up, as recommended by the American College of Obstetricians and Gynecologists \( ^{2000} \):

\( ^{1} \). EAU, Thrice-yearly examinations for the first \( ^{2} \) years and twice-yearly visits subsequently to year \( ^{3} \)

\( ^{2} \). Papanicolaou (Pap) tests and chest x-rays on a yearly basis
Radiochemotherapy

In patients with relapsed cervical cancer, if salvage treatment treatment, radiotherapy is usually directed to nonirradiated areas for palliation of symptoms. In addition, most cervical cancer patients who relapse often recur at both local and distant sites. Therefore, systemic chemotherapy is an important option for these patients. Cisplatin is the most active single agent in recurrent or metastatic cervical cancer (Fiorica, ۲۰۰۲).

Lymph node metastasis was closely related to deep muscularis involvement of the cervix and parametrial involvement; the standard type radical hysterectomy and bilateral pelvic lymphadenectomy should be performed to the patients with high risk of lymph node metastasis to ensure enough amplitude of parametrectomy and excision of positive nodes. When lymph node metastasis is confirmed after surgery, postoperative radiation can improve the prognosis (Feng et al., ۲۰۰۲).

Radical radiotherapy is considered as the treatment of choice in locally advanced cancer cervix. In late stages radiotherapy produces optimum palliation and to some extent cure. Treatment is carried out using predominant intracavitary radiotherapy, followed by external pelvic radiotherapy. The late stages (stage-IIb, IIIa and IIIb, IVa) of disease are managed with initial external radiotherapy, followed by a single intracavitary brachytherapy (Biswal et al., ۲۰۰۸).

The elderly population is increasing in number. Aggressive therapeutic intervention in this patient group may not always be possible because of age, the presence of co-morbidity, and poor functional status. Individualized management of cervical cancer in the elderly is often
practiced using either aggressive irradiation or palliation (according to the extent of the disease (Ampil et al., 2007).

The diagnosis of cervical cancer in a pregnant woman presents a therapeutic dilemma. Cervical intraepithelial neoplasia lesions or microinvasive cancer (stage Ia) can be treated by conization and cerclage with continuation of the pregnancy. Following delivery, thorough repeated evaluation is performed. In patients with more advanced cervical cancer diagnosed in early pregnancy, hysterectomy with termination of the pregnancy is recommended. Patients in advanced pregnancy have the option of premature delivery by cesarean section with subsequent definitive cancer treatment (Zaspel and Hamm, 2007).
MR Imaging of Uterine Cervical Carcinoma

MRI is the standard imaging technique used for the initial evaluation of tumor size, local spread (spread to parametrium, vagina, bladder, and rectum) and lymph nodes status in patients with cervical carcinoma (Vincens et al., 2008).

MRI has been reported to be superior to CT in the delineation of tumors of the uterine cervix. With its distinctive tissue contrast and multiplanar imaging capability, MR imaging provides excellent differentiation of tumor tissue from the normal tissue in terms of excellent soft tissue contrast resolution, three-dimensional measurement and accurate judgment of invasion of the surrounding normal tissue (Kim et al., 2002).

In early stage cervical cancer, T2-weighted MR imaging has been suggested as the reference standard for preoperative assessment. Endovaginal techniques (in-plane resolution, approximately 2 × 0.5 mm) allow precise location of small invasive cervical carcinoma (Charles-Edwards et al., 2008).

Most cervical squamous cell carcinomas grow at the squamo-columnar junction. In younger women, the SCJ is located outside the external uterine os, and the tumor tends to grow outward (exophytic growth pattern) (Fig. 9) (Okamoto et al., 2001).
Fig.(9): Cervical carcinoma with exophytic growth in a 44-year-old woman. The pathologic stage was Ib-1. Sagittal $T_2$-weighted MR image shows a slightly hyperintense, cauliflower-like tumor in the posterior lip (arrows). The tumor markedly expands the posterior vaginal fornix (Okamoto et al., 2003).

In contrast, in elderly patients, the SCJ is located within the cervical canal. In these patients, cervical cancer tends to grow inward along the cervical canal (endophytic growth pattern) (Fig.10) (Okamoto et al., 2003).

Fig.(11): Stage IIa cervical carcinoma. Sagittal $T_2$ weighted MR images show a slightly hyperintense mass that protrudes into the vaginal canal (arrow). Parametrial invasion is not seen (Okamoto et al., 2003).
Cervical cancer is characterized by higher signal intensity on T2 weighted images and is thus delineated against the cervical stroma, which has lower signal intensity. Cervical cancer typically develops as a circumscribed focal lesion arising from the mucosal layer of the cervix. It may grow superficially in a circular pattern and increases in depth with invasion of the cervical stroma (Zaspel and Hamm, 2002).

MR urography has also replaced conventional IV urography, which used to be the standard procedure in patients with advanced or recurrent cervical cancer and clinically suspected urinary obstruction (Zaspel and Hamm, 2002).

**Technique:**

MR examination is usually performed in the supine position with a phased array multicoil using a four-coil configuration (Body or endo-vaginal coil) (Manfredi et al., 2002).

Augmented vascularization at the tumor periphery and the enhancement of the adjacent cervical stroma decrease the contrast between tumor and normal tissue. Consequently, the use of contrast does not improve staging. Most of the MR imaging protocols for cervical cancer suggests IV enhanced studies as optional (Akata et al., 2002).

Contrast-enhanced images can, however, improve the diagnostic accuracy of identifying tumorous infiltration of the urinary bladder or rectum. Moreover dynamic MRI can be used to differentiate recurrent disease from post therapeutic changes (Zaspel and Hamm, 2002).
Protocol for staging of cervical carcinoma according to Nicolet and colleagues (2000)

- Sagittal and axial non-fat-saturated high-resolution $T_2$-weighted echo-train spin-echo MR images ($5$-mm section thickness) ($125$ matrix) are obtained from the lower pole of the kidneys to the vulva. Coverage of the periaortic region is imperative, even if it is at the upper limit of the phased-array coil.

- A fat-saturated $T_2$-weighted sequence is not routinely used; however, it may be useful for evaluation of pelvic soft-tissue edema. It is also preferred for evaluation of the lymph nodes, which are more clearly distinguished from the hypointense muscles and blood vessels with this sequence.

- Axial fat-suppressed spoiled gradient-echo breath-hold $T_1$-weighted images are obtained once before and twice after dynamic intravenous injection of gadopentetate dimeglumine.

Normal MR Findings of the Uterine Cervix:

In contrast to the uterine corpus, the uterine cervix shows only little variation of its zonal anatomy as depicted by MRI with age, phase of the menstrual cycle, hormone replacement therapy, or use of oral contraceptives (Klüner and Hamm, 2002).

On $T_1$ weighted sequences the normal cervical stroma is of low signal intensity with a smaller intermediate signal intensity outer layer. The differing signal intensities are attributed to differing nuclear/Cytoplasmic ratios. The endocervical canal contains mucus glands and secretions, and is visualized as a high signal stripe of variable thickness (Fig. 11) (Hoad et al., 2002).
Chapter (†)  MR imaging of Uterine Cervical Carcinoma

Fig. (††): Sagittal T2-weighted image of the normal cervix. It shows the epithelium (high signal), fibrous stroma (low), and peripheral myometrium (intermediate) of the cervix (Klüner and Hamm, ††††).

The differentiation of the cervix versus the paracervical tissue of the parametrium is best on T2-weighted images compared to pre- or post contrast T1-weighted images or CT scans (Klüner and Hamm, ††††).

Role of MRI in cancer of the uterine cervix:

Pretreatment Staging of Tumor and Assessment of Nodal Invasion:

In evaluating the stage of cervical cancer, MRI was found to have an accuracy of up to 79%, whereas clinical staging according to the FIGO system shows errors of 4–17% depending on the stage of the disease (Ozsarlar et al., ††††††).

Sagittal T1-weighted and T2-weighted images and oblique axial T2-weighted images obtained perpendicular to the uterine axis are sufficient for staging in most cases (Shiraiwa et al., ††††††††).

The most important issue in staging is to distinguish early disease (stages I and IIa) that can be treated with surgery from advanced disease
(stage IIb or greater) that must be treated with radiation alone or combined with chemotherapy (Akata et al., ۲۰۰۳).

Understaging is actually more important because surgery would be an inadequate treatment if the uterus is removed in someone with advanced disease, and curative radiative doses cannot be achieved because the small bowel drops in where the uterus would have kept it further away from the radiation source. Whereas, radiotherapy for overstaged patients would not change the prognosis (Akata et al., ۲۰۰۳).

In general as previously mentioned, staging of cervical carcinoma with MR imaging is based on the classification system of FIGO (Table ۴) (Okamoto et al., ۲۰۰۳).
Table (4): Revised FIGO staging of cervical carcinoma with corresponding MRI findings (Okamoto et al., ۲۰۰۳)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Revised FIGO staging</th>
<th>Corresponding MRI findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>Carcinoma in situ</td>
<td>No tumor mass present</td>
</tr>
<tr>
<td>Stage I:</td>
<td>Tumor confined to cervix (extension to corpus should be disregarded)</td>
<td></td>
</tr>
<tr>
<td>Ia</td>
<td>Microinvasion</td>
<td>No tumor mass &amp;/or localized widening of the endocervical canal</td>
</tr>
<tr>
<td>Ib</td>
<td>Clinically invasive; invasive component &gt; ۵ mm in depth &amp; &gt;۲ mm in horizontal spread.</td>
<td>Partial/ complete disruption of low SI fibrous stroma. Rim of intact cervical tissue surrounding tumor</td>
</tr>
<tr>
<td>Stage II: Tumor extends beyond cervix but not to pelvic side wall or lower third of vagina</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIA</td>
<td>Vaginal invasion (no parametrial invasion)</td>
<td>Segmental disruption of hypointense vaginal wall</td>
</tr>
<tr>
<td>IIB</td>
<td>Parametrial invasion</td>
<td>Complete disruption of low SI fibrous stroma with tumor signal extending into parametrium.</td>
</tr>
<tr>
<td>Stage III: Tumor extends to lower third of vagina or pelvic side wall; ureter obstruction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIIA</td>
<td>Invasion of lower ۱/۳ of vagina (no pelvic side-wall extension)</td>
<td>Segmental disruption of hypointense vaginal wall (lower ۱/۳)</td>
</tr>
<tr>
<td>IIIB</td>
<td>Pelvic side wall extension or ureteral obstruction</td>
<td>Same findings as Ib with tumor signal most frequently extending to involve obturator internus, piriiforms, or levator ani muscles. Dilated ureter</td>
</tr>
<tr>
<td>Stage IV: Tumor extends outside true pelvis or invade bladder or rectal mucosa</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVa</td>
<td>Invasion of bladder or rectal mucosa</td>
<td>Tumor signal disrupts normal tissue planes with loss of low SI of bladder or rectal mucosa</td>
</tr>
<tr>
<td>IVb</td>
<td>Distant metastases</td>
<td>Tumor masses in distant organs.</td>
</tr>
</tbody>
</table>

The precursor lesions of cervical cancer, cervical intraepithelial neoplasia (CIN) and carcinoma in situ (stage ۰), and the earliest cancer stage, microinvasive cervical cancer (stage Ia), are not amenable to clinical evaluation, nor are they detected by MRI because
they do not alter the normal morphologic MR appearance of the cervix. Colposcopy and conization is the method of choice for evaluating these early forms of cervical carcinoma (Zaspel and Hamm, 2002).

Stage Ib cervical carcinoma is the earliest stage that can be demonstrated by MRI. The average MRI detection rate is 9.7%. Stage Ib\(^1\) (diameter $<$ 4 cm) and stage Ib\(^2\) (diameter $>$ 4 cm) are distinguished on the basis of their size. Transverse and sagittal T\(^2\) weighted images depict cervical carcinoma as a high-signal intensity lesion within the low-signal-intensity oval cervical stroma. Cervical cancer at this stage is fairly smoothly marginated and completely surrounded by low-signal-intensity cervical stroma (Fig.\(^1\)) (Zaspel and Hamm, 2002).

**Fig.(\(^1\))**: a, b Stage Ib cervical carcinoma. T\(^2\) weighted images in sagittal and transverse orientation. The small cervical cancer is seen as a high-signal-intensity lesion primarily growing within the cervix. The cancer is surrounded by low- signal-intensity cervical stroma on both sagittal and transverse images. Accessory finding: uterine prolapse and leiomyomas of the anterior wall of the uterus (Hamm et al., 1999).

Since Stage Ib does not disrupt the stroma and can thus be difficult to depict. Therefore, small tumors may be more readily
identified by their early homogenous enhancement after dynamic injection of contrast material (Engin, ۶۳۴).

In stage IIa cervical cancer, infiltration involves up to two-thirds of the proximal vagina while sparing the lower third. On T₂-weighted MR images, vaginal involvement is seen as hyperintense segmental disruption or lesion in the otherwise low-signal-intensity vaginal wall. Infiltration of the anterior and posterior fornix and of the wall is best seen in sagittal orientation (Fig.۱۳) (Zaspel and Hamm, ۴۹۳).

Fig.(۱۳): Stage IIa cervical carcinoma. a. Sagittal and b. Transverse T₂-weighted MR images show a slightly hyperintense mass that protrudes into the vaginal canal (arrow in a). Most of the vaginal wall surrounding the tumor seems intact (white arrows in b); although the low signal intensity of the vaginal wall is disrupted on the right side (black arrow in b). Parametrial invasion is not seen (Okamoto et al., ۴۹۳).

The evaluation of parametrial invasion (stage IIb) is of utmost importance, as it greatly influences the therapeutic strategy. The real strength of MR imaging for cervical carcinoma is the high negative predictive value of ۹۵٪ for parametrial invasion (Koyama et al., ۴۹۳).
Presence of an intact low signal intensity rim surrounding the cervical tumor in high-resolution transverse $T_2$ weighted MR images is a generally accepted indicator of negative parametrial invasion. On the other hand, full thickness stromal invasion on MRI with loss of the low signal intensity rim of the cervix together with nodular or irregular tumor signal intensity extending into the parametrium are associated with parametrial invasion (Fig. 4). The most reliable MRI criterion of parametrial infiltration is the direct visualization of a tumor mass extending into the parametria (Fig. 5) (Jena et al., 200).

Fig. (4.1): Stage IIb cervical carcinoma. (a) Axial $T_2$-weighted and (b) axial $T_1$-weighted contrast-enhanced MR images show a necrotic cervical mass (arrows) with right parametrial invasion (short arrows) (Engin G., 200).
Fig. (9): Stage IIb cervical carcinoma in 44-year-old woman. (a) axial and (b) coronal T2-weighted images show cervical cancer (T) involving both lips of cervix. Tumor invades cervical stroma bilaterally, as shown by loss of low-signal-intensity ring, and extends to both parametria (arrows in a&b). Enlarged lymph nodes (N in b) (Sala et al., 2002).

MR imaging findings that are suggestive of pelvic sidewall involvement (Stage IIIb) include tumor within 3 mm of or abutment to the pelvic floor muscles and the iliac vessels. Loss of normal parametrial signal intensity in T1-weighted images and increased signal intensity in pelvic musculature on T2-weighted images are other suggestive findings. Ureteral obstruction and hydronephrosis at the level of the tumor is also considered to be an indication of wall invasion (Fig. 9) (Engin, 2001).
Fig. (3.1): Stage IIIb cervical carcinoma. (a) Sagittal T2-weighted MR image shows a slightly hyperintense, large, solid mass that extends from the uterine cervix to the lower part of the uterine body. It also extends to the lower one-third of the anterior vaginal wall (arrow). (b) Axial T2-weighted MR image shows that the tumor also reaches the left posterior wall of the bladder, although the thinned vesical muscular layer remains (arrowheads). (c) MR urogram clearly shows left hydronephrosis caused by tumor invasion (Okamoto et al., 2003).

Once tumor invades the adjacent organs, such as the bladder and rectal mucosa, or distant metastasis occurs, the stage is defined as IV. One of the real advantages of MR imaging is excellent negative predictive value for stage IVa disease, thus safely obviating the need of invasive cystoscopic or endoscopic staging with reduction in staging costs. Bladder or rectal invasion is frequently underestimated in the FIGO staging system, since it only concerns mucosal invasion identifiable on endoscopy (Koyama et al., 2002).

MRI findings suggesting bladder invasion include focal or diffuse disruption of the normal low signal intensity posterior bladder wall, nodular or irregular bladder wall, mass protruding into the lumen of the bladder, providing accuracy of more than 78% (Fig. 3.1). Dynamic gadolinium-enhanced T1-weighted sequences are helpful for confirming invasion and identifying fistulous tracts. Rectal invasion is
rare and appears as segmental thickening and loss of the anterior rectal wall (Fig.18) (Sala et al., 2002).

**Fig. (17)**: Stage IVa cervical cancer. a. Axial T2-weighted image demonstrates an ill-defined cervical mass causing hydroureter bilaterally (arrows). b. Sagittal T2-weighted image demonstrates a bulky cervical mass protruding into the bladder lumen with disruption of the posterior bladder wall of low intensity (arrow) (Koyama et al., 2002).

**Fig. (18)**: Stage IVa (a) Axial T1-weighted \( \text{min} \) after administration of Gd-DTPA and (b) Axial T1-weighted images in cervical cancer with infiltration of the posterior parametria. Rectal infiltration is seen as hyperintense tumor extension disrupting the anterior rectal wall (Zaspel and Hamm, 2002).
Lymph node metastasis is the most important prognostic factor in early stage cervical cancer, although it is not incorporated in the FIGO staging system. CT and MR imaging perform with similar accuracies of \( \sim 90\% \) in the evaluation of nodal involvement. Accurate cervical cancer staging is crucial for appropriate treatment selection and treatment planning (Waggoner, 2003).

On MRI, lymph node with a transverse diameter greater than \( \sim 1 \) cm is usually considered as malignant. However, the specificity of this finding is very low. Enlarged lymph nodes may be hyperplastic, and lymph nodes smaller than \( \sim 1 \) cm may contain metastatic disease. However, central necrosis within a lymph node is a useful predictor of metastatic disease. Central necrosis has a positive predictive value of \( \sim 100\% \) in the diagnosis of metastasis (Engin, 2007) (Engin, 2007).

![Diagram of Lymphatic Pathways](image_url)

Fig.(19): a–b. Lymphatic pathways of spread of cervical carcinoma (Wittekind et al., 2005).

-14-
Fig. 21: Axial $T_2$-weighted MR image shows a left necrotic inguinal lymph node (arrow) at stage IIb cervical carcinoma (short arrows) (Engin, ۶۰۰۰).

Assessment of Tumor Recurrence

Manifestations of recurrent disease in cervical carcinoma can be characterized as typical and atypical. Typical manifestations involve the vaginal vault and lymph nodes. However, with the increasing use of pelvic irradiation in the treatment of this disease, less typical patterns of recurrence are becoming more frequent. These include peritoneal carcinomatosis and solid organ metastasis to the liver, adrenal gland, lung, or bone (Fulcher et al., ۹۹۹۹).

On MRI, vaginal vault recurrence after radical surgery for cervical cancer is indicated by loss of the low-signal-intensity linear configuration of the vaginal vault and visualization of an associated soft-tissue mass of high signal intensity on $T_2$-weighted images, similar to that of the primary tumor (Fig. ۲۱) (Sala et al., ۹۹۹۹).
Fig. (17): 38-year-old woman with adenocarcinoma of cervix (FIGO stage Ib) treated with radical hysterectomy. (a) Axial T2-weighted MR image shows right recurrent mass in pelvic sidewall abutting external iliac vessels (arrow) and sacral nerve roots. Normal exiting sacral nerve roots are clearly identified on left side (arrowhead). (b) Axial T2-weighted MR image shows hyperintense recurrent mass in vaginal cuff (arrowhead) (Kaur et al., 2003).

It is more difficult to interpret MRI studies after the treatment of cervical cancer than at the time of disease staging. Radiologists and surgeons should be aware of these difficulties, and pretreatment images should be available for a more accurate appraisal of posttreatment images. Adequate sequences also are required; including T2-weighted images and dynamic sequences after injection of Gd-DTPA (Vincens et al., 2008).

T2-weighted images have low specificity for the detection of benign conditions, such as inflammation and edema that cause increased T2-weighted signal. Dynamic contrast-enhanced MRI has been shown to be helpful in improving specificity and accuracy of tumor recurrence, with maximum tumor enhancement occurring between 45 and 90 seconds after contrast administration (Fig.22) (Kinkel et al., 1992).
Fig. (3): a–d. Recurrent cervical carcinoma after hysterectomy. a&b T₂ weighted images in sagittal and axial orientation. c, d T₁ weighted images in sagittal and axial orientation 1 min after administration of Gd-DTPA. MRI after hysterectomy depicts a nodular lesion at the roof of the vagina with enhancement on the post contrast images (arrows) (Zaspel and Hamm, 2002).

Recurrent cervical cancer is also associated with bone metastases. Typical locations are the bony pelvis as well as the lumbar and other vertebral bodies. MRI with unenhanced and contrast-enhanced fat-saturated T₁-weighted sequences depicts bone metastases as hyperintense lesions in the low-intensity bone marrow with a high sensitivity (Zaspel and Hamm, 2002).

*Planning and Evaluation of Tumor Response to Radiotherapy:*

Amongst the various prognostic factors, tumor size has emerged as the most important factor to which other morphological risk factors like tumor invasion depth, loco-regional extent and lymph node involvement are related. In patients treated by radical surgery or
radiotherapy alone, size of the primary tumor is of prognostic significance irrespective of the clinical stage of the tumor (Sethi et al., 2007).

Although the actual radiotherapy (RT) procedure is usually planned by means of a CT scan, MRI has an increasing role in treatment planning and controlling radiation, as it is superior in 3D visualization of tumor volume and infiltration of surrounding tissues. Thus MRI based planning provides proper information on gross target volume (GTV) and organ volumes and dose-volume histograms which caused a change in concept in brachytherapy planning from the standard 2D to 3D (Zaspel and Hamm, 2002).

The volume of disease as assessed on MRI was thought to be a better prognostic indicator than FIGO staging (Sethi et al., 2007).

In advanced disease or when bad prognostic factors are present, the complex oncological treatment is based on the combination of external irradiation and brachytherapy with concomitant chemotherapy. Nevertheless, optimal protocol for the determination of the proper therapeutic plan remains to be defined. A unified technique to solve the problems connected to precise definition of the gross target volume (GTV) and the clinical target volume (CTV) with their geometrical change during the external irradiation as well as their dose covering during brachytherapy is nowadays becoming widely available. Reproducibility of the treatment plan along with a stable multiple exact repositioning of the patient and the treatment device is essential for the clinical outcome of the treatment (Pötter et al., 2007).
Regarding therapy the role of MRI may be classified in three main groups; 1) guided applicator positioning; 2) assisted treatment planning and; 3) treatment quality control (Fig. 23) (Hadjiev et al., 2007).

**Fig. (23):** (A) The intracervical applicator introduced through the central channel of the holder used for vaginal interposition. (B) The applicator device with MR compatible needles in the circumferential channels (Hadjiev et al., 2007).

One advantage of MR imaging to a radiation oncologist in treatment planning is the ability to view the tumor in sagittal, coronal, and axial planes. Determination of the degree of ante- or retroversion of the uterus assists with proper selection of the intrauterine tandem for brachytherapy. It may reveal vaginal extension, which can guide proper applicator selection, including the use of interstitial needles instead of ovoids (Fig. 24) (Viswanathan et al., 2008).
(Fig.†) (A) T₂ weighted MR images in axial plane from different levels, with the patient and the applicator device in treatment position. The applicator geometry is accurately visualized as well as the surrounding tissue. (B) T₂ weighted images in sagittal plane, with the patient and the applicator device in treatment position. CTV and the organs at risk are delineated on all planes (Hadjiev et al., †·†)

More and above, MRI is the first-line modality for follow up after radiation therapy. It may be performed † and †·† months after completion of irradiation and whenever tumor recurrence is suggested by the clinical or gynecologic findings (Zaspel and Hamm, †·†).

During and shortly after RT, the entire irradiated field shows a reactive signal increase on T₂-weighted images and more pronounced contrast enhancement on T₁-weighted images. This is why differentiation of tumor tissue from reactively inflamed tissue is impaired during and shortly after irradiation (Zaspel and Hamm, †·†).

Tumors treated with RT respond with a decrease in their size and signal intensity on T₁ weighted MR images. The response may be immediate (†·† months) or, in larger tumors, delayed (†·† months).
The findings of reconstitution of the normal zonal anatomy of the cervix and the presence of homogeneous low-signal-intensity stroma with shrinkage of the uterus and cervix are reliable indicators of a tumor-free postirradiation cervix and effective radiation therapy (Flueckiger et al., 1992).

Fig. (a–c): a–c. Monitoring of response to RT. a–c T2w images in sagittal orientation. a. Cervical cancer (asterisk) with infiltration of the vagina. b. Tumorous mass of the cervix has disappeared 7 months after RT. Endocervical sheath in place (arrow). c. Normal appearance of the cervix and atrophy of the uterus 7 months after completion of irradiation (arrow). Small amounts of free fluid (Zaspel and Hamm, 2002).
A complication after irradiation is the development of fistulas due to therapy-induced regression of invasive cervical cancer, which appears as a high signal intensity fluid filled structure in T₂-weighted images (Fig. 6). Contrast-enhanced T₁-weighted images identify a fistula as abnormal enhancement surrounding the low-signal-intensity fistular canal (Zaspel and Hamm, 2002).

Fig. (6): Fistula formation after radiochemotherapy. a, b T₂w images in sagittal and transverse orientation. Following radiochemotherapy of advanced cervical cancer, a fistula depicted as a high-signal-intensity fluid-filled connection is seen between the vagina and urinary bladder (arrows). There is urine in the vagina. (Zaspel and Hamm, 2002)

New advances in MRI techniques will further increase its potential as a diagnostic and follow up tool for disorders of the female pelvis, these include:

- Ultrasmall Particles of Iron-Oxide (USPO) for Lymph Nodes Detection
- MRI Diffusion Weighted Images
- Intra Vaginal Contrast Opacification

Ultra-small particles of iron-oxide (USPO):

The accuracy of MRI assessment of lymph nodes is similar to that of CT; both rely on size criteria to detect the presence of metastases.
which limits the diagnostic performance of these conventional procedures, with sensitivities for lymph node metastases ranging from \( \frac{1}{2} \) to \( \frac{1}{4} \). However, more recently, lymph node–specific contrast agents have emerged as useful tools for determining the presence of metastases in the lymph nodes independent of size (Rockall et al., 200). This contrast agent is classified as a nanoparticle, and is composed of an iron oxide core, coated with low molecular weight dextran. These MR contrast agents are collectively known as ultra-small particles of iron oxide (USPIO), and are administered intravenously (Russell and Anzai, 2002).

**USPIO Criteria as stated by Rockall and his associates in 200:**

Nodes were evaluated on the pre- and post-USPIO images.

**Criteria for benignity:** (Fig. 22)

1. Homogeneous or slightly heterogeneous complete darkening
2. Central darkening with a smooth rim of non darkening
3. Darkening of nodal tissue with central area of non-darkening, which corresponds to fatty hilum on T1 images.
Fig. (A, B): Sagittal T2*-weighted image demonstrates (A) an 11-mm short-axis node along the pelvic side wall (arrow). The node was considered malignant on standard size criteria; (B) 4 hours after administration of USPIO, the node demonstrates central darkening apart from the nodal hilum (arrow), and was diagnosed as benign. (*) external iliac vein (Rockall et al., 5200).

**Criteria for malignant infiltration:**

1. Faint darkening, but with a decrease in signal intensity of less than 50% (Fig. A, B)

2. Focal area of high signal that did not correspond to fatty hilum on T1

3. Complete uniform retention of high signal intensity
MR imaging of Uterine Cervical Carcinoma

(Fig. 28): Axial T₂*-weighted image demonstrates (A) multiple enlarged para-aortic lymph nodes (arrows), considered malignant on size criteria; (B) 4 hours after administration of USPIO, there is less than 75% decrease in signal intensity. These nodes were considered to be malignant on USPIO criteria (Rockall et al, 2001).

A significant increase in the sensitivity, with no loss of specificity, for the noninvasive detection of malignant lymph nodes in patients with cervical and endometrial cancer, for which the sensitivity increased from 75% using the standard size criteria to 93% using USPIO criteria (Pannu et al., 2000).

Therefore, USPIO-MRI has the potential to improve the surgical and nonsurgical management of patients with cervical and endometrial carcinoma in several ways:

- The preoperative localization of malignant nodes may allow tailoring of the surgical lymphadenectomy, allowing rapid
collection of any node suggestive of metastasis for frozen section, and by directing the surgeon to a node suggestive of metastasis at a site not usually accessed. This tailored approach may reduce both surgical time and morbidity without a reduction in diagnostic yield.

• When USPIO-MRI is negative, surgical lymph node sampling could be avoided altogether, with a high degree of confidence. This could be of particular value when surgical risks such as obesity and diabetes are present.

• USPIO-MRI could accurately map the extent of lymph node involvement in both the pelvis and para-aortic regions to define the radiotherapy fields. This is particularly relevant with the development of intensity modulated radiotherapy (IMRT), in which the shape of the field may be closely tailored to the individual patient (Rockall et al., 200).

**Diffusion Weighted MR Images:**

An alternative to $T_2$-weighted MR imaging is to develop image contrast by using apparent diffusivity. The motion of extracellular water measured by this technique relates to distance traveled by protons which is hindered by structural interfaces in tissues. Thus, in highly cellular tissues where extracellular water is unable to diffuse far before being blocked by cell membranes, the shortened diffusion path has been linked to a reduced apparent diffusion coefficient (ADC) (Charles-Edwards et al., 2008).

The diffusion weighted image (DWI) is an ultrafast sequence without oral or IV contrast material that can be added to routine MRI protocol. Malignant tumors are depicted as foci of increased intensity on DWI’s (McVeigh et al., 2008).
The parameters responsible for the restriction of water movement within tumor tissue remain controversial. Several factors have been shown to affect DWI’s and hence ADC values; as mentioned by Charles-Edwards et al., 2008

- Cell density
- Nuclear-to-cytoplasm ratio,
- Tissue components such as edema, necrosis, and fibrosis
- Tumor tissue.

Apparent diffusion co-efficient (ADC) values from cervical cancer tissue are significantly lower than those from non tumor-bearing epithelium. Thus, DW MR images used in conjunction with T£-weighted imaging improves the detection of small-volume early-stage invasive cervical cancer, particularly in patients that have undergone cone biopsy where granulation tissue makes interpretation of the T£-weighted images difficult as both are intermediate and/or high signal intensity in relation to the adjacent stroma, while granulation tissue will show higher ADC values. This is important in determining further treatment decisions (Ho et al., 2009).

Moreover, the high-spatial-resolution images obtained with an endovaginal coil together with DW MR imaging may allow more accurate identification of small tumors and improve treatment planning, particularly when considering fertility sparing procedures in patients with stage Ia and Ib1 invasive cervical carcinoma (Fig. 29) (Charles-Edwards et al, 2008).
Fig. (a): $T_2$-weighted (a) transverse (b) coronal MR images (c) corresponding coronal ADC map of 32-year-old woman with stage Ib tumor show cervix by using endovaginal coil (arrowhead). Area of diffuse abnormal intermediate signal intensity (arrows) is seen on $T_2$-weighted images, which corresponds to area of restricted diffusion in c (arrow), lending greater confidence to diagnosis of invasive cervical carcinoma. (Charles-Edwards et al., 2008).

Recently, it has been reported that ADC measurement has a potential ability to differentiate between normal and cancerous tissue in the uterine cervix between 1 and 3 months after termination of therapy (Naganawa et al., 2008).

Apparent diffusion coefficient (ADC) values after chemotherapy and/or radiation therapy were larger in patients than those before therapy. Thus, the expected clinical significance of ADC measurement in cervical cancer would also be in monitoring the response to radiation and/or chemotherapy (Fig. 30) (Naganawa et al., 2008).
Fig.(31): A 54-year-old woman with squamous cell carcinoma of the uterine cervix (a, b): before therapy; (c, d): after therapy. a. A transverse T2-weighted image. A tumor with increased signal intensity can be seen (white arrow). b. A transverse ADC map. The tumor is depicted as an area with decreased ADC values (white arrow). c. A transverse T2-weighted image. A tumor cannot be detected. d. A transverse ADC map. A tumor with decreased ADC value is not seen on this image (Naganawa et al., 2005).

**Intravaginal Contrast Medium**

Although MRI has been shown to be reliable, especially in determining the size and the parametrial invasion of cervical cancer, prediction of vaginal invasion is still challenging even with high-tesla scanners. It is often difficult to interpret bulky lesions that spread eccentrically in the lower portion of the cervix and vagina. As the lumen of the vagina and fornices is collapsed, it is usually complicated to differentiate invasion from obliteration (Akata et al., 2005).
Use of vaginal contrast medium is an easy, well-tolerated, and effective method to better delineate the borders of the tumor. It increases the specificity and accuracy of MR staging by showing the exact relation of the tumor with the vaginal wall and beyond (Fig. 31).

(Akata et al., 200). 

Fig. (31): Sagittal T2-weighted image in a 35-year-old woman with stage Ib cervical carcinoma. a. A large tumor at the cervix extending to the internal os is seen. Vaginal fornices appear to be invaded by mass. b. After vaginal opacification the borders of the tumor are better appreciated, and no vaginal extension is depicted. c. Although the tumor is very large, this transverse T2-weighted image delineates the well-preserved cervical stromal ring (Akata et al., 200).

Vaginal opacification could be of advantage as an alternative and overall cheaper staging system to FIGO staging given the easy accessibility throughout the world where T-MRI systems are still widely used. Thus, it has potential utility in increasing the accuracy of MR imaging in local staging and treatment planning of cervical cancer (Akata et al., 200).
Challenges in staging cervical carcinoma with MR imaging:
Pitfalls in pre-treatment staging of cervical carcinoma with MRI include: technical, patient, and tumor-related characteristics.

Table (ª): Pearls and pitfalls of MRI for Staging of cervical Carcinoma (Sala et al, 2002)

<table>
<thead>
<tr>
<th>Pearls</th>
<th>Pitfalls</th>
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<tbody>
<tr>
<td>Accurate estimation of tumor size by MRI (within 0.5 cm of measurement at pathology).</td>
<td>Parametria are located lateral and only lateral to the cervix</td>
</tr>
<tr>
<td>Intact low-signal-intensity stromal ring excludes parametrial invasion</td>
<td>Loss of low-signal-intensity stromal ring indicates full stromal but not parametrial invasion.</td>
</tr>
<tr>
<td>Recurrent vaginal vault tumor has the same signal intensity as the primary tumor.</td>
<td>Overestimation of parametrial invasion on T2-weighted images due to post biopsy haemorrhage or with large tumors due to stromal oedema</td>
</tr>
<tr>
<td>Reconstitution of normal cervical anatomy and low-signal-intensity cervical stroma indicate complete response to radio- or chemotherapy.</td>
<td>Early radiation change (within 6 months) and presence of infection may show enhancement</td>
</tr>
<tr>
<td>Dynamic contrast-enhanced MRI improves detection of small tumors and helps in differentiating tumor recurrence from radiation fibrosis</td>
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</tbody>
</table>
In year ۶۲۰۰۰, Kinkel suggested some points to be considered to avoid the pitfalls in staging by MRI:

Slice orientation perpendicular to the long axis of the cervical channel might improve false-negative findings for deep stromal invasion on T۲-weighted images in cervical cancer.

Contrast-enhanced sequences do not justify the diagnosis of parametrial or vaginal invasion in cervical cancer.

Assessment of lymph node invasion by any imaging modality has limited sensitivity in detecting lymph node metastasis smaller than ۶ mm.

Knowledge of diagnostic criteria is critical to avoid false-negative findings for bladder wall invasion.

Higher spatial resolution with dedicated multichannel pelvic phase array coils, smaller fields of view and section thickness, and careful comparison of T۲-weighted and contrast-enhanced sequences are strategies that might avoid misinterpretation of pelvic MRI in staging uterine neoplasm (Kinkel, ۶۲۰۰۰).

MRI, although not officially incorporated in the FIGO staging system, is already widely accepted as the most reliable imaging technique for the diagnosis, staging, treatment planning, and follow-up of both endometrial and cervical cancer. MRI protocols need to be optimized to obtain the best results and avoid pitfalls (Sala et al., ۶۲۰۰۰).
Gynacological malignancy Diffusion weighted MRI protocol

Advances in MRI such as increased field strength, development of imaging techniques such as parallel imaging (Deshmane A et al, 1101), and the use of novel methods of rapid data acquisition (Reischauer C et al, 1101) have markedly improved image quality in body MRI applications. However, these advances also bring new challenges because the endpoint of MRI is no longer to simply detect an abnormality but rather to play a pivotal role in diagnosis, treatment selection, treatment planning, and follow-up of both benign and malignant gynecologic conditions (Balleyguier C et al, 1100; Bharwani Net al, 1100). Sequences such as diffusion-weighted imaging (DWI) help to increase diagnostic accuracy, as in tumor staging (Sala E, Rockall A et al, 1100; Whittaker CS et al, 1100; Beddy P et al, 1101) DWI has recently been used in the diagnosis of malignant lesions, can distinguish the normal uterine cervix from cervical cancer and benign lymph nodes from malignant ones (Tuna D, et al, 1101). Nevertheless, the newer imaging techniques can be limited at times by technical and image interpretation pitfalls, which can be challenging to a novice radiologist.

Gynacological malignancy Diffusion weighted MRI protocol

Patient Preparation, Positioning, and Coil Selection

Before MRI, patients are typically instructed to fast for 4–6 hours to diminish artifacts due to small-bowel peristalsis. In addition, an antiperistaltic agent, such as butylscopolamine bromide or glucagon, is administered IV or intramuscularly at the beginning of the examination. Imaging is performed with the patient in the supine position with an empty urinary bladder. A pelvic or cardiac array multichannel surface...
coil is used. A distended urinary bladder is not recommended because it increases phase ghost artifacts and can compress the uterus. Saturation bands placed along the anterior and posterior body wall fat are useful for diminishing ghosting from respiratory motion artifact.

**Timing of MRI After Cervical Biopsy**

Many women with cervical cancer undergo MRI after biopsy. Although postbiopsy changes can interfere with image interpretation, these changes are typically limited to the cervix at the biopsy site and do not cause substantial staging errors.

**Diffusion-Weighted Imaging**

DWI is a functional imaging tool that yields information about water mobility and tissue cellularity. It also allows calculation of the apparent diffusion coefficient (ADC) from images with different b values ([Whittaker CS et al,\(^\text{4}\text{-11}\)])\(^{11}\). The ADC value, which describes water diffusibility, is decreased in the presence of factors that decrease water diffusion, such as fluid viscosity and the cell membrane (Fig. \(^\text{32}\)). The ADC value can be helpful for differentiating malignant from benign lesions ([Bharwani N et al,\(^\text{11}\); Fujii S et al,\(^\text{11}\); Naganawa S et al,\(^\text{11}\); Thomassin-Naggara I et al,\(^\text{11}\)])\(^{11}\).
Fig. (32): Chart summarizes MRI characteristics of pelvic soft tissues. ADC = apparent diffusion coefficient, Δ = subtraction reformat, ′ = chronic bleeding may cause shading on T₂-weighted images owing to different ages of blood products. (Stephanie N et al., 3110)

**Sequence**

DWI is most commonly implemented clinically as an echo-planar imaging sequence. The rapid and robust acquisition (with respect to motion sensitivity) is an important reason the echo-planar imaging sequence became the technique of choice for DWI. However, in the presence of B₀ inhomogeneity and susceptibility variations, echo-planar imaging suffers from gross image distortion due to the relatively long gradient-echo train inherent in the sequence. A second disadvantage is the relatively low spatial resolution. Parallel imaging has been used to reduce the echo-train length and thus geometric distortions on echo-planar images. Parallel imaging is based on the use of coils with multiple small detectors that operate simultaneously for acquisition of MRI data. Each detector contains spatial information that can be used as a substitute for...
time-consuming phase-encoding steps, thereby allowing reduction of both acquisition time and echo-train length.

**Imaging plane**

In the pelvis, DW images are most commonly acquired in the axial plane. Field strength is closer to homogeneous near the center of the magnet. However, acquisitions along the axis of the uterus or the cervix can improve staging accuracy (Beddy P et al, ۱۱۰۱). We typically acquire DW images in two planes, a sagittal and a short-axis view. Moreover, angling for DWI similar to that for the T۲-weighted anatomic sequences allows fused imaging and thus optimizes the anatomic correlation.

**B value and calculation of apparent diffusion coefficient**

The b value is the strength of the diffusion-sensitizing gradient. The ADC represents the gradient of the line produced between two b values on a logarithm line (linearizing the exponential decay function). ADC calculation can be performed if at least two b values are used. At a b value of · s/mm² (no diffusion sensitizing gradient), free water molecules have high signal intensity. Use of a low b value of less than ··· s/mm² results in signal loss in highly mobile water molecules, such as those in vessels or in purely cystic lesions. Using a low b value will reflect both perfusion and diffusion effects.

In highly cellular tissues, water movement is restricted. Water molecules in such tissue retain signal intensity even at high b values (···۰–···۱ s/mm²). Using high b values reflects true diffusion in the tissue. A good set of b values for separating these components includes b values of ·, ···, ···, and ··· s/mm². The ADC values calculated from values of · and ··· s/mm² would favor per-fusion contributions. The
ADC calculated from values of \(0.5\) and \(800\) s/mm\(^2\) approximates the true diffusion of the tissue \((Thoeny HC et al., 2011)\). In pelvic imaging in clinical practice, two high b values \((40 - 104\) and \(800 - 8000\) s/mm\(^2\)) are favored to save time and eliminate the perfusion effect \((Padhani AR et al., 2012)\).

**Diffusion and apparent diffusion coefficient appearance**

ADC maps are usually displayed as gray-scale images. Areas of restricted diffusion have lower ADC values and appear as a darker shade of gray on ADC maps compared with areas of freely moving water, such as simple cysts and urine in the bladder, which appear as a lighter shade of gray. By contrast, on high-b-value DW images, areas of restricted diffusion appear bright (Fig. 33).

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**Fig. (33)** : Chart shows pitfalls of diffusion-weighted MRI. ADC = apparent diffusion coefficient. \((Stephanie N et al., 2011)\)

**Parameters for optimal pelvic diffusion-weighted MRI**

The two major limitations of DWI are the low signal-to-noise ratio and susceptibility artifacts, which are associated with echo-planar
imaging. Strategies for optimizing signal-to-noise ratio are as follows: using high field strength ($^3$T vs $^1$T) (however, high field strength increases susceptibility and image distortion); minimizing TE to less than 0.1 ms, usually 0.5–9 ms; increasing the number of signals acquired to a range of 5–7; increasing the section thickness to 4–5 mm; and increasing the FOV to 42–21 cm. Strategies for minimizing susceptibility artifacts are as follows: minimizing TE, usually to 0.5–20 ms; minimizing echo-train length (achieved with parallel imaging technique); and using a wide bandwidth (0.08–2000 MHz). Other pitfalls are related to the air-tissue interface between the legs, air in the rectum, and bowel motion. Retrograde filling of the rectum with ultrasound gel, for example, decreases susceptibility-based loss of signal intensity and distortion caused by the air in the rectum (Stephanie N et al, 311).

Diagnostic Tips for Diffusion-Weighted MRI Interpretation: Pitfalls

To avoid pitfalls in image interpretation, DWI and the derived ADC maps must be evaluated in conjunction with morphologic images. DW images are derived from $T^\gamma$-weighted images. Tissues with a long relaxation time, such as simple cysts, can have high signal intensity on DW images, the so-called $T^\gamma$ shine-through effect (Koh DM et al, 00). This effect can result in erroneous image interpretation if high-b-value images are viewed in isolation without cross-reference to the corresponding ADC maps (Low RN et al, 00) (Fig. 33). Malignant tumors are generally depicted as foci of increased intensity on DW images (Fig. 33) because water diffusion is restricted in highly cellular tissues in malignant tumors (Whittaker CS et al, 00, Punwani S et al, 00). However, some well-differentiated tumors may exhibit little restriction of diffusion owing to their low cellularity. In contradiction, blood, fat, abscesses, lymph nodes, and
melanin (Fig. 32) may exhibit restricted diffusion. In these cases, reference to standard T1- and T2-weighted images may lead to the correct diagnosis.

Careful attention must be paid while obtaining ADC measurements. ADC measurements obtained from breath-hold DW images cannot be directly translated into those obtained with free-breathing respiratory-triggered techniques. ADC values may vary not only with different imaging parameters but also with different types of MRI systems. The reproducibility of ADC values has been evaluated in a research setting and found to be good (Padhani AR et al, 1112, Chenevert TL et al, 1100). A variation of less than $\pm 3.5$ in ADC values was found with the use of different MRI systems and different sequences on phantoms. These results become important for the quantitative assessment of tumor response over time, particularly in research.

The placement and size of the ROI are important for accurate ADC calculation, particularly if the lesion is heterogeneous (e.g., containing necrosis). No standardized method of ROI placement currently exists. For lesion characterization, ROIs should always be placed on the solid parts of the lesions. Areas of cystic change and necrosis should be avoided as much as possible to avoid falsely increased ADC values and thereby misclassifying the lesion as benign. Therefore, correlation with standard T1- and T2-weighted images is necessary to avoid inclusion of cystic and necrotic areas. For tumor response assessment, for example, in cervical cancer, ROIs before and after treatment must be carefully placed on the same area (Harry VN et al, 1114). Cystic change and necrosis as part of tumor response after therapy must be documented and taken into consideration.
Figure 33 shows an imaging algorithm for lesion characterization according to DWI signal intensity and findings on an ADC map.
Application of MRI DWI on cervical cancer

Staging

European Society of Urogenital Radiology and American College of Radiology guidelines (Balleyguier C et al, ۵۰۰۰; Siegel CL et al, ۵۰۰۰) call for MRI for staging clinical stage IB tumors and beyond and smaller tumors if trachelectomy is planned. On T۱-weighted images, cervical carcinomas are usually isointense to normal cervix and may not be visible. On T۲-weighted images, cervical cancer appears as a mass of intermediate signal intensity disrupting the low-signal-intensity cervical stroma. The sagittal plane allows evaluation of tumor extension into the lower uterine segment, vagina, and the anterior and posterior fat planes. The oblique axial T۲-weighted image perpendicular to the long axis of the cervix is important for assessing parametrial invasion (Shiraiwa M et al, ۵۰۰۰). Preservation of the low-signal-intensity fibrous cervical stroma, no matter how thin, virtually excludes parametrial invasion.

On dynamic contrast-enhanced MR images, small tumors are homogeneously enhancing, and enhancement occurs earlier than in the normal cervical stroma, facilitating tumor detection. Large tumors are frequently necrotic but are often surrounded by an enhancing rim that facilitates tumor delineation (Van Vierzen PB et al, ۵۰۰۰). Although the addition of contrast-enhanced sequences may improve reader confidence in tumor detection, use of contrast-enhancement has not been found to improve overall staging accuracy compared with T۲-weighted imaging alone (McVeigh PZ et al, ۵۰۰۰). Several studies have shown that the mean ADC value of cervical carcinoma is significantly lower than that of normal cervical tissue (Chen J et al, ۵۰۰۰; Chen YB et al, ۵۰۰۰; Liu Yet al, ۵۰۰۰). In cervical cancer staging, DWI findings may be clinically
relevant in the following two scenarios: isointense tumors, such as diffusely infiltrative adenocarcinomas in young women, and early cervical cancer for exact delineation of tumor margins if fertility-preserving surgery is planned (Harry VN et al,^7^). Charles-Eduard et al (Charles-Eduards EM et al,^7^) found added value of DWI and endovaginal coils in the detection of early-stage disease. Those authors evaluated 8^7^ patients with confirmed cervical intraepithelial neoplasia and 8^8^ with stage Ib^1^ cervical tumors and found that tumoral ADC values were lower than the values in nontumoral areas.

**Response evaluation**

DWI findings have been considered as a biomarker of cervical tumor treatment response (Harry VN et al,^7^). An increase in ADC was described after 8^7^ weeks of therapy before size changes occurred and was indicative of response. This technique has the potential for allowing early monitoring of the response to chemoradiotherapy.

**Tumor recurrence**

There is no consensus regarding routine imaging follow-up after radical hysterectomy. Imaging is undertaken only if indicated by clinical symptoms. Changes after radiotherapy and surgery can result in areas of fibrosis or cystic change that can be difficult to differentiate from recurrence (Addley HC et al,^7^). During the early posttreatment period (after the first cycle of chemotherapy), the specificity of PET/CT may be reduced because of the frequently indistinguishable morphologic features and intense radiotracer uptake in both inflammatory tissue and the tumor. DWI can be helpful for this indication (Fig. 4^7^). High ADC values are more likely to represent areas of edema or inflammation, and low ADC values are suggestive of the presence of active tumor cells.
Chapter (*)  

Application of MRI DWI on cervical cancer

Fig. (**A**): 57-year-old woman with cervical cancer recurrence in two separate masses. A, Axial T2-weighted MR image shows vaginal mass (arrow) and more lateral mass (arrowhead) with same signal intensity.

Fig. (**B**): 57-year-old woman with cervical cancer recurrence in two separate masses. B, Apparent diffusion coefficient map shows vaginal mass (arrow) has decreased signal intensity consistent with restricted diffusion suggestive of recurrence. More lateral mass (arrowhead) has increased signal intensity consistent with Bartholin cyst with complex contents.
Pitfalls

Retained mucus in the cervix may exhibit the T2 shine-through effect. Moreover, after cone biopsy, the area biopsied exhibits restricted diffusion due to blood products. Finally, both the desmoplastic reaction due to radiotherapeutic changes and residual tumor have low ADC values. The desmoplastic reaction, however, does not have high signal intensity on b-value images.

Cystic Lesions of the Cervix: Differentiation of Benign From Malignant Cystic Lesions

Adenoma malignum is a rare form of mucinous adenocarcinoma of the cervix with a specific clinical presentation. Presenting symptoms include a watery vaginal discharge and association with Peutz-Jeghers syndrome or mucinous tumor of the ovary. At MRI, adenoma malignum appears as a hyperintense cervical lesion on T2-weighted images and is characterized by multiple grapelike cystic clusters extending from the endocervical glands to the deep cervical stroma (Yamashita Y et al, 2022). An enhancing component is typically present. On DW images, the solid component is easily detected as an area of high signal intensity on the high-b-value image with corresponding restriction on the ADC map (Fig. 5). The imaging findings guide deep cervical biopsy because adenoma malignum cannot be diagnosed during a routine Pap test (Doi T et al, 2022). The main benign differential diagnosis of adenoma malignum is tunnel clusters, which are a specific subtype of nabothian cyst characterized by complex multicystic dilatation of the endocervical glands (Jones MA et al, 2022) (Fig. 6). The typical MRI finding is multiple cystic lesions in the fibrous cervical stroma that have regular borders. The cysts have intermediate or slightly high signal intensity on T1-weighted images and have prominent high signal intensity on T2-weighted images.
weighted images. The cysts may have high signal intensity on DW images owing to the mucinous content (T₂ shine-through). However, the lack of restriction on the ADC map enables differentiation of tunnel clusters from adenoma malignum.

Fig. (۵-۳-A): ۵۰-year-old woman with adenoma malignum. A, Axial oblique T₂-weighted MR image shows heterogeneous cervical mass with cystic (arrow) and solid (arrowhead) components invading deep stroma.

Fig. (۵-۳-B): ۵۰-year-old woman with adenoma malignum. B, Apparent diffusion coefficient map shows restriction of solid component (arrowhead) but no restriction of cystic component (arrow). Presence of mixed cystic and solid components with stromal invasion is highly suggestive of adenoma malignum, which was confirmed at histopathologic examination.
Fig. (\textcopyright-A): 57-year-old woman with tunnel clusters. A, Oblique axial T2-weighted MR images show multiple grapelike cysts (arrow) without solid component.

Fig. (\textcopyright-B): 57-year-old woman with tunnel clusters. B, Apparent diffusion coefficient map shows no restriction (arrow). At final pathologic examination, only tunnel clusters were found.
Diagnostic clues—A multicystic lesion that invades the deep cervical stroma and contains solid components may suggest a malignancy (Yamashita Y et al., 2022). In contrast, benign lesions do not usually deeply invade the cervical stroma, are small, have well-defined margins, and do not contain solid components. On DW images tunnel clusters do not have restricted diffusion, whereas adenoma malignum shows areas of restriction with decreased ADC.

Pitfalls

Tunnel clusters may have high signal intensity on high-b-values owing to mucinous content. Evaluation of the ADC map may help in the diagnosis.

Application of MRI DWI on Endometrial Versus Endocervical Adenocarcinoma

Differentiating cervical from endometrial carcinoma is important because patient care differs for the two diseases. An accurate diagnosis of cervical versus endometrial carcinoma may not be possible with routine histopatho-logic analysis. MRI may help this differentiation by depicting the bulk of the lesion in the cervix or endometrium. However, DWI itself cannot be used to differentiate the two tumors on the basis of ADC quantification (Stephanie N et al., 2011).

The peritoneal cavity is a common location of metastatic spread of gynecologic malignancies, especially in patients with ovarian cancer.

Detection

The use of quantitative and qualitative DWI has been evaluated in the detection of perito-neal carcinomatosis (Fujii S et al, 2007). The remarkable difference in contrast between peritoneal lesions and surrounding organs on DW images enables detection of peritoneal...
dissemination. Mesenteric implants, bowel serosal implants, metastatic lesions involving the peritoneal reflections around the liver, pancreas, and pelvis (surface of the uterus and bladder) are usually better seen on DW images (*Low RN et al*, 1112). *Fujii et al.* (*Fujii S et al.*, 1112) reported sensitivity and specificity of 0.9 and 0.97 for implant detection. It is important to recognize, however, that cardiac motion and susceptibility artifact from air can markedly degrade image quality at air-tissue interfaces and therefore obscure small peritoneal implants, especially on the bowel surface (*Low RN et al.*, 1112). Moreover, DWI provides little anatomic information. Therefore, it is mandatory to interpret DW images in conjunction with conventional MR images (*Bozkurt M et al.*, 1112).

The combined interpretation of DW images with conventional MR images increases the rate of detection of peritoneal deposits, particularly in the more challenging locations (*Low RN et al.*, 1112).

Mucinous implants may exhibit a T2 shine-through effect and high ADC value. The diffuse high signal intensity of the normal intestinal wall on high-b-value DW images may be misinterpreted as malignant infiltration or may mask micronodular serosal disease.

**Conclusions**

Functional imaging with DWI is becoming increasingly important in the evaluation of gynecologic cancer. DWI is of interest for tumor detection, characterization, and response to treatment. Its robust implementation necessitates optimized acquisition and experience in image interpretation. Correlation of DWI and conventional anatomic MRI sequences is critical to maximizing its value. Interpretation of DW images in isolation can lead to false-positive findings.
Pitfalls of MRI DWI

T₂ Shine-through

It is important to remember that diffusion-weighted images are intrinsically T₂ weighted and that tissues with slow T₂ relaxation rates can appear bright. T₂ shine-through refers to persistent hyperintensity seen on high b-value images with a corresponding high ADC value. The high ADC value will, therefore, also appear bright on ADC maps (Table 7). This phenomenon can cause problems in image interpretation when high b-value images are viewed in isolation without reference to corresponding ADC maps. This fact should be borne in mind when using the fusion software to superimpose high b-value images onto anatomic images (Fig 37).

Fig. (37-a): Cervical carcinoma. Axial T₂-weighted MR image (a), high b-value (b = 1000 sec/mm²) image (b), and ADC map (c) show a cervical carcinoma (arrow). Note the high signal intensity in the normal left ovary (arrowhead), a finding that represents T₂ shine-through and may cause confusion if ADC maps are not studied.
Fig. (\textsuperscript{\textcopyright} -b): Cervical carcinoma. Axial T\textsuperscript{2}-weighted MR image (a), high \(b\)-value \((b = \cdot \cdot \cdot \text{sec/mm}^2)\) image (b), and ADC map (c) show a cervical carcinoma (arrow). Note the high signal intensity in the normal left ovary (arrowhead), a finding that represents T\textsuperscript{2} shine-through and may cause confusion if ADC maps are not studied.

Fig. (\textsuperscript{\textcopyright} -c): Cervical carcinoma. Axial T\textsuperscript{2}-weighted MR image (a), high \(b\)-value \((b = \cdot \cdot \cdot \text{sec/mm}^2)\) image (b), and ADC map (c) show a cervical carcinoma (arrow). Note the high signal intensity in the normal left ovary (arrowhead), a finding that represents T\textsuperscript{2} shine-through and may cause confusion if ADC maps are not studied.
Restriction in Normal Structures

Because diffusion-weighted MR imaging demonstrates areas of restriction to water diffusion, any areas of high cellular density will have high signal intensity on high b-value images. Normal endometrium in women of reproductive age is composed of endometrial glands and of stromal cells with high cellular density and abundant cytoplasm. In a study comparing endometrial cancers with normal endometrium, Tamai et al (Tamai K et al, 2012) found normal endometrium to have high signal intensity on high b-value ($b = 8000$ sec/mm$^2$) images. However, quantitative discrimination between normal endometrium and cancer was possible due to the significantly lower ADC value of tumor; thus, the hyperintensity of endometrium on high b-value images is due to T$_2$ shine-through. Figure 31 shows a cervical cancer with a separate focal area of hyperintensity in the endometrium, which proved to be normal at subsequent hysterectomy.

Fig. (a) Cervical carcinoma in a 54-year-old woman. (a) Sagittal T$_2$-weighted MR image shows a large tumor on the anterior lip of the cervix. (b) False color map derived from a high b-value image ($b = 100$ sec/mm$^2$) shows high signal intensity in the tumor (arrow) and in the endometrium at the uterine fundus (arrowhead). (c) Fused image (b superimposed on a) helps confirm the location of the cervical tumor and the area of restriction in the fundal endometrium. No abnormality was seen in the uterine fundus at hysterectomy; thus, the endometrial findings are taken to represent restriction within the normal endometrium.
Fig. (۳۸-b) Cervical carcinoma in a ۳۲-year-old woman. (a) Sagittal T۲-weighted MR image shows a large tumor on the anterior lip of the cervix. (b) False color map derived from a high b-value image \( b = ۷۱ \text{ sec/mm}^۲ \) shows high signal intensity in the tumor (arrow) and in the endometrium at the uterine fundus (arrowhead). (c) Fused image (b superimposed on a) helps confirm the location of the cervical tumor and the area of restriction in the fundal endometrium. No abnormality was seen in the uterine fundus at hysterectomy; thus, the endometrial findings are taken to represent restriction within the normal endometrium.

Fig. (۳۸-c) Cervical carcinoma in a ۳۲-year-old woman. (a) Sagittal T۲-weighted MR image shows a large tumor on the anterior lip of the cervix. (b) False color map derived from a high b-value image \( b = ۷۱ \text{ sec/mm}^۲ \) shows high signal intensity in the tumor (arrow) and in the endometrium at the uterine fundus (arrowhead). (c) Fused image (b superimposed on a) helps confirm the location of the cervical tumor and the area of restriction in the fundal endometrium. No abnormality was seen in the uterine fundus at hysterectomy; thus, the endometrial findings are taken to represent restriction within the normal endometrium.
Tumors with Low Cellular Density

Although diffusion-weighted MR imaging has been shown to be helpful in distinguishing normal tissue or benign lesions from malignant tumors (Naganawa S et al, Inada Y et al, Tamai K et al, Fujii S et al), the success of the technique depends on the demonstration of restriction to water diffusion due to increased cellular density. In malignant tumors with low cellularity (eg, well-differentiated adenocarcinomas)

Other Causes of Hyperintensity on High b-Value Images with Corresponding Low ADC Values

The combination of hyperintensity on source high b-value images and corresponding low ADC values is typically thought to be due to high cellular density in tumor tissue (with exceptions in normal tissue as described earlier). However, similar appearances can be seen in abscesses, areas of coagulative necrosis, and inspissated mucus (Noguchi K et al, Park SH et al). In coagulative necrosis, this finding is thought to be due to the retention of cellular outlines and architecture. In abscess and inspissated mucus, water restriction may be due to the presence of a large number of macromolecules. We have noted these appearances in patients with hydrosalpinx, in some ovarian cysts, and, occasionally, within an obstructed endometrial cavity (Fig).
Fig. (۳۹-a) : Retained inspissated mucus within the endometrial cavity due to an obstructing cervical carcinoma. (a) Sagittal T۲-weighted MR image shows a cervical tumor (arrowhead) with distention of the endometrial cavity by high-signal-intensity mucus (arrow). (b) ADC map shows the mucus (arrow) with a low ADC value, a finding that is likely due to the restriction of water molecules caused by the presence of macromolecules. In such cases, anatomic images are helpful in excluding the presence of tumor within the endometrial cavity.

Fig. (۳۹-b): Retained inspissated mucus within the endometrial cavity due to an obstructing cervical carcinoma. (a) Sagittal T۲-weighted MR image shows a cervical tumor (arrowhead) with distention of the endometrial cavity by high-signal-intensity mucus (arrow). (b) ADC map shows the mucus (arrow) with a low ADC value, a finding that is likely due to the restriction of water molecules caused by the presence of macromolecules. In such cases, anatomic images are helpful in excluding the presence of tumor within the endometrial cavity.
Case No.(1):

- A 24 years old female with history of post coital pain and bleeding
- Married 3 times before and has two children from the first marriage
- History of 3 abortions in the past two years
- Clinical examination & EAU: Indurated cervix
- Patient received radiation therapy

MRI:

Posterior lip of the cervix (arrowheads) shows high signal intensity on sagittal and axial T2-weighted imaging (T2WI) (A, B) and axial diffusion-weighted imaging (DWI) (C). The apparent diffusion coefficient (ADC) map (not shown) demonstrated low ADC values (\( \text{T2WI, } ^{\text{ADC}} \times 10^{-3} \text{ mm}^2/\text{sec} \)). The lesion (arrowheads) was reduced and difficult to identify after radiation therapy on sagittal and axial T2WI (D, E) and signal intensity was decreased on axial DWI (F).

Fig.(1) MRI sagittal and axial views

Staging cervical carcinoma:

Stage IIa
Case No.(†): A 44 years old female with current complaint of irregular vaginal bleeding (metrorrhagia) and post coital dragging pain.

Married since 52 years and grandmultipara (88 childbirths)

Clinical examination revealed cervical mass with no vaginal involvement

MRI

Measuring length of normal endocervical canal above tumour on sagittal T2-W images (left) with sagittal ADC maps (right) for reference. Tumour is seen an intermediate signal-intensity mass in A and an area of restricted diffusion on the ADC map (arrows).

Fig. (†): MRI sagittal T2-W images (left) with sagittal ADC maps (right)

Staging cervical carcinoma

Stage IIa
**Case No.(*)**

- A **44** years old female with history of menorrhagia and profuse vaginal discharge.

- Married since **20** years and has three children.

- Clinical examination & EUA: An indurated cervix with no vaginal or parametrial invasion.

- The patient has undergone radical hysterectomy.

**MRI:**

Coronal $T^2-W$ (left), and corresponding $b-\cdot-\cdot-\cdot-\cdot$ s/mm$^2$ (middle) and ADC map (right) slices showing a small tumor on the left cervical lip (arrows).

![MRI](image)

**Fig.(¥£):** MRI Coronal $T^2-W$ (left), and corresponding $b-\cdot-\cdot-\cdot-\cdot$ s/mm$^2$ (middle) and ADC map (right)

**Staging cervical carcinoma**

Stage Ib$^1$
Case No. (4):

- A 45 years old female with history of profuse vaginal discharge.
- Married since 42 years and has four children.
- Clinical examination & EUA: An indurated cervix with no vaginal or parametrial invasion.
- The patient has undergone radical hysterectomy

**MRI:**

- Coronal T₂-W (top left), b-100 s/mm² diffusion-weighted (top middle) and ADC map (top right) images through the mid cervix. Tumour is outlined in T₂-W with reference to diffusion-weighted images (arrow).

**Fig. (34):** Coronal T₂-W (top left), b-100 s/mm² diffusion-weighted (top middle) and ADC map (top right) images through the mid cervix. The trachelectomy specimen (bottom left) is photographed with an overlying millimetre grid (bottom right)

**Staging Cervical carcinoma:**

Stage Ib
Case No. (๒):

A ๒ ๔ years old female with current complaint of irregular vaginal bleeding (metrorrhagia) and post coital dragging pain.

Married since ๒ ๗ years and multipara

Clinical examination revealed cervical mass with no vaginal involvement

MRI:

Transverse T۲-W (top left), b- ๗ s/mm۲ (top right) and ADC map (bottom left) showing a small tumour in the posterior endocervix (arrows) that correlates with that shown on the trachelectomy specimen (bottom right)

Fig. (๔): Transverse T۲-W (top left), b- ๗ s/mm۲ (top right) and ADC map (bottom left) the trachelectomy specimen (bottom right)

Staging Cervical carcinoma :

Stage Ib۱
Conclusion

High-quality diffusion-weighted MR imaging of the entire pelvis can now be performed as part of a gynecologic examination without greatly increasing total imaging time. Diffusion-weighted MR imaging provides important new information noninvasively. This unique modality is helpful in initial staging of known malignancies, differentiating benign from malignant lesions, assessing treatment response, and determining the presence of disease recurrence. To ensure accuracy, it is important to be aware of the potential pitfalls of diffusion-weighted MR imaging and to review findings in conjunction with findings obtained with anatomic sequences. Increasing familiarity with ADC calculation and manipulation software, including the ability to fuse anatomic and diffusion data, will allow radiologists to gain confidence and thus to provide new information to physicians who are caring for women with known or suspected gynecologic malignancies.

Table (*) : Summary of MRI DWI findings

<table>
<thead>
<tr>
<th>Signal Intensity on T2-weighted Images</th>
<th>Signal Intensity on High b-Value Source Images</th>
<th>Values on ADC Maps</th>
<th>Interpretation of Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isointensity, hyperintensity</td>
<td>Hyperintensity</td>
<td>Decreased</td>
<td>Generally high-cellularity tumor; rarely, coagulative necrosis, highly viscous fluid, or abscess</td>
</tr>
<tr>
<td>Hyperintensity</td>
<td>Hyperintensity</td>
<td>Increased</td>
<td>T2 shine-through; often, proteinaceous fluid</td>
</tr>
<tr>
<td>Hypointensity, iso-intensity</td>
<td>Hypointensity</td>
<td>Decreased</td>
<td>Fibrous tissue with low water content with or without viable tumor cells</td>
</tr>
<tr>
<td>Hyperintensity</td>
<td>Hypointensity</td>
<td>Increased</td>
<td>Fluid, liquefactive necrosis, lower cellularity, gland formation</td>
</tr>
</tbody>
</table>
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الملخص العربي

اخلصاعلمر

سرطان عنق الرحم ثالث والأورام في شبيعة لنسانية لعالمه ثانى وأر

الأورام في شبيعة الدول النامية.

وتشتت وفاة سرفاً المغلفة في تقاطع النحو وغدر قاع بشر نور .

وباستخدام لكن أشعقة لحن المغلفة في تقاطع النحو وغدر قاع بشر نور .

ا عموماً لتشخيص

ا لمريضة إجينا لى ح بالرنين لتصوير المغلفة في تقاطع النحو وغدر قاع بشر نور .

إلى الشتات أو غدر مغر وذو تكتير الأرجح يحل علاج الأدوار أو غدر وذو الالتحاوة و ليس

باستطالة شلالاتر انجر ردح في ظلاله ياعتلي يتحدنا إذا تتناك الجلطة ضروري

واستنصاهلحرم أعلاج الكيماوي والإشعاعي.

ويضيف دور أشنين للمغلفة في تقاطع النحو وغدر قاع بشر نور قيداً ولفدد

لليمفاو مايا مصلا زويغون تقفز تلاع برتين وERM سرطات إتياور والغطاسية

كما لنا تتبع نهاية تنفيذ أنواع الأورام السرطات النامية المختلفة.