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Integrated Study Master Thesis

# Residual Cervical Cancer Assessment with Magnetic Resonance Imaging After Conization – Literature Review

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## Abbrevations

ADC – Apparent diffusion coefficient

AUC – Area Under the Curve

CIN - Cervical intraepithelial neoplasia

CIS – Carcinoma in situ

CKC – Colf Knife Conization

DCE – Dynamic contrast-enhanced

DCE-MRI – Dynamic contrast enhanced magnetic resonance imaging

DWI – Diffusion-weighted imaging

EES – extracellular extravascular space

FDG-PET – Fluorodeoxyglucose Positron Emission Tomography

FIGO – Federation of Gynecology and Obstetrics

FOV – Field of view

HPV – Human Papilloma Virus

IV – Intravenous

LEEP – Loop electrosurgical excision procedure

mm – millimeters

MR – Magnetic resonance

MRI – Magnetic Resonance Imaging

Pap-test – Papanicolaoucytology test

PET scan – Positron Emission Tomography scan

SNR – Signal-to-Noise Ratio

T – Tesla

TSE – Turbo-Spin-Echo

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# Outline

1. Summary

Cervical cancer is one of the most frequent malignancies in women, often associated with the Human Papilloma Virus. Conization means the removal of a cone-shaped segment of the cervix, which can be used as a diagnostic tool and as a therapeutic procedure in the early stages of cervical cancer. Nonetheless, residual lesions can persist despite clear margins. This leads to the conclusion that accurate imaging is crucial for detecting any remaining disease. Magnetic Resonance Imaging offers excellent soft tissue contrast and is considered as gold standard for local staging, treatment planning and follow-up. Despite its advantages, post-conization or radiation induced inflammation, and fibrosis can mimic tumoral tissue on MRI images, leading to false positive findings. Due to this, careful interpretation and imaging analysis in multiple planes and a delay between conization and MRI, is necessary to reduce diagnostic mistakes. If standard sequences fail to identify residual disease, dynamic contrast-enhanced Magnetic Resonance Imaging helps in the quantification of vascular permeability parameters. These parameters offer a more sensitive approach to residual cervical disease by identifying so called "MRI-invisible" lesions. Recent research highlights the use of radiomics, where advanced computational methods extract quantitative imaging features with the goal of identifying subtle residual lesions.

2. Keywords

cervical cancer, residual cervical cancer, magnetic resonance imaging, conization, minimally invasive surgery

3. Introduction

Cervical cancer remains a major health concern worldwide. Conization, a cone-shaped removal of cervical tissue, serves both diagnostic and therapeutic purpose. Nonetheless, even with pathologically clear resection margins, residual disease can persist undetected, increasing the risk of recurrence. In clinical practice, physicians are confronted with several problems when it comes to residual cervical cancer MRI assessment. In the first six months after surgery or radiotherapy, it happens to be rather difficult to differentiate the residual tumour from the scar. Misinterpretation and false diagnosis can be made due to repairing processes, oedema, as well as inflammatory processes and fibrosis resulting from radiation. (19) To avoid false-positive interpretation, using combined MRI and FG-PET images can help the clinician making a more accurate diagnosis in the follow-up of cervical cancer. (4,12, 30) After 12 months it becomes easier to differentiate scar and residual tumour. This clinical dilemma raises the hypothesis that optimised MRI protocols, advanced with perfusion parameters and radiomic features, can improve the detection rates of

residual cancer. The primary goal of this literature review is to give a clear and structured overview of the latest literature regarding the topic of MRI assessment in residual cervical cancer after conization. It compares the sensitivity and specificity of T2w MRI and DWI/ADC mapping for post-conization residual lesions, assesses whether DCE MRI parameters enhance diagnostic accuracy in detecting residual tumors, investigates the role of radiomic feature analysis and proposes evidence-based guidelines for MRI follow-up protocols.

4. Literature selection strategy

While conducting my research for this topic it was essential to follow a clear and systematic research selection strategy to guarantee high quality studies. The search was conducted by using PubMed, Embase and Web of Science. It was limited to articles being published in English and German between 2011 to 2024 to maintain linguistic consistency and quality of sources. However, one source from 2002 was included into this review as an exception due to its ongoing relevance and basic understanding of the topic. I focused on articles, clinical trials as well as systematic reviews and published scientific books and literature to present a structured and comprehensive overview of current evidence, guidelines and diagnostic approaches for Magnetic Resonance Imaging assessment in residual cervical cancer after conization. Main keywords guiding the literature selection were “residual cervical cancer”, “magnetic resonance imaging”, “conization”. By using these terms in various combinations, I was able to evaluate literature discussing the effectiveness of MRI imaging in residual cervical cancer disease following conization. Synonyms like “cone biopsy”, “residual disease” and “persistent” were applied to ensure a comprehensive review. Studies included into my research had to meet the following criteria: 1. focus on cervical cancer post-conization, 2. use of MRI for residual disease assessment, 3. clinical trials, systemic reviews, meta-analyses that evaluated MRI performance for residual lesion detection. Exclusion criteria include: 1. studies not related to human subjects, 2. studies not involving MRI residual disease detection, 3. case reports without sufficient sample size. After initial database searches, duplicates were removed. Titles and abstracts were screened to identify relevant articles. Subsequently, the full text of eligible articles was assessed to confirm that they met the inclusion criteria. Reference lists of the selected articles were screened to find other possible relevant studies. This literature selection strategy provided a detailed, comprehensive and structured overview of the current state of knowledge regarding the topic of MRI assessment for residual cervical cancer.

## 5. Cervical Cancer: Clinical description of the disease

### 5.1. Disease mechanisms and pathology

Cancer of the cervix is apart from breast, colorectal and lung cancer the fourth most common cause of cancer in women. (46, 55) Prevalently it is caused by recurrent Human Papilloma Virus (HPV) infection. (41, 42) The most common types are HPV-16 and HPV-18. This virus is transmitted sexually and is often contracted in early adolescence or early adulthood in roughly 80% of women. (1) Another important factor contributing to an increased cancer risk is the age of first sexual intercourse. Sexual intercourse at a young age, especially prior to menarche or having a short interval between menarche and first sexual intercourse, increases the risk of having cervical cancer. (44) Full-term pregnancies or ≧4 pregnancies before the age of 18 severely increase the risk of cervical cancer following HPV infection. Smoking, co-infection with other genital infections for example chlamydia are regarded as risk factors for cervical cancer. (42) Using oral contraceptives for longer than 5 years increases the cervical cancer risk. (47, 49, 52) Furthermore, sexually transmitted diseases are associated with a risk of HPV infection. (1) This type of cancer has neither genetic nor dietary risk associations. Cancer of the cervix can be prevented by effective screening and vaccination against HPV. (40, 43, 48, 51)

Manifested symptoms or visible changes of the cervix may take up to 15 years as the disease is usually asymptomatic in the beginning. Common manifestations include irregular or heavy vaginal bleeding following intercourse; watery, mucoid, purulent, or malodorous vaginal discharge. Lower back pain or pelvic pain that radiates to the posterior side of the legs can be seen in advanced stages. Haematuria, haematochezia or even vaginal passage of urine or stool is highly suggestive of advanced stages of cervical cancer.

### 5.2 FIGO 2018

The Federation of Gynecology and Obstetrics updated their classification of cervical cancer in 2018 to differentiate better patient and cancer specific treatment options and increase survival rates as prognosis as well as treatment largely depend on tumor extent at intial diagnosis. (2, 7, 25, 54) This update pays more attention to the usefulness of MRI examination in cervical cancer through exact tumor size measurements as well as parametrial involvement. (2,36) Staging in patients with cervical cancer is the most prognostic factor, indicating a worse outcome if pelvic or para-aortic lymph nodes are affected. (1) The following table summarises the FIGO stages encompassing four stages, each with substages and subgroups: (2, 23, 25)

Table 1: FIGO: Reference 2

| Stage | 2018 FIGO Definition |
|---|---|
| I | Confined to the Cervix |
| IA | Microinvasive disease with the deepest invasion ≦ 5mm<br>not visible on MRI, can only be staged by histopathology |
| IA1 | Depth ≦3mm |
| IA2 | Depth ≧ 3mm but ≦ 5mm |
| IB | Measurable disease<br>Disease confined to the cervix with deepest invasion ≧5mm<br>More specific classification for better management |
| IB1 | ≦ 2 cm maximum diameter<br>Eligible for trachelectomy |
| IB2 | ≧ 2cm but ≦ 4cm<br>Not eligible for trachelectomy |
| IB3 | ≧4cm in maximum diameter |
| II | Extends beyond uterus<br>no involvement of lower third of vagina or pelvic sidewall |
| IIA | Upper two thirds of vagina |
| IIA1 | ≦4cm in maximum diameter |
| IIA2 | ≧4cm in maximum diameter<br>Higher risk of recurrence and nodal metastases |
| IIB | Parametrial invasion |
| III | Natural progression from stage II, depending on extent and direction of tumor growth |
| IIIA | Lower one third of vagina<br>Based on MRI: vaginal tissue below the level of bladder base<br>Best seen in sagittal plane |
| IIIB | Pelvic sidewall involvement<br>may manifest with hydronephrosis or nonfunctioning kidney<br>Hydroureter or hydronephrosis secondary to ureteric invasion |
| IIIC | Pelvic and para-aortic lymph node involvement |
| IIIC1 | Pelvic lymph node involvement |
| IIIC2 | Para-aortic lymph node involvement |

Tabel 1: FIGO: Reference 2 (continued)

| | |
|---|---|
| IV | Disease extending to adjacent organs or outside the true pelvis as metastatic disease |
| IVA | Extension through full thickness of bladder wall anteriorly or rectal wall posteriorly and into mucosa and lumen |
| IVB | Metastases to distant organs |

5.3 Diagnostics

From the age of 21 regular cervical cancer screening is recommended in the United States with Pap-smears being the current gold standard. From the age of 30 until 65 pelvic exam is recommended annually, Pap-tests should be done every three years and HPV co-testing every five years. If the patient falls in the high-risk category screening can be performed more frequently. (1) Proper screening programmes led to a decrease of 65% in the cervical cancer incidence over the last four decades, whereas the early-stage cervical cancer diagnosis has steadily increased in developed nations. (14)

If a woman presents with symptoms raising the suspicion of cervical cancer a thorough pelvic examination should be done, including a rectovaginal exam to estimate the tumor size and vaginal/parametrial involvement. A speculum examination may reveal a normal cervix in case of early stages or an invisible lesion. In advanced disease the tumor may even entirely replace the cervix. Every suspicious lesion must be biopsied. Additionally, palpation of enlarged lymph nodes is necessary as palpable groin or supraclavicular lymph nodes are commonly found in cervical cancer. As the disease usually manifests asymptomatically, this cancer can be diagnosed incidentally due to an abnormal Pap smear. In such cases, colposcopy is a definitive diagnostic test. Nonvisible lesions are evaluated through conization.

Even though imaging is not part of the routine diagnostics it can be useful for staging and evaluating women with a known malignancy to estimate and follow up residual cervical cancer. (1)

5.4 Magnetic Resonance Imaging in Cervical Cancer

Imaging in general is a great assisting tool to the clinical assessment of patients with histologically proven cervical cancer, with MRI being the best modality to assess, further stage, evaluate treatment success, detect recurrence and for follow-up examinations post-treatment, due to its great soft tissue contrast. (5,7) Even though FIGO stage 1A is not visible on MRI, imaging is still performed when invasive or microinvasive disease is established to confirm that staging

was done correctly and not under staged and to check for skip lesions or lymph node metastases, despite the risk of node metastases being low at this stage. (2)

Furthermore, MRI imaging is of utter importance when deciding on possible treatment options for different patients. For example, a young woman who wants to remain fertile a more conservative, less aggressive surgical procedure like trachelectomy should be considered. Here it is mandatory to perform an MRI to confirm the eligibility for the procedure with the tumor size being less than 2 cm, cervical length being more than 2.5cm and the distance from the tumor to the cervical os being more than 1cm. (5)

If the cervical stroma is unaffected MRI shows a low T2-weighted signal intensity. Highly indicative of involvement of said tissue can be seen by focal or diffuse full-thickness disruption of the mentioned low T2-weightes signal intensity cervical stromal ring with tissue extending into the parametrial fat. The hypointensive rim sign shows a specificity of 96-99% in MRI based excluding of parametrial involvement. (2)

### 5.5 Treatment

Proper staging and diagnostics are of utter importance to make the correct treatment plan. Possible therapy options are surgery, radiation and chemotherapy. Each can be used on its own but more commonly in combination. Furthermore, there is a difference regarding treatment with respect to FIGO staging and patient factors like for example the age and comorbidities of the patient. (1,2) Depending on her planning on being pregnant in the future, we can use fertility sparing or nonfertility sparing therapy. (1)

Surgical treatment, consisting of cryosurgery, laser surgery, loop electrosurgical excision, conization, hysterectomy and bilateral salpingo-oophorectomy, is indicated for small precancerous lesions or stage 1 cancer where the cancer is confided to the cervix according to FIGO 2018. In Germany, tumors smaller than FIGO stage 2A are predominantly treated surgically. (7) Large cervical lesions with a width of 4-5cm can be treated with a trachelectomy (fertility-sparing cervical excision with uterovaginal anastomosis) if the patient wishes to remain fertile or a radical hysterectomy (nonfertility sparing). (1)

If the cancer has a width of more than 4 cm or is already metastasised a combination therapy of radiation with chemotherapy is the standard care. In general, chemotherapy is used if the disease is too advanced and is not manageable by surgery or radiotherapy alone. Post-treatment evaluation is based on clinical examination, Pap smear and MRI evaluation. (5)

5.6 Conization

Conization is not only used to diagnose cervical dysplasia or early cervical cancer but can also be used as treatment method. As the name indicates, it encompasses the excision of a cone-shaped biopsy of the cervix to remove the lesion with its transformation zone. (3) The procedure can be done with a scalpel, a laser or by using a loop electrosurgical excision procedure (LEEP). The decision of which option should be used is based on the individual patient factors like anatomy, bleeding risk and future obstetric considerations. A young woman with ectocervical dysplasia would benefit from LEEP, while a postmenopausal woman with a distorted cervix might profit from cold knife conization. (59) The following table compares cold knife conization and loop electrosurgical excision procedure.

Table 2: CKC and LEEP: Reference 59

| Cold knife conization (CKC) | Loop electrosurgical excision procedure (LEEP) |
|---|---|
| Endocervical lesion | Ectocervical lesion |
| Small cervix or distended anatomy | Cost-effective and widely access |
| Higher risk of complications e.g bleeding | decreased risk of bleeding |
| | Normal volume and anatomy |
| Increased obstetric risk due to more tissue removal | Better Fertility and obstetric outcome |
| More precision for tailoring excisions | Difficult to tailor excisions for specific lesions |

CKC – Cold knife conization, LEEP – Loop electrosurgical excision procedure

Diagnostic conization is indicated if the histological results do not align with the cytological screening tests and if the histological test results are less severe. In case of dysplasia or unexplainably high grade or atypical glandular cell cytology and unsatisfactory colposcopy results diagnostic conization is indicated as well. Conization as a treatment method is indicated in severe dysplasia, CIN2/3, CIS, and stage IA1/IA2 squamous cell cervical cancer if the patient intents to maintain fertility. (2,3,10, 57) This treatment approach is curative if the excision is done with negative margins. (2,10, 58) Kliemann et al. suggest that a cone height of more than 18 mm is preferable to minimize margin involvement. (58) In patients with early-stage cervical cancer who undergo radical hysterectomy after diagnostic conization, 65% show no residual disease. As a result, less invasive surgeries could be considered for fertility sparing preservation in these cases, provided strict eligibility criteria are met. (10,29, 56) Advantages of conization are low peri-operative comorbidities and good reproductive results. (21, 27)

The procedure is contraindicated in case of too little cervix or if the patient is a poor surgical candidate. Conization in pregnancy is generally contraindicated due to the increased risk of haemorrhage (45) but there can be exceptions if there is a firm conviction of invasive cancer. Other contraindications include severe cervicitis as well as the patient taking anticoagulants. (10)

6. Recurrent Cervical Cancer

The term recurrent cervical cancer refers to either a local recurrent tumor or distant metastases that are commonly found within seven to 36 months after initial diagnosis. Advanced FIGO tumor stage, lymph node involvement or specific histology e.g adenocarcinoma, increase the likelihood of residual disease. (2,7) During the first two years post-treatment a follow-up visit every three to six months is advised. Three to five years post-treatment follow-up visits every six to 12 months are current recommendation standard. (1) The mentioned follow-up visits are of utter importance due to the fact that even years after treatment, residual, recurrent or new lesions can appear. (4) The prognosis of patient with recurrent disease is very bad with a median survival of seven to 17 months after residual cancer diagnosis. (7) Local recurrent tumors are more likely to appear in the area of the cervical stump (after hysterectomy) or the pelvic wall.

A study conducted by Milojkovic M. in 2002 wanted to evaluate the importance scheduled long-term follow-up visits for all patients whose stage CIN 3 was treated with conization. (4) Milojkovic M. study included 934 patients who underwent cold knife conization after being diagnosed with CIN 3. Out of 934 only three were diagnosed with invasive carcinoma of the cervix after conization, 19 patients were diagnosed with CIN 3 and only one patient showed CIN 1 after conization. (4) 23 patients were reoperated due to suspicion of residual or recurrent disease. These patients were examined for the involvement of cone margins: 11 patients showed lesions that extended to the cone margins, whereas eight showed clear cone margins. In four patients it was unknown. If the patient shows involved resection margins after conization it is highly likely that the lesion has not been excised completely. In the case of free resection margins after conization but during follow-up visits similar or more advanced lesions are detected, this is suggestive of recurrent disease. Other possibilities could be it being a residual lesion which went undetected by the pathologist due to the fact that the primary lesions showed multifocal features or there not being enough serial cross-section of the cone biopsy. (4) Patients with free resection margins repeated surgery is not recommended, especially in those women who wish to preserve fertility, as histological findings often show no residual disease. This study suggests cytological and colposcopic follow-up, with the option of surgery in case of residual or recurrent disease. In conclusion the authors of this study suggest that repeated surgery is only

necessary if the suspected residual lesion is based on cytological, colposcopic and histological findings. Pathological findings on its own (lesion extension to cone margins) is not a justification for another surgery. Furthermore, it is important to mention that complete excision does not rule out residual or recurrent disease. (4)

## 7. Magnetic Resonance Imaging Assessment

### 7.1. Indications and Contraindications

Magnetic Resonance Imaging is known for its excellent soft tissue contrast which is essential for local staging, follow-up and evaluation of therapy success. When comparing it to CT investigations, MRI is superior in assessing stromal invasion and infiltration of adjacent structures and neighbouring organs. (7) For example, MRI shows a sensitivity of over 90% for detecting parametrium infiltration whereas CT only shows 50%. (7) Likewise shows MRI a higher specificity regarding bladder infiltration compared to CT imaging. Table 2 makes it clear that hybrid imaging using PET/MRI does not exhibit higher accuracy when it comes to local staging and assigning a FIGO stage but in regard to identifying pelvic, retroperitoneal lymph node or distant metastases whole-body hybrid imaging e.g. PET-CT is superior to standard MRI investigations. (7) Most clinicians recommend MRI follow-up imaging three to six months after completion of chemoradiation therapy or brachytherapy. (5)

Recent investigations showed that combining MRI and PET might improve tumor assessment, treatment planning and treatment follow-up. (33, 50) Table 2 summarizes and compares the diagnostic sensitivity, specificity and accuracy of different imaging modalities.

Table 3: Comparison of different imaging modalities: Reference 7

| | Parametrium infiltration | | | Bladder infiltration | | | Lymph Node involvement | | |
|---|---|---|---|---|---|---|---|---|---|
| | Sens. | Spec. | Acc. | Sens. | Spec. | Acc. | Sens. | Spec. | Acc. |
| CT | 14-55% | 77-100% | 74-82% | 64% | 73% | - | 31-57% | 92-97% | - |
| MRI | 40-92% | 77-99% | 65-98% | 71-100% | 88-97% | - | 37-76% | 83-93% | 77% |
| PET/CT | - | - | - | - | - | - | 34-82% | 93-100% | - |
| PET/MRI | 90% | 94% | - | 100% | 100% | - | 83-91% | 90-94% | 87% |

CT – Computer Tomography, MRI – Magnetic Resonance Imaging, PET/CT – Positron Emission Tomography /Computer Tomography, PET/MRI - Positron Emission Tomography/Magnetic REsonance Imaging, Sens. – Sensitivity, Spec. - Specificity

### 7.2 MRI protocol

In the standardised protocol the patient is in the supine position with a pelvic phased-array coil. Although endocervical coils can improve the Signal-to-Noise ratio (SNR) as the coil is placed close to the cervix, those coils often cause discomfort for the patient and correct placement is rather difficult. Therefore, the pelvic-phased array coil is the preferred method due to its fast and universal applicability. (14, 38)

As in most uterine gynecological examinations emptying bladder and rectum before the examination is advised to get the best uterine position in order to avoid deterioration in image quality. Especially pelvic diffusion-weighted imaging (DWI) is prawn to image degradation due to rectal gases. (2) Current guidelines of the European society of Urogenital Radiology suggest that injecting an antiperistaltic agent (1mg glucagon or 20 mg butyl-scopolamine) intramuscularly before imaging (unless contraindicated e.g in diabetes) can help with reducing artifacts from small-bowel peristalsis and uterine contractions. (5) Furthermore, a vaginal filling, and as part of primary staging rectal filling, can be considered as well. (5,7) Some sources suggest that the use of ultrasound gel is an easy and well-tolerated technique for staging early cervical cancer on MRI as it increased the accuracy. (24)

Another important factor that should be considered is scan time. A long scan time increases the risk of the patient moving and therefore decreasing the image quality leading to the conclusion that the scan time should be kept as short as possible at approximately five minutes with the best possible image resolution. (12)

Typically, a 1.5- or a 3.0-Tesla magnet is used. When using the 3.0-Tmagnet, we can observe improved spatial resolution which in turn gives the possibility of a more accurate local staging and detection of residual disease after treatment. (5) By further comparing both magnets it is safe to say that the 3.0-Tmagnet mean tumor signal-to-noise ratios, mean stroma signal-to-noise ratios and mean tumor-to-cervical stroma contrast-to-noise ratios are higher. (5) Image homogeneity seems to be superior in 1.5-Tmagnet. Nonetheless, the accuracy is the same. (5)

The use of intravenous (IV) contrast medium in MRI imaging varies, with some authors recommending it for all cases, whereas others do not use it at all. In Dynamic imaging, the tumor initially shows lower contrast enhancement than the myometrium, whereas in later phases, the tumors signal intensity exceeds the intensity of the myometrium. This leads to the conclusion that interpreting imaging in the early phases of contrast enhancement is easier. Contrast medium can be particularly helpful when detecting small tumors that may be considered for trachelectomy, as the IV contrast improves the differentiation between tumor and cervical stroma, which makes it in turn easier to detect and localise the tumor. (5,7) Dynamic contrast-

enhanced (DCE) MRI enhances the reliability of correctly assessing bladder and rectal wall involvement. Furthermore, IV contrast medium can be particularly helpful in the post-treatment follow-up, as it helps to distinguish between residual or recurrent disease from radiation fibrosis and identify fistulae that can develop post radiation. (5) Fei Kuang et al. came to the conclusion that incorporating DWI combined with standard MRI surpasses standard MRI alone regarding the accuracy. This combined approach demonstrated equivalent diagnostic capability as contrast-enhanced MRI. (28)

### 7.3 Modalities

In general, primary staging should include T2weighted sequences in three different planes as T2w is the most basic and essential sequence in MRI imaging showing the uterine anatomy in great detail. (7, 12) Tumor extension into the uterus and vagina are best evaluated in the sagittal plane, while stromal and parametrial infiltration can be best analysed in the axial plane. (7) Two sequences in particular are very useful for local staging: the T2-weighted imaging modality is used in the sagittal plane through the pelvis and in the oblique plane (perpendicular to the long axis of the cervix) with a slice thickness from three to six mm, with a 0.25 gap. The orthogonal angulation thus shows the fibromuscular stroma of the cervix as a hypointense ring. A high negative predictive value regarding parametrial infiltration can be concluded if this ring appears intact in the MRI and shows no interruption in continuity. To achieve the best imaging quality the T2w images of the pelvis are done in a high-resolution small field of view (FOV) (20-25 cm) with a 512x512 matrix in the oblique plane to assess morphologic changes of the primary lesions and document any association of parametrial and vaginal tissue. (2)

The picture below, Figure 1, shows a healthy cervix with the characteristic mucosal wall layering. The mucosa of the cervical canal exhibits a strong hyperintense signal (white arrow), whereas the inner fibromuscular stroma shows a hypointense signal (white arrowhead) and the outer fibromuscular layer a higher signal intensity and is homogenously loosened (*). (7) Bladder (B) and rectum (R) are partially pictured.

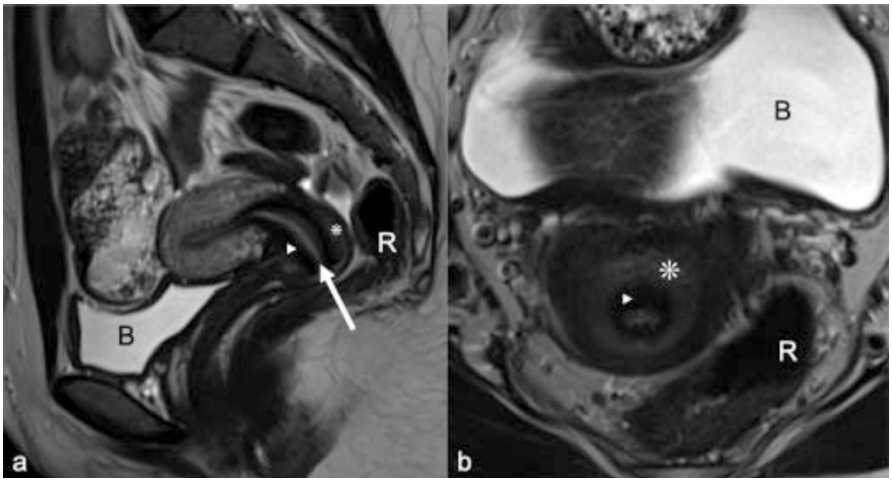


*Figure 1: Reference 7*

T2weighted sequences are preferred for localising the cervical tumor and its extension to the uterus, parametrium and adjacent organs. (5) The T2w imaging should completely cover the uterus, vagina, vulva and adnexa, highlighting the need of a localising scan prior to this imaging sequence to determine the individual anatomy of these organs. (12) Compared to small FOV, large FOV, especially in the axial plane with T1- and T2-weighted modalities shows an image from the renal hilum to the pubic symphysis, showing the pathology outside the cervix (para-aortic lymph nodes, hydronephrosis, bone involvement). If the tumor is smaller than five mm it is highly likely that it cannot be detected on the standard T2w MRI scan, making it a so called "MRI invisible" tumor with a very small volume. (12,13)

While MRI-invisble tumors in cervical cancer patients are according to Roh et al. linked to an increased risk of false negative results and underdiagnosis (14), reactive tissue changes on the other hand are leading to overestimated tumor sizes and thus to over staging. This could be caused by for example a peritumoral edema, which can also cause an increase of signal intensity in T2weighted images. (7)

DWI detects shifts between the extra- and intracellular spaces, changes in permeability and higher cell density which are all often associated with malignancy, making it a supporting asset aiding tumor detection. (31) As most gynaecological tumors show a diffusion restriction, diffusion weighted images are a great tool for assessing exact tumor size and expansion into surrounding tissues as we can observe a high contrast between early cervical cancer and normal tissue, as well as low ADC values of the tumor, thus reducing the risk of over staging. (7,12) Soft tissue differentiation, as well as contrasting lymph node and surrounding fat is useful for detecting a nodal fatty hilum. This is best done with large FOV T1-weighted imaging. DWI can be useful for detecting residual tumors or suspicious lymph nodes post-treatment, including the differentiation between benign and malignant lymph nodes, thus can be as effective as PET

scans. (26) Since tumors of the cervix have a lower apparent diffusion coefficient (ADC) compared to normal cervical tissue, with the ADC values increasing after chemoradiotherapy, diffusion weighted imaging (DWI) is advised to be performed with a b value of 0 and at least 750sec/mm$^2$, better ranging from 500 to 1000sec/mm$^2$. (2,6, 32) In general we can say the higher the b value the stronger the diffusion effects thus making it easier to differentiate between benign and malignant tumors. (12) The European Society of Urogenital Radiology mentions a study from 2009 conducted by Liu Y, Bai R, Sun H, Liu H, Zhao X, Li Y discussing the "Diffusion-weighted imaging in predicting and monitoring the response of uterine cervical cancer to combined chemoradiation" according to which the ADC values before treatment were lower in patients with a complete response compared to patients with a partial response and that those pre-treatment ADC values were negatively affected by tumor size reduction after two months of chemoradiation. This leads us to the conclusion that tumors which had higher ADC values before treatment might be more necrotic than tumors with lower values. (6) Low diffusion is not specific for lymph node involvement, even though DWI assessment has good imaging qualities of showing small cervical tumors or pelvic lymph nodes. (2)

Differentiation of the tumor from the fibrous stroma is easily done due to the intermediate T2-weighted signal intensity showing a hypointense cervical stroma which is why routine use of contrast in the MRI protocol is contradicted. Nevertheless, Akita et al. found that contrast-enhanced T1-weighted imaging is more sensitive when detecting small tumors which are less than two cm and is a useful asset when evaluating patients' eligibility for fertility-sparing treatment. (5,6)

### 7.4 Reporting and description of lesions

When describing the lesion, it is essential to describe the tumor size in three dimensions and evaluation is done in at least two orthogonal views. As mentioned above, cervical tumors are recognisable as hyperintense mass on T2weighted imaging. Accurate measurement must be ensured as the size can influence possible treatment options. (6) For local staging it is necessary to evaluate vaginal, parametrial or isthmic extension. When talking about vaginal extension it should be clarified if the given extension is anterior or posterior, if it reaches the upper 2/3 of the vagina (FIGO IIA) or if the invasion is limited to the lower 1/3 (FIGO IIIA). In the case of parametrial invasion, oblique T2weighted imaging nicely shows a disruption of the hypointense line circumscribing the cervix (hypointensive rim sign). Additionally, parametrial involvement can be suspected when alongside stromal invasion, there is parametrial tumor invasion, spiculated tumor-parametrial interface or tumor encasement of peri-uterine vessels. Another supportive sign of parametrial involvement is the presence of hydronephrosis. Isthmic invasion

often cannot be accurately evaluated, which does not make it any less important as it can highly influence further treatment planning, specifically brachytherapy. (6, 53)

As mentioned above, lymph node spread gives important prognostic information regarding tumors. Lymph nodes are considered suspicious if pelvic or abdominal lymph nodes are larger than one cm in the short axis. Nonetheless, especially smaller pelvic lymph nodes still could show signs of malignancy. Therefore, general signs of malignancy like round shape, irregular margins, signal intensity resembling those of the primary tumor and signs of necrosis, need to be evaluated. (6)

The MRI protocol for post-treatment evaluation is the same as for cervical cancer staging. Complete remission can be concluded of there is no evidence of lesions in the cervix or in adjacent organs, the cervical stroma is homogenous and if after contrast medium IV injection the cervix shows homogenous and delayed uptake of contrast medium. It is always recommended to compare pre- and post-treatment images to improve tumor recognition and re-staging. (6)

## 7.5 Clinical examples

The following sequence, Figure 2, 3, 4, shows the MRI images of 23-year-old woman with an abnormal cervical smear at screening. Figure 2 depicts a 1.4-cm tumor in the sagittal T2weightes sequence with intermediate signal intensity on the anterior cervix. (2)

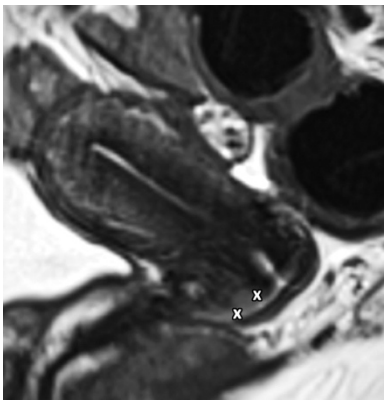


*Figure 2: Reference 2*

Figures 3 and 4 are taken in the axial plane in the diffusion-weighted sequence with 3 exhibiting a distinct ADC map. (2)

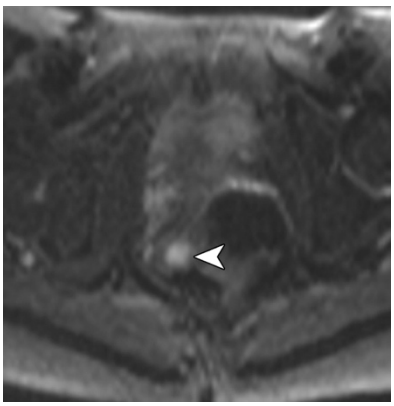


*Figure 3: Reference 2*

In Figure 4 the arrowhead indicating the tumor with evident restricted diffusion. We can see no disease outside of the cervix indicating that this is FIGO stage IB1. (2)

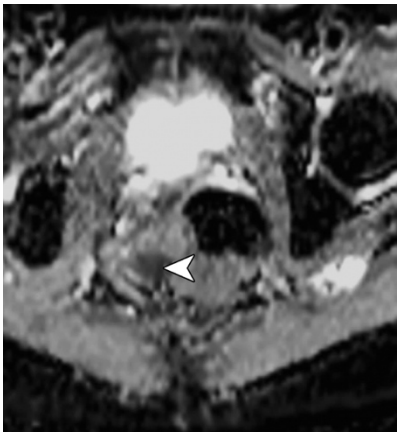


*Figure 4: Reference 2*

The next clinical example exhibits FIGO stage IB3. A 46-year-old woman presents with a 3-month history of vaginal bleeding and undergoes MRI assessment. Figure 5 shows a 4.3cm cervical tumor with intermediate signal intensity in the sagittal T2weighted image (calipers). The white arrows indicate how the tumor invades the upper vagina with a rim of increased T2weighted signal intensity fluid between tumor and vaginal wall. In general, we can say that loss of this typical T2w signal intensity in the vaginal wall if continuous with the primary cervical tumor, suggests vaginal involvement. We can conclude that the vaginal wall is not infiltrated with there is a surrounding rim of T2w signal intensity. Nevertheless, images in two orthogonal planes are of utter importance as muscle invasion can be mimicked by T2w signal intensity caused by fluid or inflammation. (2)

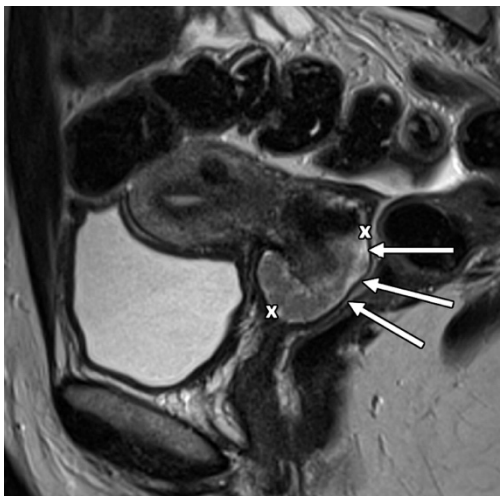


*Figure 5: Reference 2*

In the next scenario a 31-year-old undergoes MRI for investigation of subfertility *(*Figure 6, 7, 8*)*. Figure 6 shows a 2.6cm tumor of the posterior cervix in the sagittal 2Tw sequence, indicated by the calipers. There is no vaginal or parametrial invasion. Figure 7 is shown in the axial plane in the T2w sequence. Figure 8 shows a fused FDG PET-CT scan in the axial plane. In both the arrowhead indicates a 1.7cm short axis right obturator lymph node exhibiting an increased T2w signal intensity and peripheral FDG uptake suggestive of central necrosis. The white arrow highlights a 1.1cm left external iliac lymph node raising concern for a possible disease involvement due to its round shape and signal intensity similar to that of the primary tumor. We can also observe a corresponding uptake on the FDG PET/CT scan. Staging according to FIGO should be IIIC1. *(2)*

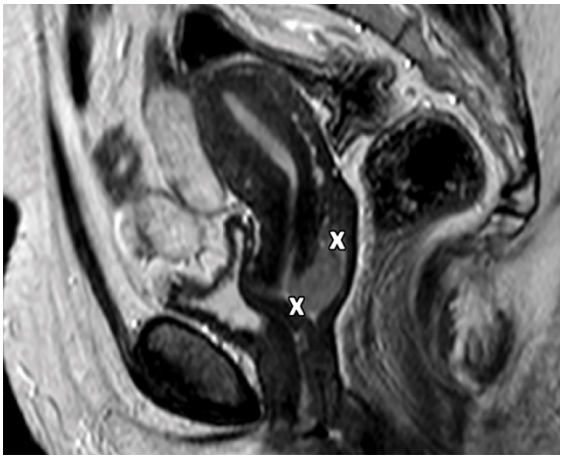


*Figure 6: Reference 2*

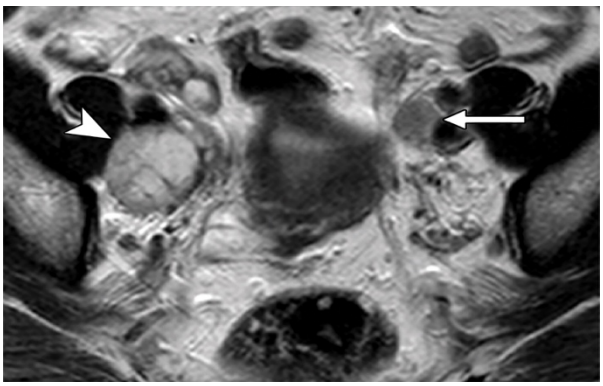


*Figure 7: Reference 2*

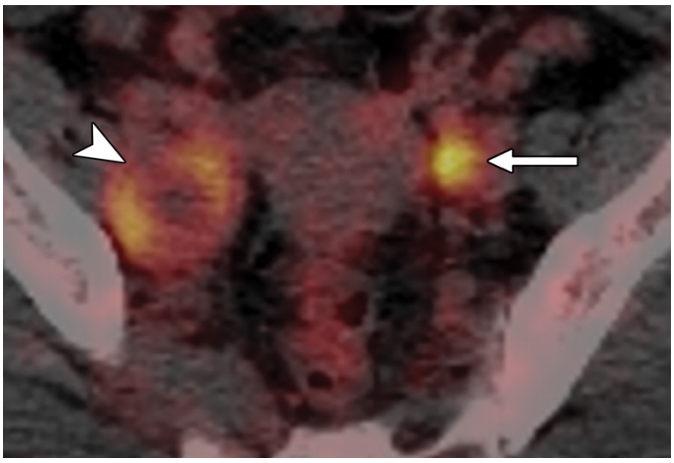


*Figure 8: Reference 2*

The next case discusses the MRI images of a 35-year-old woman who presented with intermenstrual bleeding. Before discussing figure 9, 10, 11 it is important to mention that due to partial volume artifacts in T2w large FOV imaging can lead to the false diagnosis of parametrial or local organ infiltration. In order to clearly picture local organ infiltration, T2w small FOV axial oblique imaging perpendicular to the long axis of the cervix, along with sagittal imaging, is crucial for precisely defining the tumor´s margin in relation to parametrium, bladder and rectum. Figure 9 illustrates the axial large FOV T2w sequence of a cervical mass (*). Additionally, we can observe that the fat layer that usually separates the bladder from adjacent structures is lost and that there is an intermediate T2 weighted signal intensity, indicated by the arrow, which invades the bladder. This raises the question of a possible bladder invasion. To further stage this patient we must analyze MRI images in different planes. Figure 10 shows the sagittal view and figure 11 an axial oblique small FOV T2w image perpendicular to the ling axis of the cervix. Both images show that the fat plane, which was suspected to be disrupted in figure 5a, is preserved and that there is a normal low T2w signal intensity of the posterior bladder wall, excluding bladder wall infiltration. The arrow in figure 10 shows a cervix tumor measuring

7.9cm with parametrial invasion and a tongue of the tumor extending into the lower 1/3 of the vagina. All in all, this can be classified into FIGO IIIA. (2)

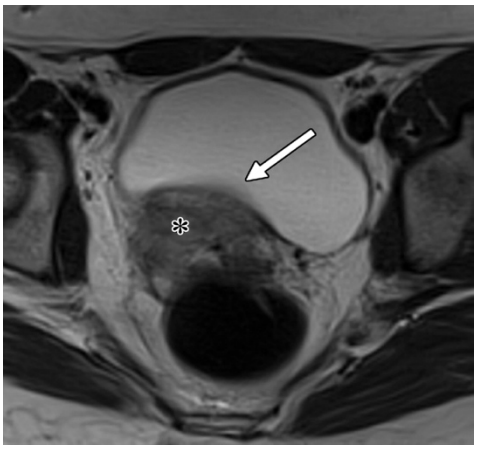


*Figure 9: Reference 2*

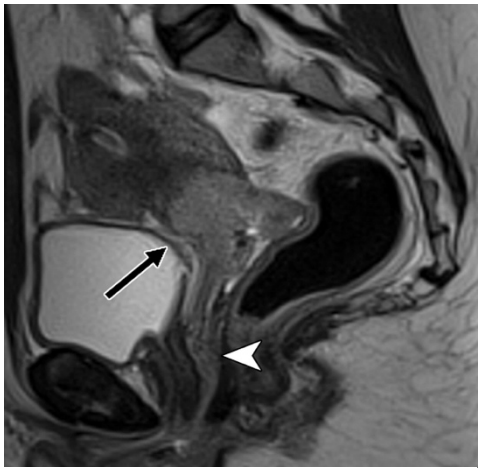


*Figure 10: Reference 2*

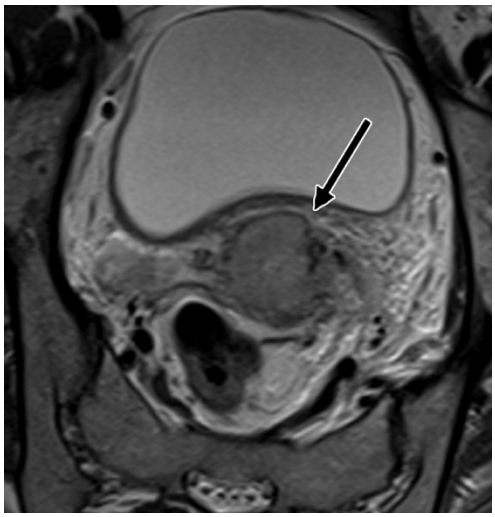


*Figure 11: Reference 2*

## 7.6 Therapy and recurrent tumor evaluation

MRI is a standard part of imaging diagnostic in recurrent disease. Some studies and articles suggest that the use of contrast medium helps with detecting local recurrent tumors. Identifying recurrent tumors is best done with T2weighted images, as the tumor exhibits an intermediate to hyperintense signal. A significant T2w-signal decrease should raise the suspicion of cervical fibrosis due to radio chemotherapy. Diffusion-weighted imaging can also add up to the post treatment diagnostic work up, as an increased loss of signal intensity, especially with high b-values, suggests recurrent vital tumor tissue. (7) A study conducted by Bae JM, Kim CK, Park JJ, Park BK in 2016 evaluated if diffusion-weighted magnetic resonance imaging could predict tumor recurrence of uterine cervical cancer after concurrent chemoradiotherapy. The authors showed that there was a significant difference regarding ADC values in patients with and without recurrent disease during radio chemotherapy. The ADC values of patients with recurrent disease displayed a smaller increase compared to the patient group without recurrent disease. (8) This leads to the conclusion that DWI allows us to predict a possible early recurrence. (7) Fei Kuang et al. support the conclusion that ADC values are indeed reliable for differentiating cervical cancer and normal cervical tissue. (34) When evaluating a patient post-conization the MRI can show a triangular tissue defect at the vaginal exocervix. Nevertheless, as mentioned before small cervical tumors can be invisible in MRI images indicating a possible smaller tumor burden, but it does not rule out a negative histological result. (10,12,15)

Figure 12, 13 are both taken in the sagittal plane, depicting the uterine cervix of a 44-year-old woman with confirmed Stage IB1 cervical adenocarcinoma after conization 11 weeks before imaging was done. (16) Figure 12 shows a T2w MR image with the white circle highlighting a hyperintense are surrounded by hypointense tissue. As discussed before hypointense regions on T2w imaging indicate normal cervical stroma, whereas lighter hyperintense regions might indicate tumoral tissue. Figure 13 was done in the contrast-enhanced T1w fat-suppressing modality showing normal enhancement. After the patient went radical vaginal trachelectomy no residual invasive disease could be found, but residual high-grade intraepithelial neoplasia was discovered. (16)

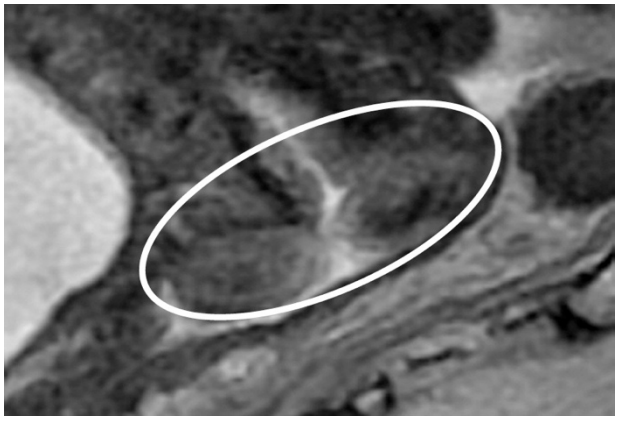


*Figure 12: Reference 16*

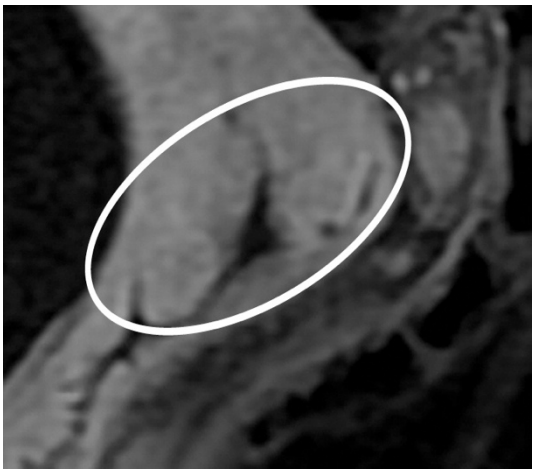


*Figure 13: Reference 12*

8. Discussion

Despite that MRI assessment in residual cervical cancer has many advantages as described above, there are some factors that have to be considered. One being that lesion detection and characterisation is limited in conventional MRI based on morphological changes. (10) Firstly, false positive images showing a larger extent of parametrial invasion may be caused by post biopsy inflammation, which is why there should be enough time in between MRI and biopsy. In this case DWI is a useful modality. If post biopsy inflammatory changes are suspected by radiologist, the MRI examination should be repeated. The following figures 14, 15 of a 42-year-old woman with IA1 cervical cancer highlight this problem:

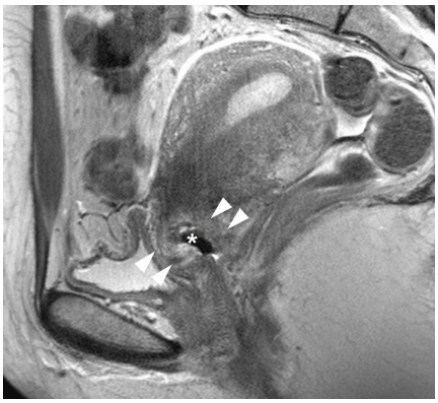


*Figure 14: Reference 12*

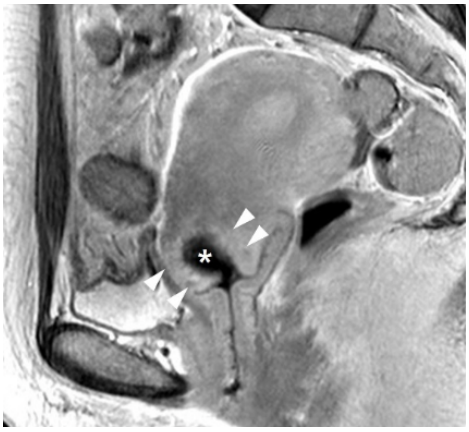


*Figure 15: Reference 12*

Figure 14 is taken in the sagittal plane in the T2 weighted imaging modality. The white asterisk shows a brighter signal compared to the surrounding tissue. On T2w images normal cervical stroma appears hypointense, while tumoral tissue appears rather hyperintense. This hyperintense region seems to expand into the cervical canal leading to the suspicion of an infiltrative process. But here the hyperintense region is not caused by a tumor but rather due to post-conization inflammation. Figure 15 shows the pelvic scan of the same patient in the delayed contrast-enhanced sagittal plane. Here the asterisk shows a hematoma within the cone biopsy defect. The white arrowheads show tissue margins that delineate abnormal tissue from the cervical stroma and surrounding tissue. Just like the asterisk the arrowheads highlight a poorly demarcated enhancement indicating post-biopsy inflammation. In this patient residual cancer and parametrial invasion was ruled out. (12) This clinical example showed that differentiating between actual residual disease and post-conization inflammation is very hard and other imaging modalities and techniques as discussed later on need to be considered in the process.

Secondly, false parametrial or local organ involvement can be caused by volume artifacts at T2-weighted large FOV imaging in the axial plane. In this case it is of utter importance to perform T2-weighted small FOV in the axial oblique plane perpendicular to the long axis of the

cervix in combination with imaging in the sagittal plane to outline the tumor margins in relation to parametrium, bladder and rectum.

Thirdly, as described above, stage IVA shows tumor involvement not only in the serosa but also in bladder or rectal mucosa. If the radiologist suspects bladder invasion, usually cystoscopy is done to confirm the stage.

Even though MRI shows promising results in allowing the non-invasive visualisation of cervical cancer, the traditional MRI approach relies on morphological analysis to predict the residual status and has not been widely adopted. This is related to the complexity of summarizing these morphological features and maintain consistency on a large scale as well as the fact that the captured level of information by the human vision is not adequate to distinguish the disease or is not adequate for a diagnosis. A new promising technique called radiomics transforms images into high-dimensional, mineable data through feature engineering and machine learning methods. Recent development in medical imaging, especially in the field of radiomics, facilitate the efficient extraction of imaging features. Said features provide valuable insight into the temporal variability at multiple biological levels including genes, proteins, cells, microenvironments, tissues and organs and non-invasively acquires intratumoral heterogeneity. A study by Mengfan Song, Jing Lin, Fuzhen Song, Dan Wu, and Zhaoxia Qian conduct an investigation into the performance of an MRI-based radiomics model evaluating the residual status of carcinoma in situ after conization. The authors obtained 156 features derived from 3D features attained from 3D tumor regions in MR images with the intention of improving the reproducibility and effectiveness of radiomic models. The developed model assists in identifying patients at high risk for residual disease, whereas those at low risk may not require an intensive treatment approach during follow-up. The study proved that despite residual disease not being easily visible to radiologists, it is indeed present on MR images and can be identified through the help of radiomic features. Radiomic features are commonly associated with tumor heterogeneity, complexity and entropy, the authors suggest that residual disease might also represent a form of normal tissue variation or inflammation which can accurately be captured by radiomic analysis. (9)

In comparison to normal uterine tissue, tumor tissues exhibit more neovascularisation. In case of limited sensitivity when analysing residual tumor after conization during early stages in conventional MR imaging, dynamic contrast-enhanced MRI is the advised non-invasive imaging modality to characterize tissue vasculature and shows increased sensitivity to tumor angiogenesis. It has been used in the diagnostic process of early esophageal and cervical cancer

and assessing the treatment response. However, the DCE-MRI parameteres have not yet been used in the detection of residual cervical disease. A study conducted by Huang, J.-W. et al. analyzed the value of DCE-MRI in detecting MRI-invisible residual cervical cancer after conization. (10) 59 patients with cervical cancer invisible on MRI but positive conisation results were included in this study. Inclusion criteria were patients that underwent cervical conisation less than 2 weeks before MRI and radical hysterectomy one week after MRI, patients had to undergo complete MRI including DCE-MRI and no obvious cervical lesions were detectable on MRI after conisation. Excluded from this study were failure of DCE-MRI technique or no surgery after MRI, as well as patients with visible lesions on MRI. The study used 3T MRI scanners with a 16-element pelvic phased-array coil. According to the standard protocol the images were obtained in the transverse plane with T1-weighted Turbo-Spin-Echo (TSE) images, and in the transverse, coronal and sagittal plane with T2-weightes TSE images. Diffusion-weighted-imaging was done with a single-shot echo-planar imaging with a b-value of 1000s/mm$^2$. Additionally, a DCE-MRI three-dimensional (3D) T1-weighted gradient recalled echo sequence was obtained. After that intravenous contrast agent was injected followed by a 15ml saline flush. DCE-MRI was continued for four additional minutes after contrast injection. (10) The images were individually evaluated by two genitourinary radiologists with six and nine years of pelvic MRI experience. They were blinded to all clinical and pathological information. In case of different opinions, a consensus was reached. “MRI-invisible cancer” is defined as cervical cancer that is not detectable on T2w images, DWI/ADC images or contrast-enhanced T1w images after conisation. Tumor size, histological type, lymph node metastasis and lymphovascular invasion were analysed from the hysterectomy specimen. DCE-MRI used the “Omnikinetics” software with the two-compartment extended tofts model to analyse how the contrast agent moves in the cervical tissue. The following key parameters were measured: volume transfer constant (Ktrans), rate constant (Kep), volume of EES (Ves), blood plasma volume (Vp). Ktrans measures the rate at which the contrast agent moves from the blood plasma into the EES, reflecting the tissue permeability. Kep measures the rate at which the contrast agent moves back from the EEs into the blood plasma, reflecting the rate of contrast agent washout. Ves indicates the amount of extracellular extravascular space in the tissue which can be important for understanding the tumor´s microenvironment. Vp shows the fraction of tissue volume that is occupied by blood plasma, which is useful for assessing the tissue vascularity. For further evaluation the radiologists drew a region of interest (ROI) around the cervix extending five mm into the myometrium. Parametric maps of Ktrans and Kep were created to visualise tissue blood flow and vascularity to assess the tumor characteristics. (10) Out of the 59 patients included into this study 34 patients were confirmed to have residual cervical cancer at surgery. 30 of those

were appointed to FIGO class IB and four to stage IIB. 29 patients were diagnosed with squamous cell carcinoma and five with adenocarcinoma. In nine patients, lymph node metastases were confirmed, whereas lymphovascular invasion was only confirmed in four patients. It was found that Ktrans and Ve values were significantly higher in patients with residual disease than in those with no residual disease. Kep and Vp showed no significant difference between the groups. The ROC analysis was performed to find the optimal threshold values of Ktrans and Ve to distinguish between the two groups. Ktrans showed a higher Area Under the Curve (AUC) than Ve, making it the better parameter to differentiate between residual and no residual disease. (10) As already mentioned above key prognostic factors include tumor size, lymphovascular invasion, lymph node metastasis and depth of stromal invasion, with tumor size being the only factor which can be assessed preoperatively. Studies show that if the long axis-diameter of the tumor exceeds 20mm, it is linked to poorer ling-term survival rates. (11) Due to the fact that MRI-invisible cervical tumors have a high risk of metastatsis (9 out of 34) and lymphovascular invasion (4 out of 34) it is of utter importance to quickly identify those invisible residual cervical cancers. Angiogenesis is fundamental to tumor growth, invasion, metastasis and recurrence. When a lesion exhibits greater vascular permeability, it has a stronger attachment to tumor tissue. Ktrans was found to be associated with vascular permeability which in turn reflects angiogenesis in residual cervical cancer. All in all, we can conclude that the preliminary results by Huang, J.-W. et al. show that DCE-MRI quantitative parameters can indeed be used to detect MRI-invisible residual cervical cancer after conization. Nontheless, it is very important to mention that DCE-MRI parameter values and their repeatability might have a significant variability depending on the analytical methods that were applied. It is highly unlikely that absolute values of DCE-MRI markers can be compared across different studies if the analysis methods are not standardized. (17)

The following images show the MRI results of a 35-year-old woman with MRI-invisible residual cervical cancer but positive conization pathology. (10) Figure 16 shows the axial DWI sequence. Here we can see a bright hyperintense region suggesting restricted diffusion due to high cellularity. This might indicate tumor tissue. Figure 17 shows the ADC map. We can see a hypointense dark area in the same region where DWI in figure 16 is hyperintense. Low ADC values suggest restricted diffusion characteristic for tumor tissue. Figure 18 shows a metastatic lymph node in the axial DWI sequence as hyperintense region. Figure 19 shows the sagittal T2w sequence with no visible cancer. This result is consistent with the previous claim that T2w imaging alone might not be sufficient to detect residual disease. Figure 20 shows the contrast-enhanced images with no visible cancer. Even with contrast enhancement residual disease might

not be detectable. Figure 21 shows the color-coded Ktrans map and figure 22 shows Kep map where a heterogenous abnormal intensity was identified. Ktrans being the perfusion parameter for vascular permeability suggests that areas with heterogenous abnormal intensity, as it can be seen in figure 21, suggest increased vascularity and permeability correlating to a possible tumor and angiogenesis. Kep being the rate constant of contrast medium return suggests that areas of heterogenous abnormal intensity, as seen in figure 22, could reflect tumor vascularization. Even though that figure 19 and figure 20 show no cancerous lesions the other sequences suggest residual disease.

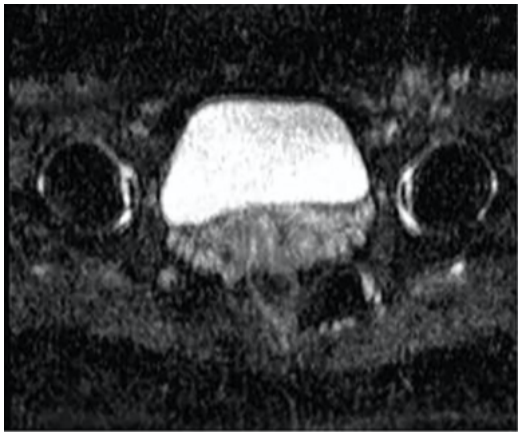


*Figure 16: Reference 10*

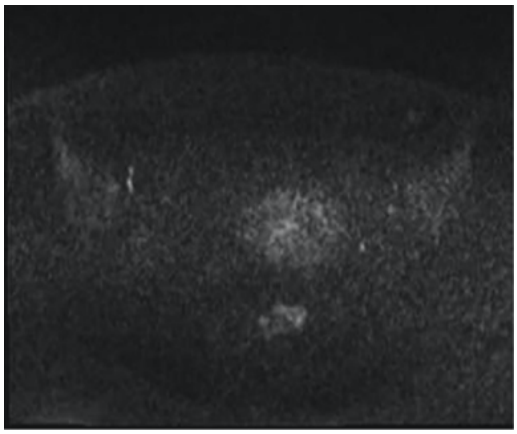
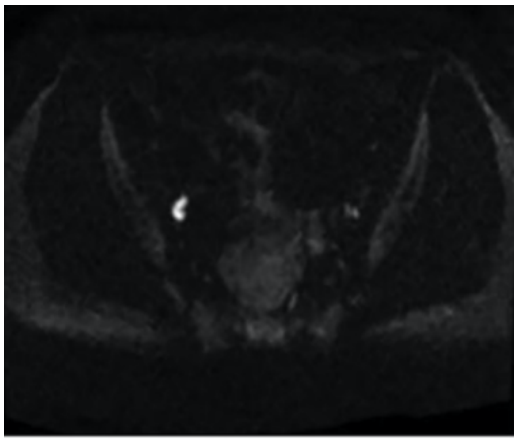


*Figure 17: Reference 10*



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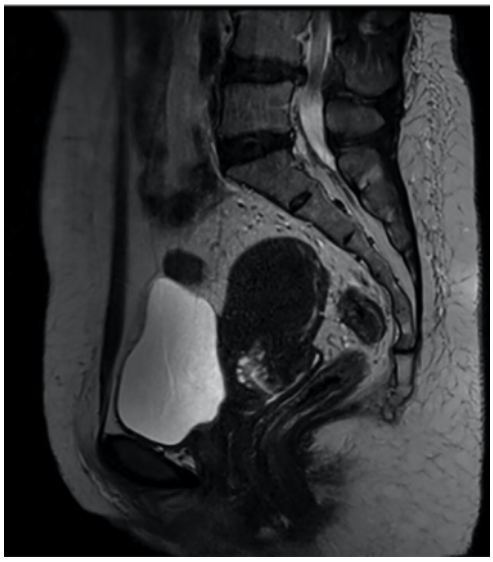

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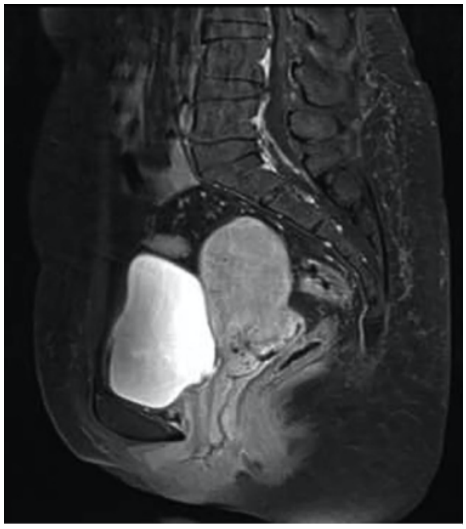

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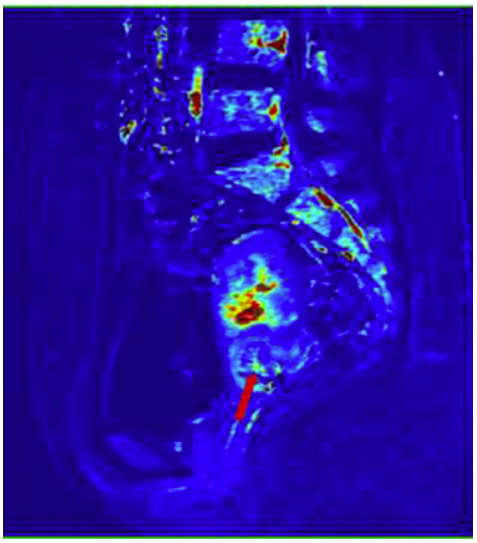

*Figure 21: Reference 10*

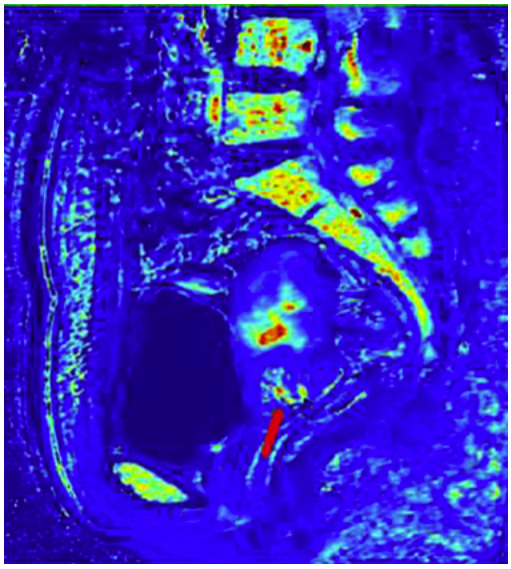

*Figure 22: Reference 10*

## 9. Conclusions and recommendations

Cervical cancer remains a major health concern for women worldwide. It leads to the necessity of further expanding educational health programs as a key strategy to reduce the risk of developing the disease. As mentioned in this review there are many risk factors that are indeed modifiable and could be avoided, if patients were even more and better educated. By giving adolescents comprehensive education on sexual health and sexually transmitted infections, like the Human Papilloma Virus, are transmitted and could be prevented. Encouraging and supporting safe sex practices, Human Papilloma Vaccination and regular screening could help adolescent to be proactive about their own health. Furthermore, spreading awareness about risk factors like smoking could also decrease the number of cervical cancer patients. Routing these programs into

general school curricula, could lead to implementing lifelong preventive habits, thus leading to lower infection rates, early detection of lesions, and a decrease in cervical cancer cases. (47)

Determining the correct residual tumor size after conization is of utter importance for further treatment planning, especially for those patients who are considered for fertility-sparing treatment options. Thus, the ability of Magnetic Resonance Imaging when distinguishing residual disease has become a fundamental requirement. This literature review showed that early-stage cervical cancer may remain undetected following conization as standard sequence imaging on its own frequently fails to identify tumors smaller than five millimetres, as post-biopsy inflammation, oedema or scarring can mimic pathological enhancement on Magnetic Resonance Images. (19, 20, 39) Nonetheless, multi-planar imaging supported by special modalities like diffusion-weighted imaging and dynamic-contrast enhanced Magnetic Resonance imaging likely increases the detection of residual cervical cancer. (22, 35) Restricted diffusion and increased vascularity highlighted by these techniques are highly linked to tumoral tissue and viability. Furthermore, new techniques in computational methods like radiomics show promising results in the detection of fine details not always detectable by the human eye alone. Even though new emerging technologies show promising results, it became clear that those are not yet well explored and need further evaluation and optimization. In such cases conducting a larger scale validation could be useful. Performing prospective studies with standardized protocols could confirm the universal utility of advanced imaging and radiomics for detecting small residual cancerous cervical lesions leading to refined guidelines.

Another important aspect that cannot be ignored is the need of actively integrating Magnetic Resonance Imaging into multidisciplinary diagnostic and treatment planning for gynaecological malignancies. Facilitating radiologists' expertise in interpretating those images will enhance future patient outcomes. (37)

Additionally, this review mentions the potential benefit of combining Positron Emission Tomography Computer Tomography and Magnetic Resonance Imaging. Supporting the assessment of local tumor extent and soft tissue contrast with metabolic data could be helpful when differentiating between post-conization inflammation and viable residual cancer. Here, more in depth hybrid studies, for example comparative and longitudinal studies, should be done to further clarify and optimize the approach of combining both radiological modalities regarding residual cervical cancer. It is also important to mention that in order to fully implement Positron Emission Tomography Computer Tomography and Magnetic Resonance Imaging it is necessary to define clear clinical guidelines and assess cost-effectiveness.

10. References


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