



Added Value of Perfusion in Gynaecological Imaging

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Abstract

Owing to the high prevalence of gynecological malignancies worldwide, it is of utmost importance to detect these malignancies early, thus reducing their morbidity and mortality rates. Imaging plays a significant role not only in detection but also, owing to the new functional techniques including perfusion MRI, in staging and directing treatment planes. In this article we review the different perfusion techniques used in endometrial, cervical and ovarian malignancies and the importance and potential benefits for their use. The importance of early and proper diagnosis of gynecologic malignancies lies in the fact that they contribute to a large number of female mortality and morbidity worldwide.

Abbreviations: MRI: Magnetic Resonance Imaging; DCE-MRI: Dynamic Contrast Enhanced MRI; MVD: Microvessel Density; VEGF: Vascular Endothelial Growth Factor; IAUGC: Initial Area Under the Gadolinium Concentration-Time Curve; TAH-BSO: Total Abdominal Hysterectomy and Bilateral Salpingo-Oophorectomy; ESUR: European Society of Urogenital Radiology; FIGO: International Federation of Gynecology and Obstetrics; SI: Signal-Intensity Curve

Introduction

In 2006, 41,200 new uterine body cancer cases were diagnosed, 20,180 ovarian cancer cases, and 9,710 cervical cancer cases [1,2]. Diagnostic imaging plays an important role in diagnosing and staging gynecologic neoplasms and thus helps in treatment decision-making. Recent advances in MRI such as increased field strength, development of parallel imaging [3,4], and the use of novel methods of rapid data acquisition have markedly improved image quality in body MRI applications [4]. MRI plays a pivotal role, owing to its good soft tissue resolution that allows accurate topographic assessment of the tumor (size, location, extension and nodal involvement) [5].

Unfortunately, conventional T1 and T2 sequences cannot provide adequate information about the tumor's microenvironment. Also, owing to the similar morphological appearance, conventional imaging has a limited value in assessing tumor's response to therapy and differentiating between residual /recurrent disease and post-treatment fibrosis [5,6]. Recently, the advancement of contrast enhanced Magnetic Resonance Imaging (MRI) has led to offering an in vivo functional examination, where information on the structure and function of the tumor microvasculature can be provided [7]. Many studies now support the use of functional MRI in assessment of tumor response to therapy with promising results, particularly in cervical cancer [5]. DCE-MRI has the ability to noninvasively assess tumor perfusion and capillary permeability

and thus assessing the anti angiogenic response of tumor tissue after therapy, which allows evaluation of treatment response earlier than using the conventional methods of assessing tumor size [8].

The early predictability of tumor response after therapy provides a golden opportunity to quickly change failed treatment regimens, limiting the related side effects and high costs and instituting these regimens with more successful ones [5,9]. Dynamic contrast enhanced MRI (DCE-MRI) is performed by acquisition of multiple sequential images before, during and after the passage of contrast material through a specific area of interest [8]. As the contrast material passes through a certain area, its paramagnetic effect increases the signal intensity; the degree of enhancement depends on various factors. In the early phase of enhancement (vascular phase), blood flow, vascular density, capillary permeability, and capillary surface area play a major role, while later in the interstitial phase, by extra vascular space volume [10].

This gives an idea about tumor microvasculature through variations in tissue enhancement over time. It has been shown that the more intense the enhancement of a tissue is, the more it is rich in vascularity. The rate of enhancement of a tissue (as demonstrated by the rate of wash-in and wash-out) is directly proportional to the expression of angiogenic factors such as micro vessel density (MVD) and vascular endothelial growth factor

(VEGF) [8]. So, variation in contrast enhancement is the result of variation in tumor histopathological features. Aggressive tumors mostly show rapid and intense enhancement and washout, due to high vascularity and strong expression of VEGF [8]. The use of post therapy DCE-MRI in cervical and endometrial cancer may be able to predict which patients are at risk of early recurrence and therefore super select patients suitable for more aggressive surgery [5]. In general, DCE perfusion MRI is very safe. Besides the general MRI risks and contraindications, IV infusion of a gadolinium- based contrast agent is done at a fairly rapid injection rate, so it is contraindicated in patients with renal failure [11].

Ovarian cancer

Five-year survival rates of patients diagnosed with ovarian cancer decreased from 90% in stage I to 30-40% in stage III and IV [12,13]. This dramatic decrease makes it of utmost importance to diagnose malignant ovarian masses as early as possible. DCE MRI is a non-invasive method that allows detection of ovarian malignancy early. Several studies were made proving its ability to differentiate between benign, borderline and high-grade ovarian tumors as well as its ability to differentiate between ovarian masses and pedunculated subserous uterine fibroid [7,14-16]. and to prove its ability to predict early response to therapy [10]. DCE MRI in cases of ovarian cancer is done using a T1-weighted

gradient-echo sequence that is acquired so that the solid ovarian tumor tissue (i.e., solid portion, papillary projections, or thickened irregular septa) and the uterus are seen in a single image. After gadolinium injection, images are obtained at five-second intervals for two minutes, beginning immediately after the bolus injection. Followed by post contrast axial and sagittal T1- weighted gradient-echo images with breathhold [14,16].

Ovarian tumor detection and characterization:

According to the enhancement pattern of the solid component within an adnexal mass, DCE MRI is able to differentiate between benign, borderline and malignant ovarian neoplasms. The more malignant lesions exhibit earlier and greater maximum enhancement. This variation of enhancement is attributed to the fact that malignant lesions have immature microvasculature with defective pericyte layer and over expression of VEGF receptors (VEGFR-2) [7,15,16]. DCE MRI can be performed by either qualitative or quantitative analyses.

In qualitative analysis, three curves are seen in the early phase of enhancement (<2min), all are in comparison to the enhancement dynamics of the myometrium: [7,15,16].

- a) **Type 1 curve:** gradual enhancement never exceeding the enhancement of the myometrium, this is the benign curve (Figure 1).

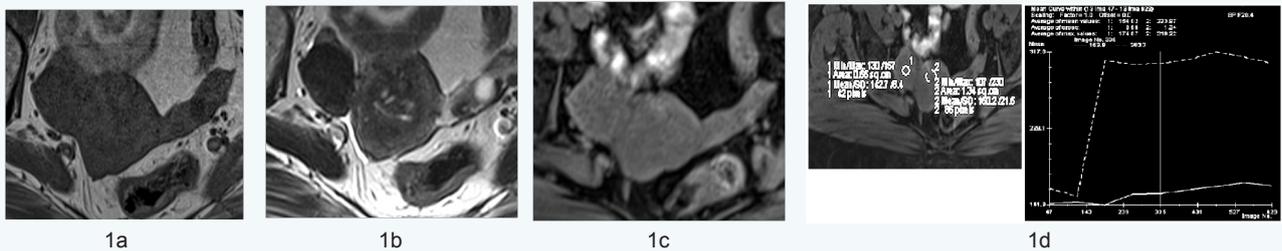


Figure 1: Ovarian Fibroma in a 61 years old patient
Figure 1a: T1W
Figure 1b: T2W MR images showing a well defined right sided solid hypointense adnexal mass
Figure 1c: Post-contrast T1W shows mild homogenous enhancement
Figure 1d: Dynamic contrast enhancement (DCE) curve shows a type 1 curve. The dotted line representing the enhancement of the myometrium and the continuous line is the enhancement of the solid mass

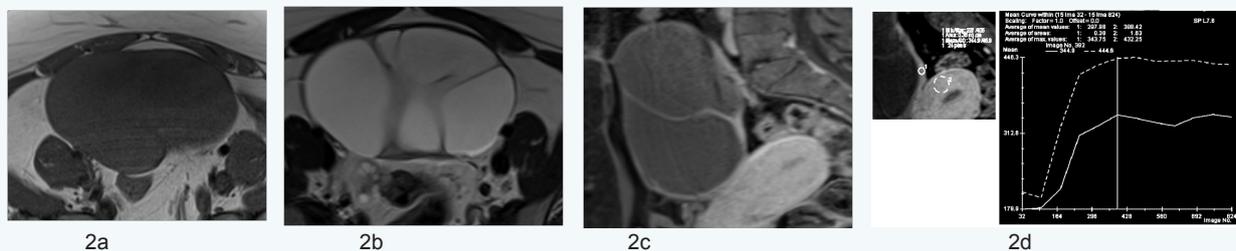


Figure 2: 37 years old patient with borderline mucinous cystadenocarcinoma
Figure 2a: Axial T1W
Figure 2b: Axial T2W MR images showing multi-cystic ovarian mass with homogeneous hypointense T1 signal and homogeneous hypointense T2 signal with multiple thick septations (> 3 mm).
Figure 2c: sagittal postcontrast T1W images showing enhancement of these septations.
Figure 2d: DCE curve showing type 2 curve.

b) **Type 2 curves:** early enhancement exceeding that of the myometrium followed by a plateau (Figure 2).

c) **Type 3 curves:** early and late enhancement exceeding that of the myometrium, this is specific to invasive malignancies (Figure 3).

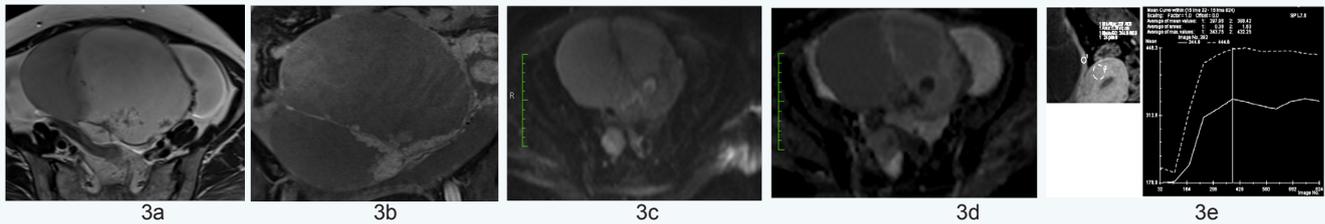


Figure 3: 33 years old women with invasive malignant cystadenocarcinoma

Figure 3a: Axial T2W showing stained glass appearance, suggestive of mucin containing lesion.

Figure 3b: Axial postcontrast T1W images, shows enhancing papillary projections.

Figure 3c and d: ADC and diffusion weighted images showing restricted diffusion in the solid projections.

Figure 3e: DCE curve is a type 3 curve (malignant curve). The continuous line represents the enhancement of the myometrium and the dotted line represents the enhancement of the solid components.

The importance of DCE MRI in ovarian cancer cases lies in its ability to differentiate between borderline and invasive malignancies. Since both are morphologically similar, so conventional MRI won't be of help. Patients with borderline ovarian tumors are young and usually want to preserve their fertility. And so, correct preoperative diagnosis and complete staging may give them the chance to do conservative surgeries [14,17,18]. Moreover, preoperative MRI suggesting borderline pathology was shown to help pathologists when intraoperative histology is required [14,19].

Differentiating ovarian tumors from pedunculated subserous fibroids: Solid pelvic masses are sometimes

very confusing, and when large, it is often impossible to determine their exact tissue of origin. Of special interest is the differentiation between ovarian fibromas and subserous uterine fibroids. Both are morphologically similar, however, it is important not to misdiagnose or confuse them owing to their different management options.

Both usually present as a T2-weighted solid homogenous or heterogeneous hypo intense mass with regular outlines [7]. DCE MRI easily differentiates between both, where ovarian fibromas show a type 1 curve (Benign curve) and subserous pedunculated fibroids show a type 2 curve (paralleling the myometrium) [7,16] (Figure 4).

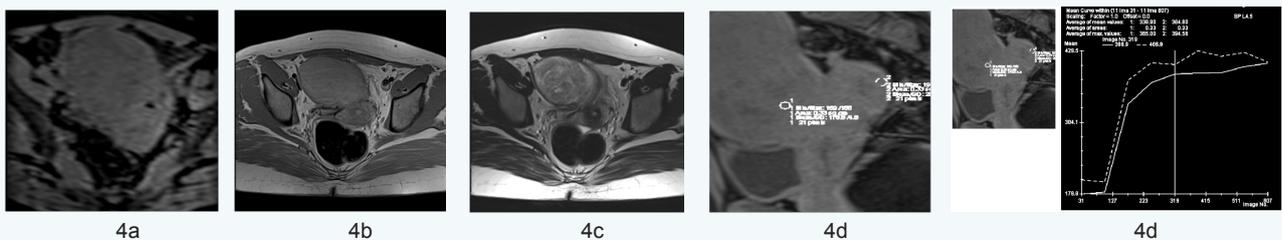


Figure 4: 20 years old women with a pelvic mass.

Figure 4a: Axial post-contrast T1W image showing a heterogeneously enhancing lesion.

Figure 4b and 4c: Axial T1 and T2W images showing isointense lesion with T2 hyperintensities.

Figure 4e: DCE curve shows a type 2 curve. This is a case of sub serous uterine fibroid. Ovarian fibroma would have similar MRI features but would show a type 1 curve.

The dotted curve represents the enhancement of the myometrium and the continuous line represents the enhancement of the solid mass.

Predicting response to treatment: Using quantitative DCE analysis, (within the region of interest), the following parameters can be calculated; the volume transfer constant (K trans), the rate constant (kep), the fractional volume of the extra vascular extracellular space (ve), the fractional plasma volume (vp) and the initial area under the gadolinium concentration-time curve

(IAUGC) [5,20]. Sala et al. [21,22] investigated the response of neo adjuvant chemotherapy in 22 patients with advanced primary ovarian cancer using both DWI and DCE-MR. In the primary ovarian lesion, responders showed a significantly larger increase in the ADC and in V (e) parameter of DCE as a result of the cytotoxic effect of platinum-based chemotherapy, but no

significant changes were found in omental or peritoneal deposits. The authors suggest the use of ADC and V (e) parameters as response markers to platinum-based therapy [22].

Predicting recurrent disease: In patients with asymptomatic residual disease after chemotherapy, Mitchell et al. [17] found that relapsed patients who eventually developed clinically progressive disease showed higher percent change of the enhancing fraction of the tumor 4-8 weeks post-baseline. Authors suggested that DCE MRI was able to predict relapse early. They also suggested that there is a positive relationship between the circulating tumor angiogenesis biomarkers (soluble vascular endothelial growth factor receptor-1 and -2) and the K trans, as well as a negative relationship between them and Vp [10,22]. This has the advantage of predicting chemo-resistance and therefore providing individualized patient treatment, reducing unnecessary costs and side effects [10].

Endometrial Cancer

Endometrial cancer is staged using the International Federation of Gynecology and Obstetrics (FIGO) system [23]. Since the condition is predominantly treated surgically, staging according to the revised FIGO classification is mainly surgical [24]. Surgery is used to initially treat patients as well as to identify patients who need further therapy according to various factors, the most important of which is the depth of myometrial invasion, because it directly correlates with tumor grade, cervical involvement and the presence of lymph node metastasis [25-27]. The incidence of loco-regional lymph node metastases increases from 3% with superficial myometrial invasion (stage IA) to 46% with deep myometrial invasion (stage IB) [24,25].

Evaluation of the depth of myometrial invasion remains inaccurate in many cases by gross inspection at surgery or at frozen-section analysis [25,28,29]. The standard treatment of low-risk patients is total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH-BSO), with lymph node sampling of suspicious lymph nodes only. On the contrary, in high-risk patients, TAH-BSO as well as radical lymph node dissection should be made. This requires a specialized center with gynecologic-oncology surgeon [24]. Over-treating low risk patients results in increasing their morbidity. Furthermore, the recent introduction of laparoscopic techniques offers an alternative approach for these patients [25,30,31].

Accordingly preoperative MRI may play an important role owing to its ability to accurately detect the depth of myometrial invasion as well as the local and distant spread of endometrial tumors [24]. DCE MRI in cases of endometrial carcinoma is done using a 3DT1-weighted gradient-echo sequence. Images are taken before contrast medium injection and then at sagittal oblique planes at 1 min, and 2 min after injection and at axial oblique plane 3 min after injection [24].

Endometrial Tumor Detection and Staging:

A. Tumor detection: Endometrial cancers can be seen as a slowly enhancing area as compared to the enhancement of the surrounding myometrium [7]. So in the early phase of enhancement, a hypointense area is seen as compared to the myometrium, whereas later, an increase in the signal intensity is noted, which could be seen as a hypointense area (in 70% of patients), isointense area (in 20%) or a hyperintense area (in 10% of cases) [6,7]. Unfortunately, there are no specific imaging findings to differentiate endometrial cancer from endometrial hyperplasia or endometrial polyps, so MRI plays a limited role in tumor characterization.

Some studies suggest that Diffusion weighted imaging and ADC value would be of help, where ADC value of carcinoma ($0.88-0.98 \times 10^{-3} \text{ mm}^2/\text{s}$) is significantly lower than of endometrial polyps ($1.27-1.58 \times 10^{-3} \text{ mm}^2/\text{s}$) and of normal endometrium ($1.53 \times 10^{-3} \text{ mm}^2/\text{s}$) [32]. To date, the standard of care is as follows; following presentation, the initial examination of choice is TVUS. Abnormally thick endometrium ($\leq 5 \text{ mm}$) warrants endometrial sampling [33]. After histopathological confirmation of endometrial carcinoma, MRI is recommended for proper staging.

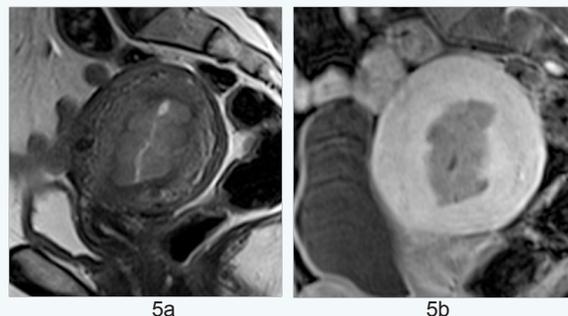


Figure 5: Known endometrial cancer presenting for staging.

Figure 5a: sagittal T2W image showing endometrial thickening with suspicious involvement of the junctional zone.

Figure 5b: Dynamic T1W image clearly shows that the tumor involves less than 50% of the myometrium. This is stage 1A cancer.

B. Tumor staging: DCE MRI plays a vital role in staging of endometrial cancer. Based on the FIGO system, it is important to determine the depth of the myometrial invasion and differentiate correctly between stages 1A (<50% myometrial invasion) and stage 1B (>50%). More than 50% myometrial invasion is associated with higher relapse rate, especially when combined with high tumor grade and histological subtype (28,49). The incidence of presence of metastatic lymph nodes increases from 2.4% in low risk patients to 9% in intermediate risk patients and to 24% in high risks ones [24]. In order to adequately assess

the myometrial extension on conventional T2W images, the junctional zone has to be seen clearly. However, sometimes this is not the case. As hormones affect the junctional zone, it is not

clearly visualized in post-menopausal women; in these cases assessment with combined DCE MRI and DWI is important [7] (Figures 5 & 6).

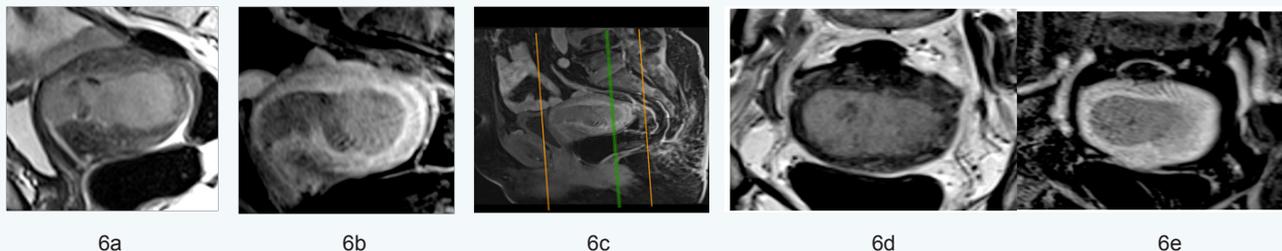


Figure 6: A patient with endometrial cancer presenting for staging.

Figure 6a: Sagittal T2W axial.

Figure 6b: Sagittal dynamic T1 postcontrast sequence (2 minutes after injection of contrast).

Figure 6c: Myometrium involvement was difficult to assess on the sagittal images. Oblique axial images on the uterine body are therefore important.

Figure 6d: Oblique axial T2W

Figure 6e: Oblique axial dynamic T1W after 3 minutes of contrast administration. Both showing >50% myometrial invasion. This is a stage 1B cancer.

It has been pointed out that at 50-120 seconds after contrast administration, the contrast between the hypointense endometrial tumor and the enhancing myometrium is maximum allowing for easy detection and accurate assessment of deep myometrial invasion. Delayed enhancement at 3-4 minutes is the best for assessing cervical stromal invasion (FIGO II) [24]. DCE MRI was shown to be useful if cervical extension is suspected because of the poorly vascularized cervical stroma [7].

C. Predicting response to treatment: The presence of hypoxia as a result of changes in tumor microvasculature and consequently changes in tumor perfusion one of the risk factors associated with resistance to treatment [1,20]. Theoretically speaking, the ability to measure the extent of hypoxia is of value in predicting response to therapy and to identify the patients who may benefit from additional therapeutic measures [5], but studies are lacking [10].

Cervical cancer

Staging of cervical cancer is also based on FIGO criteria, but in cervical cancer as opposed to endometrial cancer, the FIGO criteria are CLINICAL, owing to the fact that cervical cancer is most prevalent in developing countries with limited resources [24]. Clinical staging is somewhat misleading as compared to the surgical staging with nearly 32% of cases with stage IB disease and 65% with stage III disease being falsely staged. It is also highly inaccurate in predicting tumor size, parametrial invasion, pelvic sidewall invasion and lymph node metastasis, which are important prognostic factors that preoperative MRI excels at detecting [24,25]. It is important to distinguish early disease (with no parametrial invasion; stage I and IIA), which can be treated with surgery from advanced disease (with parametrial

invasion; stage IIB and higher), which should be treated by chemo-radiotherapy [25]. DCE MRI in cervical carcinoma cases is not routinely done, as T2W images clearly detect the tumor as well as its extent [34]. DCE MRI in cervical carcinoma cases is done using a T1 turbo spin echo sequence in either the axial or coronal planes. Five acquisitions are obtained, each lasting for 30 seconds, starting after administering the whole dose of contrast material [6].

Cervical tumor detection: Cervical masses are seen as well defined T2 isointense areas within the T2 hypointense cervical fibrous stroma, which if small, can be difficult to visualize [7]. Several studies suggested that DCE MRI does not add additional information and its use is not encouraged [24,35]. However, other studies suggest that it could be helpful when the tumor is not visualized in T2W images, especially small tumors that should be considered for trachelectomy. The tumor enhances early (30 seconds) as compared to the cervical stroma, so early acquisitions will show the cervical mass as an enhancing area with surrounding non-enhancing stroma. However, late acquisitions will not be able to show the tumor as both, the tumor and the cervical stroma are enhancing [6-8].

Accordingly, DCE MRI should not be part of the routine MRI protocol of cervical carcinoma, and its use should only be limited to specific occasions; small tumors not seen on T2W images and in post-treatment follow up [47], as recommended by the European Society of Urogenital Radiology (ESUR) guidelines for staging cervical carcinomas [24,34,36]. Other studies suggest that DCE MRI also has a role in determining the exact endocervical extent of the tumor as well as differentiating between cervical and endometrial carcinomas [34].

It is not advised to measure the tumor on DCE MRI as the enhancement of the surrounding normal stroma tends to exaggerate measurements [7].

Predicting Response to treatment and predicting recurrence: Internal areas of necrosis that are commonly seen in large tumors seen as low enhancing areas, an indicator of poor vascularity and hypoxia, are associated with poor response to treatment. On the other hand, highly vascular tumors are more radiosensitive [5], with lower rate of recurrence [10,37] (Figure 7). So DCE MRI has the theoretical advantage of non-invasively measuring tissue hypoxia, instead of using the invasive polarographic electrode. It is believed that tumors that respond well to early treatment show an increase in tumoral enhancement and have a lower rate of recurrence [10].

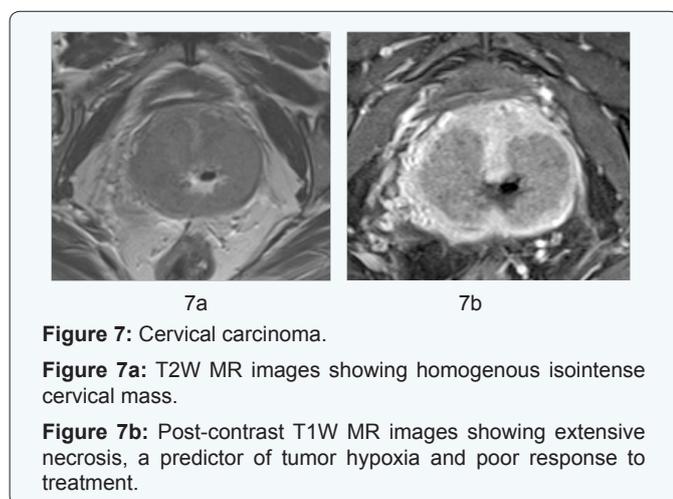


Figure 7: Cervical carcinoma.

Figure 7a: T2W MR images showing homogenous isointense cervical mass.

Figure 7b: Post-contrast T1W MR images showing extensive necrosis, a predictor of tumor hypoxia and poor response to treatment.

Accordingly, tumors with persistent low perfusion throughout treatment means poor treatment response and hence poor prognosis [5,38,39]. Low perfusion can be measured by:

- i. Quantitative analysis, where some studies postulated low perfusion is the lower 10th percentile of the signal-intensity curve (SI 10%) [5,39], while other considered SI 15% is more specific [5,40].
- ii. Qualitative analysis, where low perfusion is less than that of the normal cervical tissue [5]. Still, DCE MRI is still used as an investigational method and its evaluation in this area is still ongoing [6,10].

Post-therapy DCE-MRI to differentiate post-treatment fibrosis from recurrence: DCE MRI is able to differentiate between post-radiation fibrosis and early recurrence according to various studies [7]. It is believed that if persistent enhancement is present at the site of the cervical tumor or the surgical bed, residual disease is likely with high risk of recurrence and poor prognosis and adjunctive therapy should be advised [5,9,41]. In a small study conducted by Boss et al. [5,42] done on patients after radiotherapy, early enhancement at the original site of the tumor (<6 seconds) was associated with poor prognosis and denoted recurrence, whereas delayed enhancement (>6

seconds) was associated with good prognosis and was the result of post-radiotherapy fibrosis. Still, these are all investigational studies and more studies are needed in this field.

Conclusion

DCE MRI is a valuable problem-solving tool in gynecological malignancies, which can answer a lot of questions guiding gynecologists to less invasive therapeutic options, which could preserve fertility in young women and decrease morbidity and mortality rates in the elder group.

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