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Carcinoma of the uterine cervix – Aspects on preoperative staging and assessment of treatment effect using magnetic resonance imaging

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Carcinoma of the uterine cervix – Aspects on preoperative staging and assessment of treatment effect using magnetic resonance imaging

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

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Magic happens when you don’t give up, even though you want to.

To Alexander and Beatrice

POPULAR SCIENCE SUMMARY OF THE THESIS

Cancer in the uterine cervix (CC) is as common as colonic cancer in women worldwide. Only breast cancer and lung cancer are more common. Unfortunately, CC affects the young, with half of the patients being younger than 50 years. In 2020, 565 women were diagnosed with CC in Sweden. Due to regular screening programs, the disease is often diagnosed at an early stage with good prognosis, but overall, the 5-year survival is merely 50%. A suspected CC needs to be confirmed usually by excising a cone-formed piece of the uterine cervix, so called conization, for histopathological diagnosis. For small, shallow tumours, the conization at the same time serves as the treatment. When the tumour is obvious, a small tissue sample is instead collected for histopathological diagnosis and the more invasive conization can be avoided. Small tumours are treated with surgery i.e., removal of the uterus and lymph nodes, and sometimes also the ovaries. Complications are common, including symptoms from the urinary bladder, the bowel, leg oedema and sexual problems. Locally advanced tumours are instead treated with a combination of chemotherapy and radiotherapy. Sometimes surgical treatment must be supplemented with chemoradiotherapy (CRT) often resulting in higher morbidity.

As the extent of the tumour determines the choice of treatment, accurate tumour staging is crucial. When the first study of this thesis started, the tumour stage was established through clinical examination under anesthesia (EUA), even though most patients with biopsy verified CC since 2003 also underwent a magnetic resonance imaging (MRI) as part of the diagnostic work-up at Karolinska. Gynaecological malignancies, although except for CC, are often primarily evaluated with transvaginal ultrasound (TVS), performed by gynaecologists. Imaging was incorporated as an adjunct to clinical tumour staging for treatment decisions by the Federation of Gynaecology and Obstetrics (FIGO) in 2009, but in the revised FIGO staging from 2018, imaging is an integral part of the work-up, contributing to more accurate staging, including evaluation of lymph node metastases, which is an important prognostic factor.

CRT is successful in merely half of the patients. There is no consensus on the optimal time-point for imaging to evaluate treatment response, but this is usually performed about 3 months after the treatment. This wait is a tough period for many patients before they learn whether the treatment was successful or not. Therefore, an earlier and predictive imaging evaluation would be advantageous, to identify patients who will benefit from the treatment, versus those who will not, and instead should receive other treatments. This would enable more individualized treatment, decrease adverse effects and morbidity, and potentially improve therapy outcome.

Study I included 57 patients with CC who underwent MRI before surgery. Two experienced radiologists reviewed three different combinations of MRI-sequences to identify those necessary for adequate tumour staging. The first basic standard protocol included transaxial and sagittal T2-weighted images, and transaxial T1-weighted sequences. Addition of oblique

sequences altered the tumour stage in 4/57 (7%) of patients, three patients were upstaged, and one was downstaged, while further addition of contrast-enhanced sequences showed even less impact with upstaging of one patient (2%). Thus, addition of oblique and contrast-enhanced MRI-sequences had little impact on the staging and are therefore redundant. Information on previous conization was found crucial for the reviewing radiologist to avoid MRI interpretation errors.

Study II In this study the10-year outcome was compared in 102 women with visible versus non-visible tumours on MRI, all treated with surgery. 42 of the patients received brachytherapy before surgery to shrink the tumour. 56 of the patients had visible tumours, and 46 had non-visible tumours on MRI. Conization was performed prior to MRI in 13/56 (23%) vs 25/46 (54%) of those with visible and non-visible tumours, respectively. At follow-up 18/102 (17.6%) women had relapsed and 15/102 (14.7%) were diseased. Similar 10-year outcome was found regardless of visibility on MRI. Outcome was significantly better for patients having performed conization compared to those who had not.

In *Study III* 60 patients with all stages of CC were examined with both MRI and TVS. The agreement regarding tumour staging was compared among experienced and less experienced radiologists and gynaecologists in their image review. All MRI reviewers and all less experienced gynaecologists attended a short training session prior to their review. It was found that the agreement was higher among MRI reviewers, regardless of experience, than for TVS reviewers. Only for one of the measured staging parameters, agreement was associated with the gynaecologists´ experience.

Study IV is a pilot-study including 15 patients, aiming to explore the value of anatomical MRI (T2-weighted sequences) and functional MRI (diffusion-weighted sequences) to differentiate patients with successful treatment from those with unsuccessful treatment outcome, and to define the best time point for this assessment in relation to the administered treatment. MRI was performed before and at 3, 5, and 12 weeks after treatment start. The maximum size of the tumour was measured, visibility on functional images and apparent diffusion coefficient (ADC) were recorded. 8/15 patients had “successful” treatment, and 7/15 relapsed during the study period. A combination of tumour size at MRI before treatment together with visibility on diffusion-weighted sequences of the tumour at 5 weeks, seems to predict treatment success.

ABSTRACT

Background Uterine CC mainly affects young women as it is caused by persistent HPV infection most often acquired during adolescence. Early-stage disease is treated with surgery, and locally advanced disease with chemoradiotherapy. Both treatment methods are associated with infertility and morbidity. Combined treatment modalities (both surgery and CRT) should be avoided as this has negative impact on morbidity. The choice of treatment depends on the tumour stage at diagnosis, and accurate initial staging is therefore essential. MRI has been an integral part of the routine diagnostic work-up for CC patients at Karolinska since 2003. MRI is also an important tool in the evaluation of treatment, which traditionally is performed after the treatment is completed. However, identification of imaging parameters for prediction of the treatment effect early during the therapy, would provide more individualized treatment. This would enable early change of the treatment strategy for those predicted to experience treatment failure and may contribute to less morbidity in others.

Aim The overall aim of this thesis was to identify an optimal examination protocol for MRI of the pelvis in patients with biopsy verified CC scheduled for surgery, improve identification of risk factors for recurrence, and identify MRI standards for therapy monitoring, in particular the timing of MRI in relation to treatment.

In *Study I* 57 patients with early-stage disease treated with surgery were evaluated with three different sets of MR protocols. We found that magnetic resonance tumour (mrT), magnetic resonance lymph node (mrN) and magnetic resonance distant metastases (mrM) stages were the same for a basic standard protocol including transaxial and sagittal T2-weighted images, and transaxial T1-weighted sequences, as for protocols with the addition of oblique and/or contrast-enhanced sequences. The inter-observer agreement was “good” between readers for all three protocols. The agreement among readers was negatively affected by prior conization of the patient.

Study II included 102 patients comprising the patients in study I with the addition of patients receiving brachytherapy prior to surgery. Two main groups were compared regarding 10-year outcome, those with visible and non-visible tumours on pre-treatment MRI. Tumour recurrence was seen in 17.9% of patients with visible tumour, and in 17.6% of patients with non-visible tumours. Recurrence free survival (RFS) was longer for patients having undergone conization prior to MRI than for those who had not.

Study III The inter-observer agreement among experienced and less experienced observers of MRI and TVS was investigated in 60 patients with all stages of CC for this study. For all MRI observers, the inter-observer agreement was “good” for assessment of stromal- and parametrial invasion (PMI). Only for tumour detection was inter-observer agreement lower for the less experienced observers. For TVS observers, the agreement was “moderate” for assessment of tumour detection, stromal- and parametrial invasion. The agreement was significantly higher among experienced TVS observers regarding PMI.

Study IV was designed as a pilot-study including 15 patients with stage IB2-IIIB scheduled for concomitant chemoradiotherapy (CRT). MRI was performed at baseline, 3 weeks, 5 weeks, and 12 weeks after treatment start. During follow-up, 7 patients relapsed, ("poor prognosis group", PP), 8 patients did not relapse ("good prognosis group", GP). We compared tumour size, change in size (Δsize), ADC and change in ADC (ΔADC), and tumour visibility on MRI at all four time points between the PP and GP group. By combining tumour size at baseline with tumour visibility on DWI at 5 weeks, the area under the curve (AUC) in receiver operating characteristics (ROC) analysis reached 0.83.

The findings of this thesis confirm the value of MRI for CC staging and therapy follow-up. In early-stage disease, unequivocally without parametrial invasion, evaluation consisting of a basic standard protocol including transaxial and sagittal T2-weighted images, and transaxial T1-weighted sequences is not improved by addition of oblique and contrast-enhanced sequences. Interpretation of the images is affected by prior conization but the clinical importance of detecting small tumours on MRI can be questioned as tumour visibility in early-stage disease does not affect long term outcome. Interobserver agreement is higher for MR than for TVS. A reasonable level of inter-observer agreement can be achieved for both experienced and less experienced observers of MRI and TVS, after attending a short basic training session on evaluation of cervical tumours. Prediction of disease recurrence seems feasible by combining visibility on high b-value diffusion-weighted imaging (DWI) at 5 weeks after treatment start with tumour size at baseline MRI. For all four studies in this thesis, the limited number of patients must be considered, and results need to be confirmed in larger cohorts.

LIST OF SCIENTIFIC PAPERS

I. **Preoperative MR staging of cervical carcinoma: are oblique and contrast-enhanced sequences necessary?**

Fridsten S, Hellström A.C., Hellman K, Sundin A, Söderén B, Blomqvist L
Acta Radiol Open 2016 Vol. 5 Issue 11 Pages 2058460116679460

II. **Visible vs non-visible tumours on MRI in uterine cervical carcinoma – a ten-year follow-up**

Fridsten S, Sundin A, Blomqvist L, Hellman K
Manuscript

III. **Interobserver agreement of transvaginal ultrasound and magnetic resonance imaging in local staging of cervical cancer**

Pálsdóttir K, Fridsten S, Blomqvist L, Hasselrot K, Alagic Z, Sundin A, Epstein E
Ultrasound Obstet Gynecol 2021 Vol. 58 Issue 5 Pages 773-779

IV. **Uterine cervical cancer; early treatment assessment with T2- and diffusion-weighted MRI**

Fridsten S, Hellman K, Sundin A, Blomqvist L
Manuscript

Scientific papers not included in the thesis

Impact of MRI in the management and staging of cancer of the uterine cervix

Stenstedt K, Hellström A.C., Fridsten S, Blomqvist L
Acta Oncol 2011 Vol. 50 Issue 3 Pages 420-6

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LIST OF ABBREVIATIONS

AC	Adenocarcinoma
ACRIN	American College of Radiology Imaging Network
ADC	Apparent Diffusion Coefficient
AUC	Area under the curve
CC	Cervical carcinoma
CIN	Cervical intra-epithelial neoplasia
CT	Computed Tomography
DDR	Deoxyribonucleic acid
DNA	DNA damage response
Dnr	Diary number
DWI	Diffusion weighted imaging
EBRT	External beam radiation therapy
ESUR	European Society of Urogenital Radiology
^{18}FDG/PET/CT	^{18}Fluorodeoxyglucose positron emission tomography and computed tomography
FIGO	The International Federation of Gynaecology and Obstetrics
GOG	Gynecologic Oncology Group
GP	Good prognosis group
GdCA	Gadolinium contrast agent
HPV	Human papillomavirus
ICBT	Intracavitary brachytherapy
IVIM	Intravoxel incoherent motion
ƙ	Cohens Kappa
MR	Magnetic Resonance
MRI	Magnetic Resonance Imaging
mrT	Magnetic resonance tumour stage
mrN	Magnetic resonance lymph node stage
mrM	Magnetic resonance distant metastasis stage

OS	Overall survival
pN	Pathological lymph node stage
pM	Pathological distant metastasis stage
PP	Poor prognosis group
pT	Pathological tumour stage
PACS	Picture Archiving and Communication System
PET/CT	Positron Emission Tomography and Computed Tomography
PMI	Parametrial invasion
RFS	Recurrence Free Survival
ROC	Receiver operating characteristics
ROI	Region of interest
SCC	Squamous cell carcinoma
TVS	Transvaginal ultrasound
VAS	Visual Analogue Scale

1 INTRODUCTION

1.1 EPIDEMIOLOGY

Cervical cancer (CC) is the third-fourth most common malignancy in women worldwide after cancer in the breast and lung, competing with colon cancer [1-3], corresponding to approximately 600 000 new cases, and 340 000 deaths in 2020, mainly affecting women younger than 50 years of age. CC constitutes more than 11% of all new cancers in the age group 20-49 years, only breast cancer has a higher incidence worldwide [4]. Its incidence is much higher in developing countries, accounting for 15% of female cancers, as opposed to 3.6% in industrialized countries [5, 6]. In 36 countries, mainly in Africa and South America, the most common cause of cancer related deaths in women was CC, in 2020 [7]. Almost 50 000 women in Europe suffered from uterine cervical cancer in 2012. In Sweden 541 women were diagnosed with CC in 2016, with the highest incidence in the age group 35-39 years, and with a second peak in those around 70 years [8, 9]. The age standardized incidence rate of CC in Sweden dropped from 15.1 cases/100 000 in 1970 to 8.8 cases/100 000 in 2016 [9]. This difference was due to the initiation of cytological screening programs in the 1960's and 1970's. Even though 82% of women aged 23-60 years participate in this screening program, there was a 20% increase in the incidence of CC during 2014-2015 compared to 2002-2013, when the national incidence was around 450 cases yearly. In 2020, there were 565 new cases in Sweden, corresponding to an incidence of 11/100 000 and 106 deaths. The incidence in 1970 was 19.2/100 000 with 339 deaths [10, 11]. The incidence in adenocarcinomas (AC) increased approximately 30% compared to 12% increase in squamous cell carcinomas (SCC) between 2007 and 2016 [12].

1.2 SCREENING

Population-based screening to detect precursors of CC and early detection of invasive disease was introduced in Sweden in 1964, every third year in women 23 to 50 years, and every seventh year in those 51 to 64 years. However, it was not until 1977 the screening had become a routine in the whole country. A quarter of all patients are diagnosed with CC after 65 years of age, often at an advanced stage with poor prognosis [13]. The 5-year relative survival is 95% among women participating in the screening compared to 69% among symptomatic cancers [14]. The introduction of the screening programs has significantly reduced mortality among patients diagnosed before 40 years of age, because of earlier diagnosis of invasive disease. The same trend has not been seen in patients diagnosed at an older age, due to less extensive screening and a strong association between older age and poor prognosis [15, 16]. However, the screening program has in recent years been extended to 64 years of age to include more older women.

1.3 HPV

Sexually transmitted infection with Human Papilloma Virus (HPV) is involved in the development of CC [17]. There are hundreds of different strains of HPV of which forty are sexually transmitted [18, 19]. Some strains have an oncogenic potential, so-called high-risk HPVs (HRHPV). The most common strains of HRHPV are HPV16, 18, 31, 33, 35, 45, 52 and 58. HPV 16 and 18 are found in more than 70% of all invasive CCs and HPV 16, 18 and 45 are present in 94% of the cervical adenocarcinomas [20].

Development of invasive CC involves a gradual carcinogenesis from pre-cancerous lesions, cervical intraepithelial neoplasia (CIN) 1-3. DNA methylation is important in this process as it regulates the expression of several genes, and it has been shown that HPV methylation is significantly higher in CC than in CIN3 [21]. Genomic instability is the result of over-expression of oncogenes as well as down-regulation of tumour suppressor genes [22].

HPV inactivates part of the DNA damage response (DDR) [23]. There are two important viral oncogenes, HPV-E6 and HPV-E7 [24]. The E7 oncoprotein inactivates Retinoblastoma 1 (Rb 1) tumour suppressor gene affecting proliferation signals leading to uncontrolled growth. E6 degrades the p53 tumour suppressor which constitutes an integral component of DDR, thereby impairing activation of cell cycle checkpoints to provide time for DNA repair and the induction of apoptosis upon DNA damage [23].

In order to prevent CC, vaccines against HPV 16 and 18, Gardasil® and Cervarix®, were 2012 introduced nationwide in Sweden for girls aged 9-13 years, in Sweden [25], and in boys 2020.

1.4 HISTOLOGY

The most common form of CC is squamous cell carcinoma (SCC) which accounts for 70-80% of all CC followed by adenocarcinoma (AC) constituting 20-25% of CC [9, 26, 27]. These two forms differ in several respects, smoking being a risk factor for SCC, but not for adenocarcinoma, while obesity is associated with AC, but not with SCC [28] and presence of HPV 18 is seen in 50% of AC compared to 15% in SCC [29]. Adenocarcinoma is associated with a poorer prognosis and higher risk for distant recurrence [30, 31]. However, with early node negative SCC and AC, i.e., stages I-IIA, in patients treated with hysterectomy and lymphadenectomy the 10-year survival was the same [27]. Less common types are adenosquamous carcinoma, a mixed tumour with both glandular and squamous cell origin, and the rare, but very aggressive, neuroendocrine small cell carcinoma. At diagnosis, 73% of patients with these aggressive tumours present with extra-pelvic disease to lymph nodes, lungs, liver, brain or bone [32, 33].

1.5 PROGNOSTIC FACTORS

In the majority of women infected with HPV, the infection is transient. Immune competence plays a role in the path of the HPV infection and cervical carcinogenesis. HPV infection is

found in more than 25% of women within a year after becoming sexually active. The risk of becoming infected is associated with early age of sexual debut, number of sex partners and duration of use of oral contraceptives. Intrauterine device (IUD)is suggested as a protective cofactor in the development of cancer, possibly by triggering cellular immunity [34]. Smoking doubles the risk of CIN3/CIS and invasive CC with duration and intensity, as well as reduces the risk two-fold by quitting [35].

Prognostic factors are clinical stage, lymph node metastases, neuroendocrine differentiation, and age. Other prognostic factors, evaluated in the surgical specimens, include tumour size, parametrial involvement, depth of stromal invasion, histological subtype and lymphovascular space invasion (LVSI). The 5-year survival is only 10% for advanced disease stage IVB, compared to almost 100% in stage IAI disease [36]. The 5-year survival rate is 66%, 40%, 42% and 22% for stages IIB, IIIA, IIIB and IVA respectively [36, 37]. Clinical stage and presence of positive lymph nodes are the only independent prognostic factors for 10-year survival rates in patients with stage IA2-IIB. LVSI has a negative impact on 10-year overall survival [38].

Both Cisplatin and radiotherapy activate signaling within the DNA damage response (DDR). Tumour cells respond to damage by activation of DDR.

The expression of vascular (VEGF) and epidermal (EGFR) growth factors, as well as tumour hypoxia affects survival ([39].

The receptor tyrosine kinase (RTK) signaling pathways play an important role in cell proliferation, differentiation, survival, migration, and adhesion. Co-expression of RTKs is associated with aggressive biological behavior. For example, positivity for EGFR and HER2 correlates with presence of lymph node metastases and shorter RFS in AC. Cetuximab is an EGFR targeting agent, and trastuzumab targets HER2 [40].

High signaling via IGF-1R (Insulin-like growth factor-1 receptor) and reduced apoptotic signaling, leading to tumour initiation and progression, are associated with poor response to radiotherapy and an increased risk for relapse [41]. Small molecule tyrosine kinase inhibitors and antibodies have mainly experimentally been used as IGF-1R signaling inhibitors with promising results in ovarian and endometrial cancers [42].

1.6 SYMPTOMS

In the early stages, there are seldom any symptoms, and most early-stage carcinomas are detected through the screening programs. In more advanced stages, symptoms such as vaginal discharge and vaginal bleeding in conjunction with intercourse, and pelvic pain are common.

1.7 DIAGNOSIS

The tumour can often be visualized at gynaecologic examination and the histology verified by a tissue biopsy. When malignant cells are captured at screening, invasive disease is often

determined by biopsy or cone biopsy where the latter can serve both as a diagnostic tool, but also constitutes the treatment, when the tumour is limited to the resected cone.

1.8 STAGING

CC is the only gynaecological disease that still is staged clinically. In 1928 a need for statistical data on radio-therapeutic results for uterine CC was acknowledged. This could only be accomplished given that different institutions produced results in a uniform and consistent manner. The first staging system was published in 1929, known as the League of Nations Classification for Cervical Cancer, which provided a set of recommendations and guidelines to classify cervical cancer into different stages [43, 44]. There have been changes in the classification since then, and it still constitutes the basis of the current staging system. The International Federation of Gynaecology and Obstetrics (FIGO) has been the main sponsor for the last 60 years, and also includes other gynaecological cancers than CC.

The clinical CC staging according to the FIGO system [45] included gynaecological examination during anesthesia, cystoscopy, rectoscopy, intravenous urography and chest X-ray. This staging was not based on scientific rationale but instead accomplished to be able to include countries with high incidence of CC and limited radiological resources, and thereby to compare results globally. However, clinical staging has several integral limitations. Notably, the most important prognostic factor [46, 47], lymph node status is not considered. Also, the craniocaudal length of the tumour, another prognostic factor, is disregarded [48]. Clinical staging underestimates the spread of CC, compared to surgical exploration including paraaortic lymph node sampling, in up to 32% in stage IB, and in 44–67% of those with stage II–IV disease [49]. A decrease in accuracy from 79% to 53% was seen excluding patients with stage ≤ IIA [50]. The FIGO staging system was revised in 2009 [51] promoting diagnostic imaging for assessment of tumour size [51]. Tumour volume and presence of PMI should be registered if MRI was performed. However, the value of MRI both for staging and monitoring treatment response, as well as for planning radiotherapy and detection of relapse was evident already in 2005 [52]. MRI adds important information, especially when examination under anesthesia is difficult, such as in obese or pregnant patients [53]. For study I and II in this thesis, the FIGO staging from 1994 was applied [54] and for study III and IV the staging was performed according to FIGO 2009 [55].

The most recent update on FIGO staging was published 2019 [56] now including imaging and pathology in addition to clinical findings, and finally incorporating the important prognostic factor “lymph node metastasis” into the staging system. A pictorial overview of the 2018 Figo staging system is shown in Figure 1. When in doubt between two stages, the lower stage should be assigned.

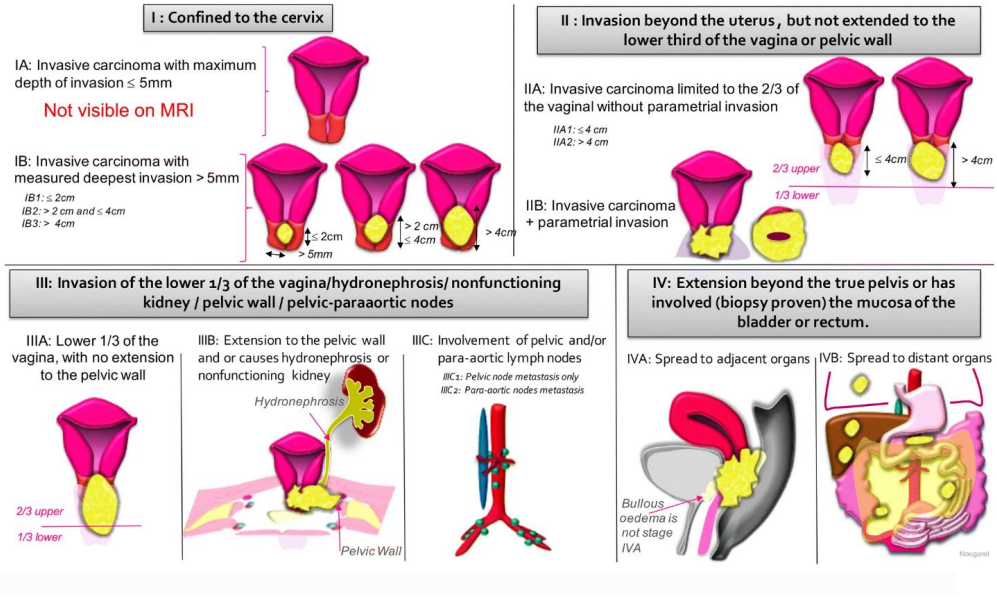


Figure 1. Pictorial overview of the 2018 FIGO staging system. Reprinted with permission from Bhatla, N., et al., *Revised FIGO staging for carcinoma of the cervix uteri.* Int J Gynaecol Obstet, 2019. **145**(1): p. 129-135.

1.9 TREATMENT

The treatment strategy depends on the tumour stage at diagnosis. Surgery is the treatment of choice in early stages. Depending on size and extension, different types of surgery are offered. When the tumour is less than 2cm, fertility sparing surgery, trachelectomy, including pelvic lymphadenectomy is one option. For microscopic tumours, conization is a treatment alternative. All other treatment options result in secondary infertility, and early menopause if the ovaries are removed.

In more advanced tumours less than 4cm, and confined to the cervix, radical hysterectomy and pelvic lymphadenectomy is the treatment of choice. Patients with tumour extending beyond the cervix, including lymph nodes positive at ^{18}F-FDG PET/CT [57], or exceeding 4cm in size, will be offered radiotherapy with concomitant chemoradiotherapy (CRT) and brachytherapy.

Patients selected for surgery might need chemoradiotherapy (CRT) after surgery, for example in the case of positive lymph node metastases. Further, patients having other risk factors at histology such as tumour in the outer 2/3 of the cervical stroma, tumour larger than 4cm or positive LVSI might also be recommended additional radiotherapy [58-60]. However, the survival benefit of adjuvant CRT compared to radiotherapy alone in node-positive early-stage CC is only seen in SCC, not in AC [61].

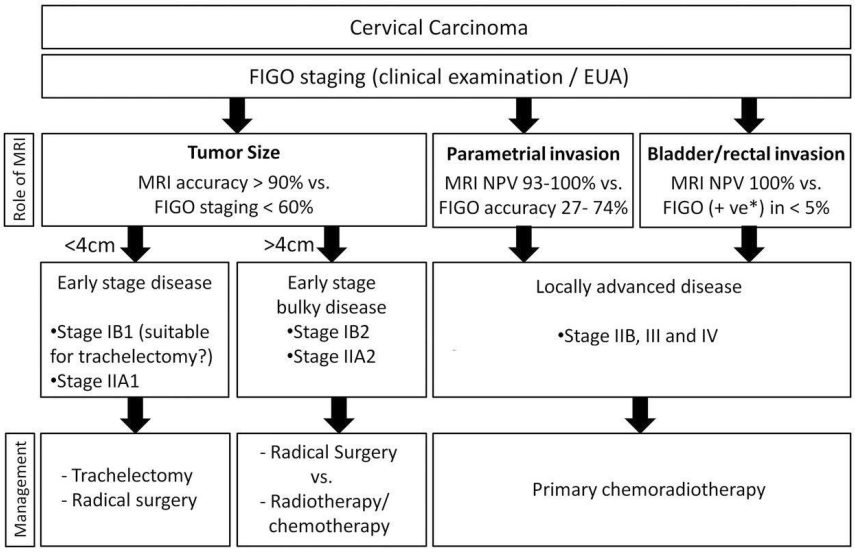


Figure 2. Chart shows potential role for MR imaging in evaluation of patients with cervical carcinoma. Note that presence of enlarged lymph nodes does not change FIGO staging of cervical carcinoma; however, clinical management pathway will alter depending on presence or absence of lymphadenopathy. Lymph nodes can be assessed with MR imaging, CT or PET/CT. *EUA*=examination under anesthesia, *NPV*=negative predictive value, +ve*=positive cystoscopy and/or sigmoidoscopy finding in <5% of cases. Reprinted with permission from Sala E, R.A., Freeman SJ, et al, *The Added Role of MR Imaging in Treatment Stratification of Patients with Gynecologic Malignancies: What the Radiologist Needs to Know.* Radiology, 2013. **266**(3): p. 717-40.

1.10 TREATMENT STRATEGIES ACCORDING TO FIGO STAGE 2009

Primary surgical treatment:

Stage IA1 without LVSI

- Simple hysterectomy or cone biopsy

Stage IA1 with LVSI, IA2 (with or without LVSI)

- Simple hysterectomy with vaginal cuff or trachelectomy or cone biopsy
- Pelvic lymphadenectomy or sentinel node biopsy

Stage IB1 and IIA1

- Radical hysterectomy +/- salpingoophorectomy or trachelectomy if tumour <2cm
- Pelvic lymphadenectomy

Primary chemoradiotherapy:

Stage IB2, IIA2, IIB–IVA (and earlier stages with unequivocal lymph node metastases)

- External radiation of tumour, cervix, uterus and pelvic lymph nodes.
- Intrauterine brachytherapy and concomitant cisplatinum weekly, optimally for 6 cycles.
- If necessary, boost of lymph node metastases +/- extended field (paraaortic)

Adjuvant therapy after primary surgery:

- Lymph node metastases (pN+)
- Surgical margin <5mm
- Tumour ≥ 4 cm
- Parametrial involvement
- Neuroendocrine small cell carcinoma
- Individual assessment in combinations of narrow margin, LVSI, deep stromal invasion, tumour size and histology

1.11 OUTCOME/SURVIVAL

The 5-year age standardised relative survival for CC in Sweden has merely increased to the current 69%, compared to 60% 50 years ago. This is in contrast to the 5-year age standardised relative survival in breast cancer, which has increased to 90% from 63% [62]. Bjurberg et al. found 74% 5-year overall survival for patients with CC in 2011-2015 [63]. The prognosis is dependent on the FIGO stage including lymph node metastases and the 5-year survival ranges from 10% for stage IVB disease to almost 100% in stage IA. Prognosis is also correlated to high-risk histological tumours such as adenosquamous and neuroendocrine carcinomas [64].

1.12 DIAGNOSTIC IMAGING

1.12.1 MRI

MRI is routinely used to evaluate patients with CC [65]. The extent of the primary tumour and soft tissue disease is best visualized with MRI [66] and allows for assessing tumour size, location, parametrial and side wall involvement, bladder or rectal wall invasion as well as lymph node metastases. Small volume tumours i.e., <1cm can be difficult to detect with MRI and may on T2 weighted images be indistinguishable from post biopsy inflammatory changes [67]. According to an ACRIN/GOG trial, MRI was insufficient in evaluation of the cervical stroma [68], even if earlier studies have shown an accuracy of 76% [69, 70].

MRI is superior to clinical staging regarding tumour size, ranging between 70-94% [69, 71-74]. Staging accuracy for MRI ranges between 75-96% [70, 72, 75-78] and 86% for CC stage IIB or higher compared to 47-66% for clinical staging, ranging between 78% (stage I) and 23% (stage III). The sensitivity for detecting PMI on MRI is reported to be 74% (range, 68–79%) [76]. With an intact stromal ring around the cervix on MRI, the negative predictive value of PMI is 94–100% [52, 79-81]. Functional MRI with diffusion-weighted imaging

(DWI) has also emerged as an important tool with improved accuracy for initial staging, response assessment and treatment follow-up in CC [82].

Patient preparation is essential to minimize bowel motion artifacts and achieve optimal imaging. Patients are therefore instructed to fast for at least 4 hours prior to examination as well as administering a tiny bowel enema, to empty the rectum. Antiperistaltic agents are administered by an intramuscular injection of glucagon or butyl-scopalamine, immediately prior to imaging.

In 2011, the female imaging subcommittee of the European Society of Urogenital Radiology (ESUR) published a consensus document on how to perform MRI in CC and what must be included in a pretreatment protocol, i.e., a combination of at least two T2-weighted (T2W) sequences obtained in the sagittal and oblique planes (perpendicular to the cervical canal) and T1-weighted (T1W) sequences of the upper abdomen and pelvis [83]. Since then, the role of functional MRI with diffusion weighted imaging (DWI) has also been investigated.

1.12.2 Diffusion weighted imaging (DWI)

Diffusion weighted imaging (DWI) with MRI including measurement of the Apparent Diffusion Coefficient (ADC), is emerging as a non-invasive biomarker for tumour characterization and prediction of response [84].

DWI is based on the Brownian motion, or free diffusion, of water molecules. This phenomenon is named after the botanist Robert Brown, who in 1827 observed the movement of pollen grains in water. Albert Einstein in 1905 explained the effect caused by water molecules colliding randomly with microscopic particles. In 1855, Adolf Frick mathematically described diffusion, the net movement of a substance from a region with high concentration to a region of low concentration. Einstein linked diffusion to Brownian motion and was able to prove the existence of atoms and molecules. Biological tissues, and tumours, are complex structures with few similarities to Einstein's model of Brownian motion, which is why the mechanisms behind diffusion of water in tissues remain unclear [85].

The use of DWI allows for detection of both solid and cystic lesions but should be used in conjunction with other imaging sequences. Both detection and characterization of lesions depend on tissue cellularity. DWI is achieved by applying varying degrees of diffusion weighting whereby several so called b-values (typically 3) are used, that will allow for calculating the ADC, result of which is displayed in a separate image volume. Increased cellularity is associated with impeded diffusion and a reduction in the ADC, a quantitative measure of tissue diffusivity. The apparent diffusion of water in tissues also reflects the tortuosity of the extracellular space, integrity of cell membranes and viscosity of fluids [86]. The movement of water molecules is not random in biological tissues but impeded due to interaction with tissue compartments, cell membranes and intracellular organelles and can be categorized as intracellular, extracellular, or intravascular. Greater movement of water molecules is seen in tissues with low cellularity, or tissues consisting of cells with disrupted membranes [87].

Impeded or “restricted” diffusion is typically seen in tumours, cytotoxic edema, abscesses, and areas of fibrosis. However, certain normal tissues that are highly cellular also demonstrate restricted diffusion, such as lymph nodes and the endometrium, and should not be misinterpreted as pathological findings.

Adding DWI to conventional MRI imaging sequences is beneficial as it contributes to a higher reader confidence, higher sensitivity of tissue infiltration and improved tumour-grading in CC [88]. Higher ADC values are associated with more favorable histology and differentiation [84].

1.12.3 IVIM (Intravoxel Incoherent Motion)

IVIM is an extension of DW-MRI by using an increased number of b-values i.e., additional degrees of diffusion weighting. In biologic tissues, microscopic motions of water include both diffusion and microcirculation in the capillaries. IVIM refers to microscopic movement of water molecules due to diffusion and capillary perfusion, initially described by Le Bihan et al. in 1986 [89]. IVIM images are quantified by ADC, which integrates the effect of both microcirculation perfusion and pure molecular diffusion. At low b values, data obtained are dominated by perfusion effects, while signal at high b values is mainly attributed to diffusion. Perfusion effects may consequently be accentuated by acquiring data at multiple low b-values, allowing maps to be made of pseudo-diffusion or perfusion-related incoherent microcirculation (D*), and perfusion fraction (f).

IVIM adds another dimension to the MRI information that may be utilized during the treatment, possibly distinguishing responders from non-responders. It is currently not used in clinical practice in the evaluation of CC, but studies have shown promising results in early treatment prediction and response monitoring [90, 91].

1.12.4 Contrast agents

Gadolinium chelate contrast agents (GdCA) are paramagnetic and affect the proton’s relaxation time in tissues containing contrast agent and water. For MRI of the pelvis, extracellular contrast agents are used, which are excreted by filtration through the kidneys, potentially nephrotoxic. A rare disease, nephrogenic systemic fibrosis (NSF), was first described in 1997 in patients with chronic kidney disease, and later, in 2006, associated with the administration of GdCA. The disease includes fibrosis of the skin, but can also affect internal organs, and may be lethal. Patients at risk are those with severely impaired renal function, and patients in dialysis. Therefore, all patients should be screened for impaired renal function [92] before receiving GDCA. In 2014, it was reported that GdCA could accumulate in the brain [93]. Therefore, GdCA should be used with care, and only when there is a clear indication for contrast-enhanced MRI.

1.12.5 Ultrasound

Transvaginal ultrasound (TVS) can be used in staging of CC but is not part of the routine. Fischerova et al. have shown similar accuracies for transrectal ultrasound and MRI regarding

tumour detection and parametrial infiltration [94]. Moloney et al. reported higher sensitivity rates for TVS than for MRI, 86% vs 40% for detection of parametrial infiltration. However, both the specificity rates and the accuracy rates were higher for MRI compared to TVS, 79 vs 20% and 89% vs 79% respectively [95]. Ultrasound is dynamic, and the operator can feel resistance and use the “sliding organ sign”. Ultrasound is operator dependent and information on nodal status is not possible due to its narrow field of view [66].

Ultrasound has not proven satisfactory in evaluating treatment response to chemoradiation-based therapy in patients with locally advanced CC [96] nor in detecting residual disease after chemoradiotherapy [97].

1.12.6 ^{18}FDG-PET/CT

^{18}Fluorodeoxyglucose-positron emission tomography/computed tomography (^{18}FDG-PET/CT) may be used in the initial evaluation of CC, but is not yet well established [98]. Small tumours, 7 mm or less may be detected with ^{18}FDG-PET/CT [99]. Because of its low 53% accuracy for local staging PET/MRI with sensitivity and specificity exceeding 90% is desirable but is not yet used in the clinical setting [100]. The sensitivity for detection of lymph node metastases with ^{18}FDG-PET/CT ranges between 79-91% and the specificity ranges 95-100%. The accuracy decreases for small lymph nodes, less than 5mm [101]. For detecting lymph node metastases in CC, ^{18}FDG-PET/CT has the highest specificity, and DWI-MRI shows the highest sensitivity [102]. Despite this high specificity, microscopic metastases will still be missed. Also, distant metastases are detected with ^{18}FDG-PET/CT. Combined imaging including morphological, functional, and metabolic data facilitates treatment planning, treatment response assessment, surveillance, and prediction of prognosis [103].

2 LITERATURE REVIEW

Study I At the start of this PhD project, our protocols for primary MRI work-up in patients with biopsy verified CC agreed with the ESUR (European Society of Urogenital Radiology) guidelines [83]. This included at least two T2-weighted sequences in sagittal, axial oblique or coronal oblique planes of the pelvis, and T1-weighted transaxial sequence from the left renal vein to the symphysis for lymph node detection. T2-weighted images are best for detection and delineation of the tumour and its relation to the uterus, parametria and adjacent organs [73]. At the time, contrast-enhanced sequences were considered merely optional for staging although required for treatment follow-up. ESUR also suggested that contrast-enhanced sequences improved visibility of tumours <2cm. DWI was also considered optional, however recommended for detection of residual disease after chemoradiotherapy and aiding in evaluation of lymph nodes. Following the revised FIGO staging 2018 [54], the ESUR imaging guidelines were updated [104] and the MRI protocol now includes both T2-weighted sequences and DWI, preferably applying matching acquisition planes, field of view and slice thickness for direct comparison. T2-weighted sequences are acquired in the sagittal and axial oblique (perpendicular to the cervix) planes and transaxial T1-weighted sequences without and with fat saturation are now recommended as is DWI, but contrast-enhanced MRI remains optional. Another addition in the guidelines is a structured MRI report, including tumour size (largest dimension), distance tumour-internal cervical os (for fertility preservation), parametrial invasion, vaginal invasion, hydronephrosis, pelvic side wall invasion, bladder/rectal invasion, lymphadenopathy, adnexal mass/es, associated benign conditions and anatomic variants. Of note is that evaluation of the depth of stromal invasion is not included in the structured report, despite its prognostic significance [58-60]. The recommendation to use FDG-PET/CT in patients with FIGO stage ≥ IB3 for nodal and distant staging is also new since 2019. IVIM is not discussed in the guidelines. In the last 5 years, more than 20 studies on MRI-based radiomics in CC have been published regarding identification of prognostic factors, seven of which are focusing on prediction of lymph node metastases [105-107]. This is however not used in the daily routine.

Study II Prognostic factors in early-stage disease are tumour size, depth of stromal invasion and lymphovascular space invasion (LVSI) [58]. In the 1990's, before using MRI in the clinical work-up, clinical stage was one of the most important prognostic factors in CC patients [108, 109]. In more advanced tumours, prognostic factors identified on MRI are related to size and invasion of surrounding tissues, such as parametria, uterine body, vagina, pelvic side wall and bladder, together with pelvic lymph node metastases [110, 111]. The development in diagnostic imaging and staging has significantly improved since the addition of DWI and acknowledgement of lymph node metastases [54, 112]. The 5-year survival depends on the clinical stage and ranges from almost 100% for stage IA1 to 10% in stage IVB [38, 113]. In Sweden, the 5-year survival in CC was 69% in 2012-2016 and 60% in 1967-1971 compared to breast cancer with corresponding 5-year survival increasing from 64% to 90% from 1967- 2016[62]. This is consistent with global data on survival rates

ranging from 50 to70% [6, 114]. Despite high-resolution MRI, small tumours < 1cm may not be detected on MRI, and prior conization with loss of tumour volume can lead to misinterpretation, and thereby hampering the evaluation [115, 116]. There is a risk for underestimation of tumour when it is undetected on MRI [117]. High RFS is reported for MR-visible and MR invisible IB1 tumours as well as over 90% 5-year survival rates [118].

Study III MRI is used in the routine work-up of CC [65]. The extent of primary disease is best visualized by MRI due to excellent soft tissue contrast, enabling assessment relevant for staging such as location and tumour size, involvement of parametria end pelvic side wall, invasion of urinary bladder or rectal wall and presence of pelvic lymph node metastases. Already in 2003 MRI was shown to be superior to CT in CC staging [76]. The clinical evaluation of tumour size is inferior to that of MRI [71-74]. In a meta-analysis from 2013, Thomeer et al. compared clinical staging to staging according to MRI in patients with advanced stages of CC (≥ IIB) and found MRI significantly better than clinical examination in ruling out PMI and advanced disease [119]. MRI has a reported sensitivity for detection of PMI ranging between 68 and 79% [76]. More importantly, the negative predictive value (NPV) reaches 100% when the low signaling stromal ring around the cervix is intact [46, 52, 79, 80]. MRI detection of small tumours i.e. <1cm, is poor [50, 120]. For MRI evaluation of stromal invasion, the statements in different reports are conflicting, spanning from "not accurate" to 79% accuracy [50, 68, 70]. Several studies have compared MRI and TVS in patients with early-stage disease and found similar accuracy for assessment of stromal invasion and parametrial invasion, but higher detection rates by TVS for tumours <1cm [94, 95, 121]. Among experts with more than 10 years of experience, TVS was to MRI for assessing PMI although the level of experience for the MRI reviewers was not reported in this study [122].

As described in the Materials & Methods section, the MR examinations were performed using 4 different scanners, consisting of either 1.5T or 3T systems. Even though 3T systems can provide better image quality, due to the better signal-to-noise ratio, the image homogeneity is inferior, and the diagnostic accuracy regarding preoperative staging is not improved by using a 3T system [123].

Study IV MRI is widely used for the evaluation of treatment response [124]. The importance of volume regression rate during treatment on sequential MR examinations was reported in 1996 [125]. High resolution T2-weighted sequences are essential for response evaluation [70, 71], and is further improved by adding DWI [126, 127] as it contributes to improved tumour grading, sensitivity of tissue infiltration and reader confidence [88]. A review from 2015 [128], included four studies evaluating therapy response at 2 and 4 weeks after treatment start, and found the pooled mean ADC similar in patients with complete, partial or no response, demanding larger studies. Most of the earlier studies evaluated the response around 30 days after treatment start [129, 130].

3 AIMS OF THE THESIS

The overall aim of this doctoral thesis was to explore imaging in pretreatment staging and treatment assessment of uterine cervical carcinoma, its impact, and how it can be improved for the benefit of the patients.

The specific aims of each study were as follows:

Study I: To compare different combinations of MR sequences in preoperative staging to determine which sequences are necessary.

Study II: To explore the clinical impact of long-term outcome in visible versus non-visible uterine cervical tumours at baseline on high resolution MRI.

Study III: To assess the interobserver reproducibility among experienced and less experienced observers, using transvaginal ultrasound (TVS) and MRI in the evaluation of local tumour extension.

Study IV: To evaluate the best time point for predicting recurrence in patients receiving CRT using T2- and diffusion-weighted MRI.

4 MATERIALS AND METHODS

4.1 ETHICAL CONSIDERATIONS

All four studies were approved by the regional ethics committee in Stockholm, Sweden (Study I Dnr 2008/533-31/2, study II Dnr 2015/1876-31/2, study III Dnr 2011/1925-31/3 and study IV Dnr 2015/1901-31/4).

For all four studies, the images were pseudonymized at review.

For study I and II, the MR images and the patients' medical records were reviewed. None of the patients included in these studies were asked to participate or informed about the study. The medical records were reviewed several years after the initial diagnosis, when some of the patients were already diseased, and the ethics committee waived informed consent.

For study III and IV, written informed consent was provided by all participating patients without any tempting benefits such as financial compensation, and with the possibility to exit the study without any explanation, at any time during the study.

In none of the studies, were the patients expected to benefit from participation. Where informed consent was obtained, patients agreed to participate to improve the situation for other women in the future.

4.2 STUDY POPULATIONS

All study populations originate from patients with biopsy proven CC in the Stockholm-Gotland region, referred to the Karolinska University Hospital for treatment.

The different cohorts of patients and their inclusion in the four studies in this thesis are shown in Figure 3.

Study I and II emanate from a cohort of 345 consecutive patients with CC diagnosed between January 2003 and December 2006 (Figure 4). Study I included 57 patients having undergone primary surgery, and in Study II, 41 patients having received brachytherapy prior to surgery were added, as well as four patients examined according to a MR-protocol unsuitable for study I (n=102).

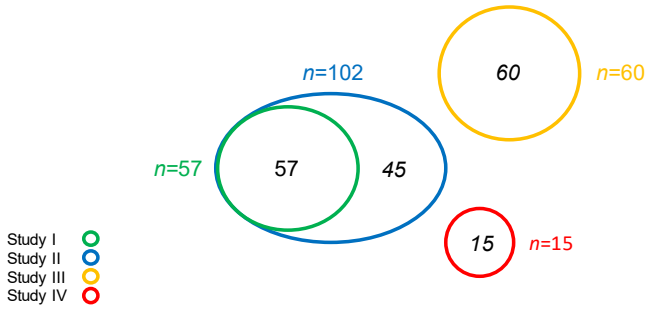


Figure 3. Cohorts of patients and their inclusion in the four studies.

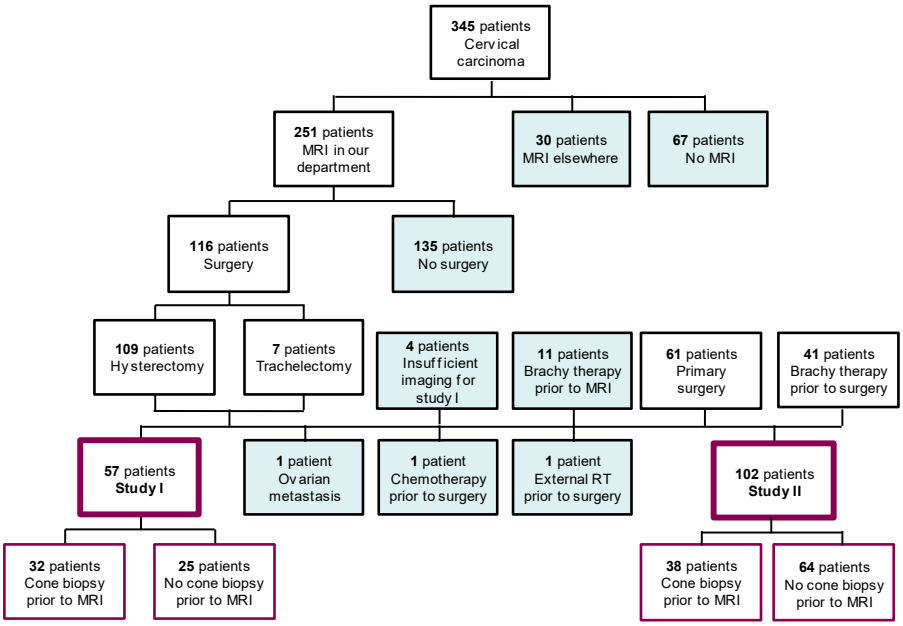


Figure 4. Flowchart for study populations for study I and II.

From a second cohort comprising 483 patients, who were diagnosed with CC between July 2011 and August 2015, 89 patients who had undergone transvaginal ultrasound (TVS) were eligible for Study III [139]. After excluding patients with insufficient imaging material (MRI *n*=16, TVS *n* =11) and a final histological diagnosis other than CC, the final cohort comprised 60 patients (Figure 5).

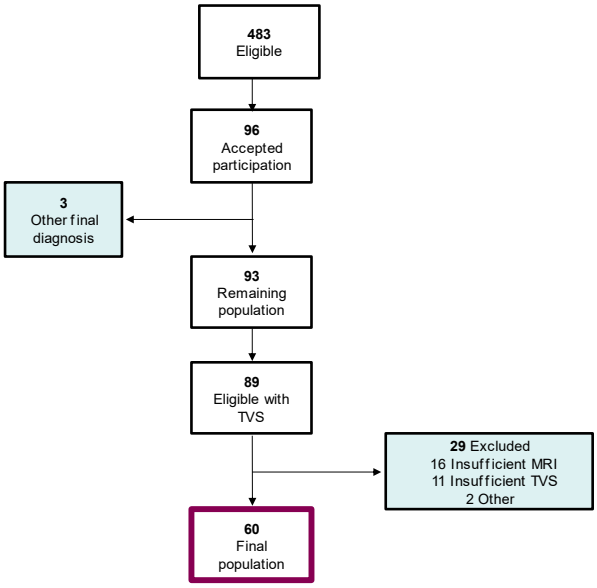


Figure 5. Flowchart for study population in study III.

In study IV we aimed to recruit 15 patients scheduled for CRT. The inclusion period started in October 2016 and was completed in March 2018. Out of 39 consecutive patients who were asked to participate, 29 agreed, three had altered treatment plan, four had final histopathological diagnosis of endometrial carcinoma, five patients discontinued the study and two had deviating MR-protocols.

4.3 METHODS

4.3.1 Study I and II

4.3.1.1 Treatment

The 57 patients included in study I underwent primary surgery i.e., hysterectomy including pelvic lymphadenectomy or trachelectomy. In study II, 41 patients prior to surgery additionally received brachytherapy, comprising two treatments with a three-week interval. Postoperatively, the treatment was supplemented with additional EBRT and/or chemotherapy, depending on surgical and histopathological risk factors for recurrence [59, 140, 141].

4.3.1.2 Magnetic resonance imaging

MRI was performed on a 1.5T system, median 20 days (1-97) days prior to surgery using three different protocols. Protocol A included T2-weighted sagittal, transaxial and T1-weighted transaxial sequences of the pelvis, and transaxial T2- weighted and fat suppressed T1-weighted sequences from the diaphragm to the promontory. Protocol B consisted of T2-weighted sequences of the pelvis in an oblique axial plane perpendicular to the tumour/cervix, and in an oblique coronal plane parallel to the longitudinal axis of the tumour/cervix. In protocol C, intravenous gadolinium-chelate contrast-enhanced T1-weighted transaxial images of the pelvis and the upper abdomen were acquired (Figures 6-8).

4.3.1.3 Image analysis

Two radiologists reviewed the images, first individually and then in consensus.

The reviewers were first presented to protocol A without oblique or contrast-enhanced images, then they were also presented with the oblique images (protocol A+B) repeating the above evaluation. Finally, contrast-enhanced images were added to the review (protocols A+B+C). In study I, histopathology and surgical findings were used as the gold standard.

The image reading was performed according to a standardized protocol, recording presence of tumour, size in three orthogonal planes, involvement of cervical stroma (none, partially, or complete), distance to internal cervical os, presence of parametrial invasion, presence of metastatic lymph nodes and their location (common iliac sin or dx, external iliac sin or dx, internal iliac/obturator sin or dx) and presence of hydronephrosis. The readers also defined a mrTNM and mrFIGO stage.

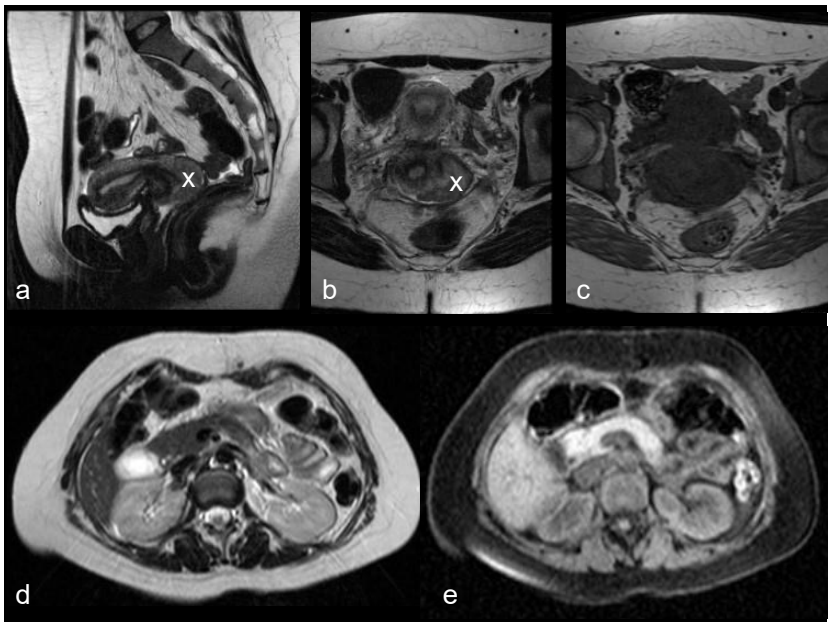


Figure 6. MR protocol A: T2-weighted sagittal (a) and transaxial (b) images of the pelvis, T1-weighted transaxial images of pelvis (c) and transaxial T2-weighted images of the upper abdomen (d) and T1-weighted images of the upper abdomen (e). A cervical tumour bulging into the left fornix is indicated with ‘‘x.’’

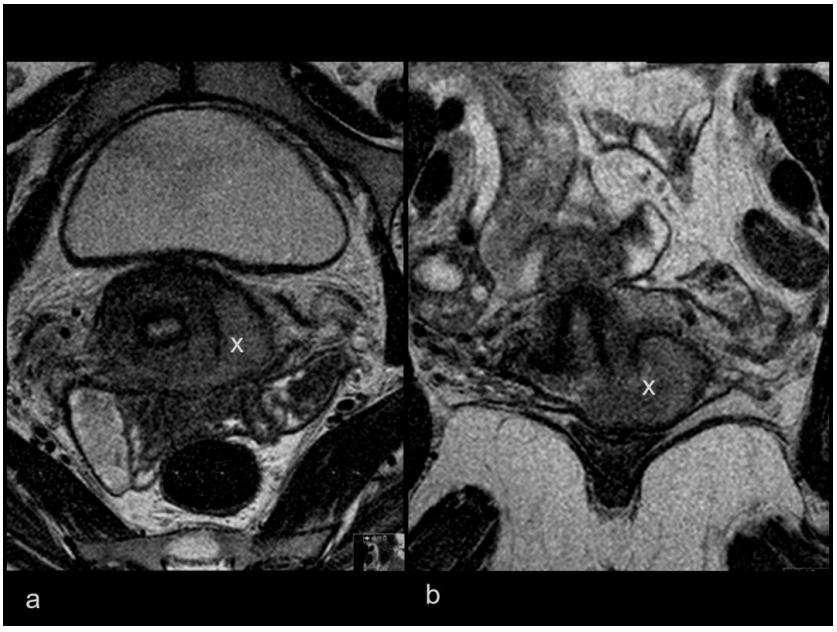


Figure 7. MR protocol B: T2-weighted axial oblique images perpendicular to the cervical canal (a) and coronal oblique images parallel to the cervical canal (b). A cervical tumour bulging into the left fornix is indicated with ‘‘x’’.

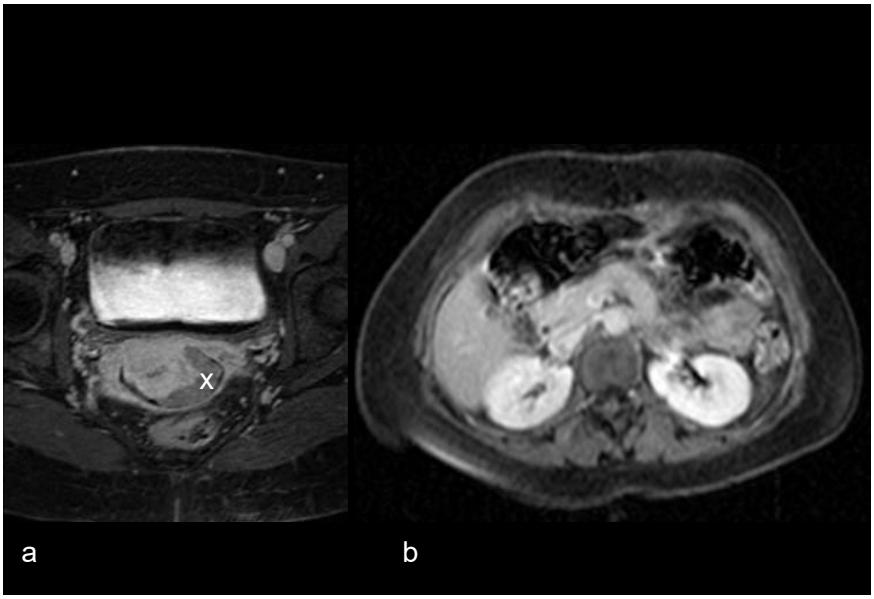


Figure 8. MR protocol C: T1-weighted contrast-enhanced transaxial images of the pelvis (a) and the upper abdomen (b), tumour is indicated with an "x".

4.3.1.4 *Clinical follow-up*

In study II, the patients were followed for a median 11.5 years (range 9.6 – 13.7). During the first 2 years, clinical follow-up took place every 3-4 months, then every 6 months for the following three years. Biopsies and/or MRI, CT or PET/CT were performed in case of suspected relapse.

4.3.2 Study III

4.3.2.1 Magnetic resonance imaging

MRI was performed according to clinical routine, using 4 different scanners [142]. The protocols included T2-weighted transaxial and sagittal images, oblique axial, and oblique coronal images, T1-weighted transaxial images of the pelvis before and after intravenous administration of a gadolinium-chelate contrast agent. Diffusion-weighted images were excluded from review as they were not available for the whole study cohort, due to alterations in the routines during the study period.

4.3.2.2 Transvaginal ultrasound

The examinations were performed by two ultrasound experts, either transvaginally or transrectally according to Fischerovas systematic method [143] using two ultrasound systems [142]. Still images and videos were recorded in the sagittal plane and transverse plane focusing on the cervix. The material included between 3 and 10 videos with and without

Doppler. In some cases, when videos were unavailable, still images with Doppler over the cervix were reviewed instead.

4.3.2.3 Image analysis

There were two groups of observers for TVS and MRI, respectively. One group of experts in CC imaging, and one group without such experience. All MRI observers attended an introductory 2-h workshop on CC imaging. All TVS observers received a written manual on how to review the TVS examinations. The less experienced observers also attended a 1-h workshop on CC imaging. All MRI and TVS observers answered the following questions: (1) Is there a visible primary tumour? (Yes/No); (2) Does the tumour infiltrate > 1/3 of the cervical stroma? (Yes/No); and (3) Is there parametrial invasion? (Yes/No). For each question, they additionally rated their confidence regarding the finding on a visual analog scale (VAS) ranging between 0 and 100, where 0=very uncertain and 100=absolutely confident. They also rated the image quality for each examination on a VAS of 0–100, where 0=very unsatisfactory and 100=perfect. The answers were submitted using an anonymized link to an online survey (Survey Monkey®; see links: TVS Survey (http://www.huxa.net/kp/survey-us.html) and MRI Survey (http:// www.huxa.net/kp/survey-mri.html).

4.3.3 Study IV

4.3.3.1 Treatment

All patients were scheduled for external beam radiotherapy (EBRT) and intracavitary brachytherapy (ICBT) with CT- and MRI-based planning, as well as concurrent weekly intravenous chemotherapy (Cisplatin, 40mg/m2), 6 cycles. The standard dosage of radiotherapy was 45Gy to the pelvis and 50Gy to the tumour volume, in 25 fractions. Patients with paraaortic lymph node metastases received an extended field radiation up to Th12-L1 in 25 fractions up to 45Gy.

4.3.3.2 Magnetic resonance imaging

All patients were scheduled for MRI at baseline, “time point 1” (TP1), at 3 weeks “time point 2” (TP2), at 5 weeks “time point 3” (TP3) and at 12 weeks after treatment start “time point 4” (TP4). MRI was performed using a 3T-scanner. The MRI protocol of the pelvis included T2-weighted sequences in the transaxial, sagittal, oblique coronal and oblique axial planes, T1-weighted transaxial sequences and transaxial diffusion weighted sequences. ADC maps were automatically generated, using b-values 50 and 100.

4.3.3.3 Image analysis

Two radiologists reviewed the images according to a standardized protocol, first individually, then in consensus. On the baseline examination, maximum size, extent of local tumour spread to adjacent tissues and organs, presence of lymph node metastases and bone marrow metastases were recorded, and an MRI-based tumour stage was assigned. On all examinations, tumour size and presence or absence of remaining high signal intensity in the

tumour on high b-value DWI were noted. Maximum tumour length was measured on T2-weighted images, in the appropriate anatomical plane, Figure 9. ADC was measured with a circular ROI including as much as possible of the tumour in one transaxial image, avoiding necrotic areas, (Figure 10).

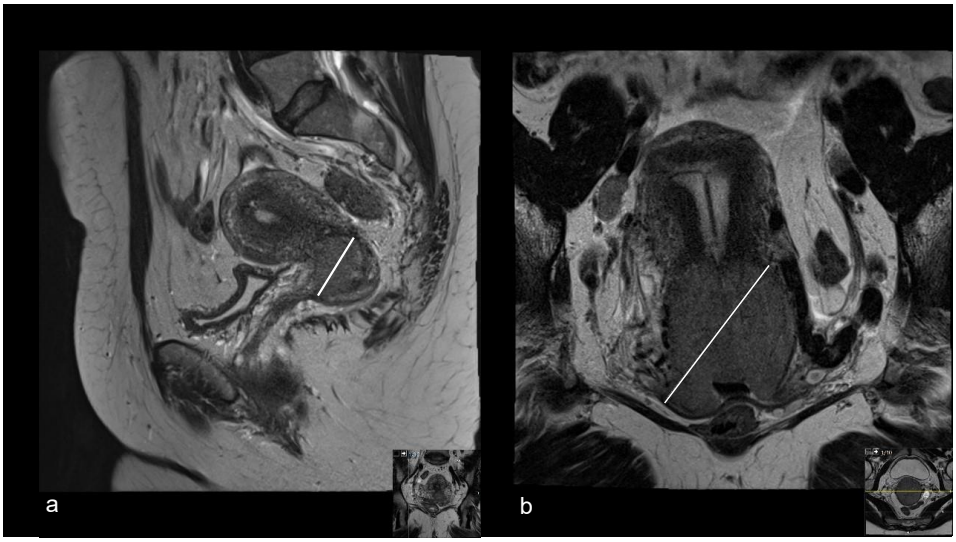


Figure 9. Examples of maximum tumour length measurements (white line) on T2-weighted sagittal image (a) and on coronal oblique (b) image.

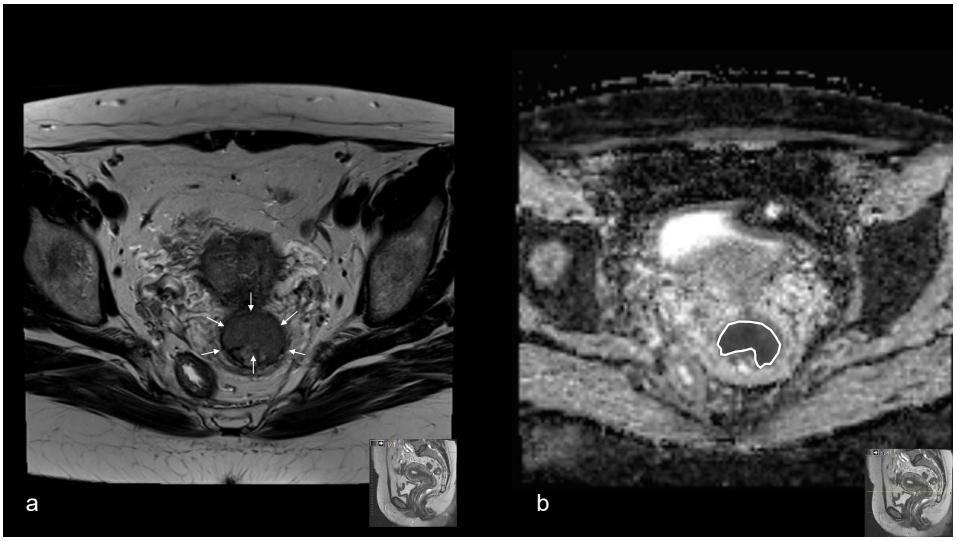


Figure 10. T2- weighted transaxial image (a) with white arrows delineating the tumour and ADC map (b) with white region of interest placed to measure the ADC.

4.4 STATISTICAL ANALYSIS

4.4.1 Study I-IV

Study I, utilized descriptive statistics and sensitivity and specificity for presence of tumour (T) and lymph node metastases (N) as identified by MRI, calculated with histopathology as the standard of reference. Cohens Kappa (k̂) was calculated for rater pairs. k̂ measurements were interpreted as follows: <0 (no agreement), 0–0.2 (poor), 0.2–0.4 fair, 0.4–0.6 (moderate), 0.6–0.8 (good), >0.8 (very good agreement).

In study II, frequencies and percentages were calculated for categorical variables, and for medians and ranges for continuous variables. Kaplan-Meier statistics was used for calculating the RFS.

In study III, the chi-square test was used for all categorical data, the independent two-sample t-test was used for normally distributed continuous data and the Mann–Whitney U-test was used for non-normally distributed data. Fleiss kappa (κ) was calculated for a group of multiple raters. Agreement was interpreted as being "poor" for κ=0–0.2, "fair" for κ=0.21–0.40, "moderate" for κ=0.41–0.60, "good" for κ=0.61–0.80 and "very good" for κ=0.81–1. Observer confidence and image quality (VAS) was tested with the Wilcoxon rank-sum test, and Spearman's correlation was performed to correlate observer confidence with image quality.

In study IV the patients were divided into two groups: those with and those without recurrence during follow-up, "poor prognosis" (PP) and "good prognosis" (GP), respectively. The area under the ROC-curve (Receiver Operating Characteristic-curve), AUC (Area Under Curve) was estimated together with a 95% confidence interval. Student's t-test was used for calculating differences in Δ size and Δ ADC between GP and PP at different time points. Intraclass Correlation (ICC) was calculated for inter-rater reliability. Repeated measures ANOVA was calculated for differences in tumour size between GP and PP at different time points.

A p-value < 0.05 was considered significant in all four studies. The analyses were performed using the following software programs; SPSS (Statistical Package for Social Sciences) software version 20-25 (IBM, Armonk, NY, USA), Procedure Logistic in software package SAS 9.4 (©2016, SAS Institute Inc., Cary, NC, USA) and TIBCO® Statistica™ version 13.0 (©2018, TIBCO Software Inc.).

5 RESULTS

5.1 STUDY I

A total of 57 patients were included in the study, 32 had cone biopsy median 30 days (range 8-150 days) prior to MRI.

The assessment of mrT stage was altered in 4/57 (7%) patients adding oblique sequences (protocol B), 3 patients were upstaged, and one was down staged. Adding contrast-enhanced sequences (protocol C), 1/57(2%) patient was upstaged. The agreement between mrT stage and pT stage was 37/57 (65%) for protocol A and protocol A+B+C. For protocol A+B, the agreement was similar, 36/57 (63%).

The sensitivity and specificity for detecting residual tumour on MRI after conization was 57% (8/57) and 94% (17/18) respectively, compared to 43% (9/21) and100% (4/4) for patients without conization.

Lymph node metastases were present in 6/57 (11%) in the final surgical specimen, 2 were detected on MRI, one was suggested at MRI without confirmation at histopathology i.e., with sensitivity 33% (2/6) and specificity 98% (50/51). The mrN and mrM stages were the same for all three MRI protocols.

The Kappa agreement between MR readers for mrT stage was 0.65 for protocol A and A+B+C, and 0.62 for protocol A+B, i.e., “good” agreement between readers for all three MRI protocols.

The agreement among readers was better for MRI aquired without prior conization with ƙ 0.69-0.78 for the different protocols, compared to ƙ 0.58-0.62 for MRI after conization. The agreement increased when MRI protocols were subsequently added.

The Kappa for mrN stage was “moderate” ƙ 0.55 for all protocols.

Agreement between mrT stage and pT stage was similar, regardless of protocol. The mrN and mrM stages were not altered by adding protocols B or C. Also, agreement was similar regardless of additional protocol for mrT, mrN and mrM stages.

5.2 STUDY II

The ten-year follow-up included 102 patients of whom 60 underwent primary surgery. The patients were divided in two main groups: those with visible and non-visible tumours on MRI. Clinical parameters are shown in Table 1.

Recurrence was discovered median 20.6 months (range 3.8-40.3) after surgery in 17.6% (18/102) of the patients. Ten patients presented with local recurrence, 1 had distant metastases, and 7 presented with local recurrence and distant metastases. Median 33.5 months (range 12.4-80.1) after surgery 21.6% (22/102) of the patients were diseased due to CC (n=15), other cancer (n=4) and other/unknown causes (n=3). Tumour recurrence developed in 17.9% (10/56) of patients with visible tumours and in17.4% (8/46) among

patients with non-visible tumours. RFS was similar in patients with visible and non-visible tumours (p=0.706) (Figure 11). In a further analysis, when groups of patients with tumours of different sizes on MRI (1-19mm, 20-39mm, ≥40mm) and those with non-visible tumours were compared, RFS was similar between the four groups (Figure 12). Although not reaching statistical significance in the Kaplan-Meyer analysis, RFS was nevertheless shorter for patients with non-visible tumours, compared to those with tumours measuring 1-19mm on MRI (p=0.176). The RFS pattern for patients with tumours measuring 20-39mm, resembled that for patients with non-visible tumours, and the shortest RFS, although not statistically significant, was found for tumours ≥40mm (Figure 12). RFS for patients having undergone conization was longer than for those who had not, Log-rank test p=0.024) (Figure 13).

Table 1. Clinical parameters.

Variable	**MR visible**	**MR non-visible**
Age, years (range)	38 (28 - 67)	39 (27 - 62)
Conization, *n* (%)	13 (23)	25 (54)
Histopathology		
Squamous cell carcinoma, *n* (%)	34 (60)	27 (59)
Adenocarcinoma, *n* (%)	12 (21)	17 (37)
Adenosquamous carcinoma, *n* (%)	2 (4)	1 (2)
Other, *n* (%)	2 (4)	1 (2)
Mixed, *n* (%)	6 (11)	2 (4)
pLVSI+, *n* (%)	14 (25)	9 (20)
mrN MRI+, *n* (%)	17 (30)	0
pN+, *n* (%)	23 (41)	4 (9)
Treatment		
Surgery only, *n* (%)	9 (16)	38 (83)
Pre op brachytherapy, *n* (%)	38 (70)	4 (9)
Post op radiotherapy, *n* (%)	34 (61)	7 (15)
Post op chemotherapy, *n* (%)	28 (50)	5 (11)
Follow-up time, years (range)	11.9 (9.6 - 13.8)	10.5 (10.0 - 13.8)
Recurrence, *n* (%)	10 (18)	8 (17)

Figure 11. RFS for tumours visible versus non-visible on MRI.

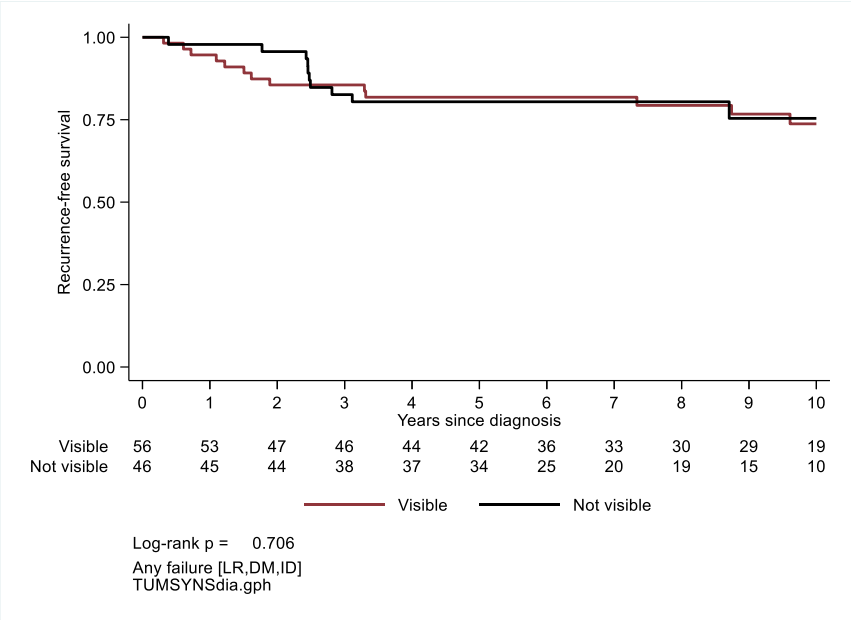


Figure 12. RFS for tumours of different sizes.

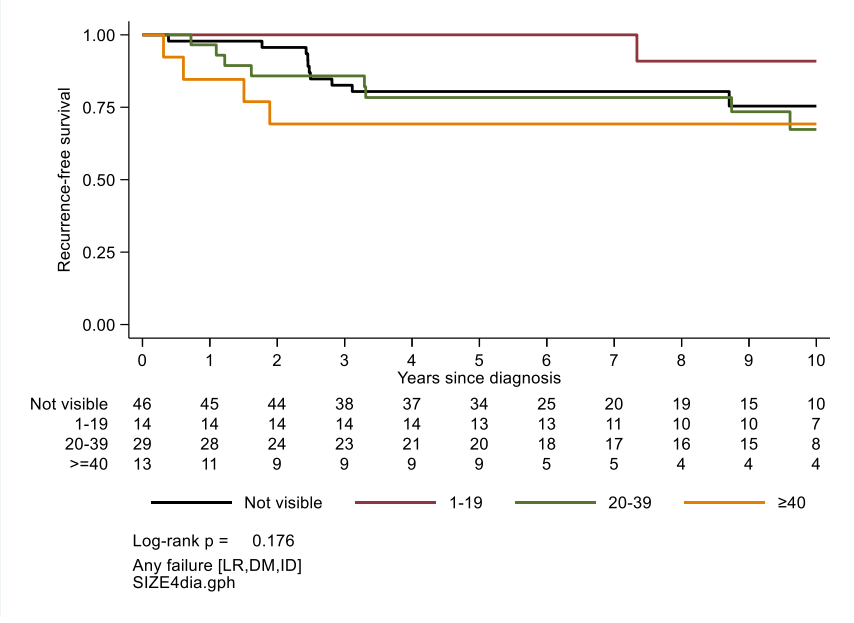
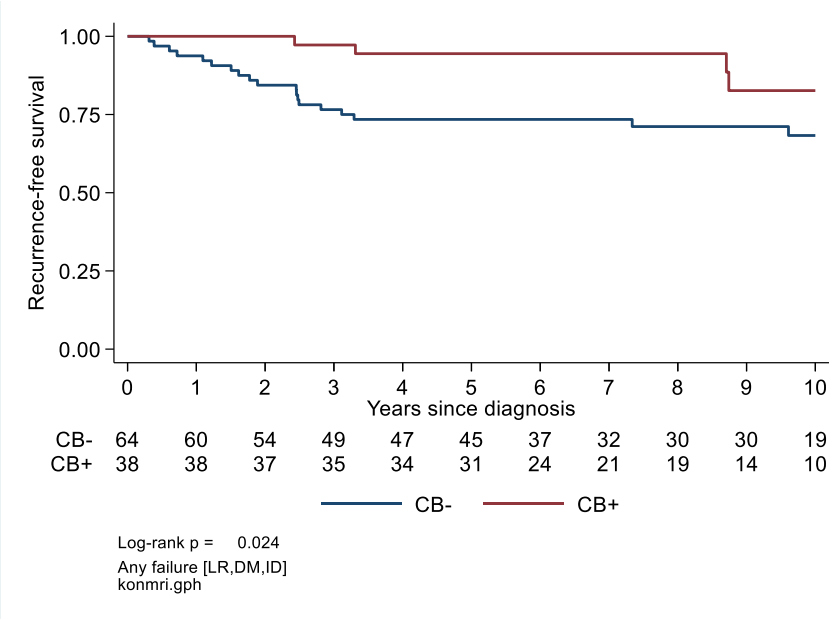


Figure 13. RFS for non-conizised (CB-) versus conizised (CB+) patients.



5.3 STUDY III

Experienced and less experienced observers in pelvic MRI or TVS reviewed images of 60 patients with CC with all clinical stages. Their demographic data are presented in Table 2.

The inter-observer agreement for all MR observers was “good” for assessment of stromal- and parametrial invasion with ƙ-values of 0.69-0.8, as well as for experienced observers regarding tumour detection. The agreement was “moderate” for the less experienced MR observers with ƙ 0.51.

Among the TVS observers, the inter-observer agreement was “moderate” for assessment of tumour detection, stromal- and parametrial invasion with ƙ-values of 0.44-0.57. The experienced TVS observers showed significantly better agreement than the less experienced observers regarding parametrial invasion with ƙ-value of 0.57 vs 0.44.

When the patients who had undergone conization prior to imaging (*n*=19) were excluded from the analysis, the inter-observer agreement for tumour detection of the remaining 41 patients decreased for all MR observers but remained unchanged for all TVS observers.

The observer confidence was higher among experienced MR and TVS observers, than for the less experienced MR and TVS observers (p=0.001).

Table 2. Demographic statistics of the study group including 60 patients with cervical carcinoma.

Characteristics	Value
Age (years)	46 (24-85)
Tumour stage (FIGO)	
IA1	1 (1.7)
IA2	1 (1.7)
IB1	34 (56.7)
IB2	1 (1.7)
IIA	7 (11.7)
IIB	13 (21.7)
IIIB	2 (3.3)
IV	1 (1.7)
Histology	
Squamous cell carcinoma	40 (66.7)
Adenocarcinoma	18 (30.0)
Other	2 (3.3)
Treatment	
Diagnostic cone biopsy	19 (31.7)
Surgery	31 (51.7)
Chemoradiotherapy	29 (48.3)

Data are given as median (range) or *n* (%).
FIGO (Federation of Gynaecology and Obstetrics).

5.4 STUDY IV

The median follow-up was 83.3 months (range 24.7-101.3.) Out of 15 patients with clinical stages IB2-IIIB (FIGO 2009), 7 relapsed during follow-up ("poor prognosis group", PP). The remaining 8 patients were without relapse ("good prognosis group", GP). Clinical features are presented in Table 3. Median time from diagnosis to relapse was 6.5 months (range 6.3-38). Table 4 shows localization for recurrence. At the end of the study, 3 patients were diseased, all belonging to the PP group.

Table 3. Clinical features of the study group of 15 patients.

Clinical features	
Median age (range)	48 (36–72)
Histopathology	
Squamous cell carcinoma	10 (67)
Adenocarcinoma	4 (27)
Adenosquamous carcinoma	1 (7)
Tumour stage (FIGO)	
IB2	2 (13)
IIA	2 (13)
IIA2	1 (7)
IIB	7 (47)
IIIA	1 (7)
IIIB	2 (13)
Median size in mm (range)	47 (23-105)
Metastases on PET/CT	6 (40)
Lymph nodes, pelvis	6 (40)
Lymph nodes, paraaortic	3 (20)
Follow-up time in months (range)	33 (10–41)
Outcome	
Complete response	8 (53)
Recurrent disease	7 (47)

Data are given as median (range) or *n* (%).

Table 4. Distribution of localization of recurrence.

Patient	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Cervix	x				x		
Pelvic lymph nodes	x				x		
Paraaortic lymph nodes			x	x	x		
Mediastinal lymph nodes	x	x		x		x	
Lungs		x				x	
Bone marrow	x						x
Brain					x		

The maximum tumour size was larger for patients with PP compared to GP at all time points (p=0.03). The Δ sizes were similar for PP and GP between time points TP1-2, TP1-3 and TP1-4. At baseline, TP1, all tumours were visible on DWI, at TP2 13/15, at TP3 8/15 and at TP4 2/15 patients had remaining focal high signal intensity on high b-value DWI. The sensitivity and specificity for visible tumour on DWI was best at TP3, 83% and 63% respectively, 5 weeks after treatment start. Using this result, tumour size was combined with visibility of tumour on DWI at the different time points. By combining "maximum tumour size at baseline" with "visible tumour on DWI" at TP3 in a ROC curve led to AUC=0.83. When using only "visible tumour on DWI" resulted in AUC=0.73. This, and other combinations of size and visibility at different time points, are depicted in Figure 14 a-d. The

results in the ROC- analyses, were not improved by other combinations of size and visible tumour on DWI.

The mean ADC was similar in PP and GP patients, except at TP4 when there was no remaining tumour visible on DWI among patients with GP. Similarly, between different time points, Δ ADC was the same for PP and GP.

ICC for inter-rater reliability regarding tumour size was 0.87-0.998, and 0.21-0.62 for ADC measurements. Due to missing data, this could not be calculated for TP4.

Figure 14a. ROC curve for visible tumour on DWI at time point 3 (5weeks after treatment start), red dotted line (model2), tumour size at time point 1, green dotted line (model3) and a combination of the two above, blue line (Model).

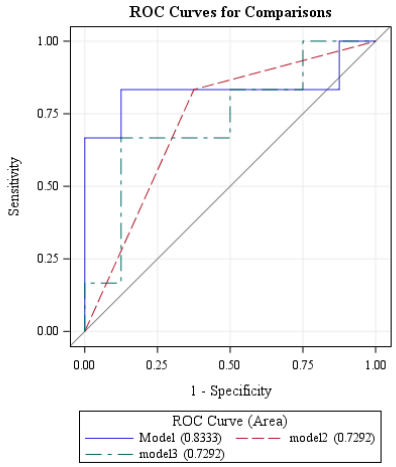


Figure 14b. ROC curve for visible tumour on DWI at time point 3 (5weeks after treatment start), green dotted line (model2), and tumour size at time point 3, and a combination of the two above, blue line (Model).

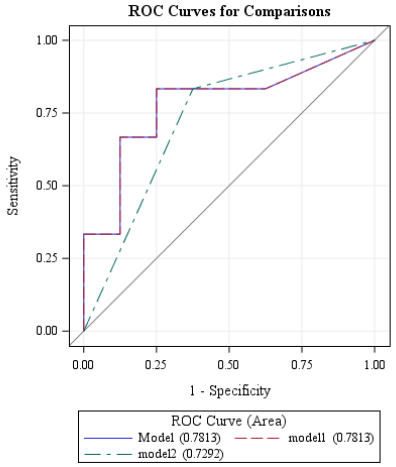


Figure 14c. ROC curve for maximum tumour size, red dotted line, and visible tumour on DWI at time point 2 (3 weeks after treatment start), green dotted line, and a combination of the two above, blue line.

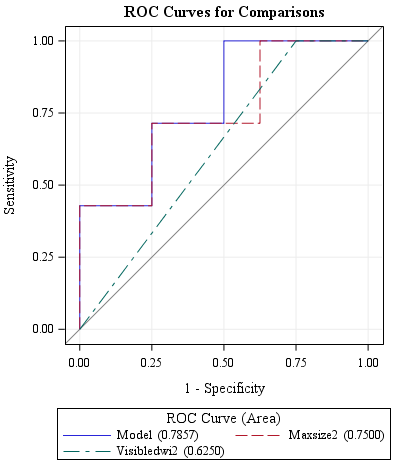
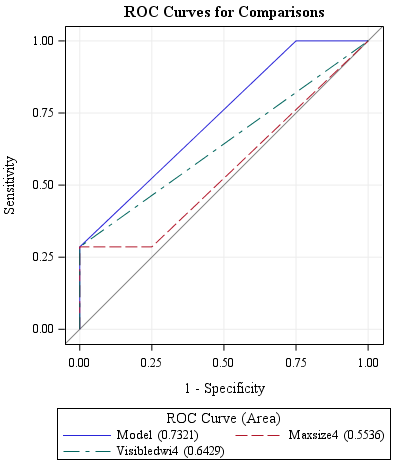


Figure 14d. ROC curve for maximum tumour size, red dotted line, and visible tumour on DWI at time point 4 (12 weeks after treatment start), green dotted line, and a combination of the two above, blue line.



6 DISCUSSION

Study I included patients with CC who underwent primary surgical treatment and for whom a final histopathology report was available. The diagnostic capacity of three MR protocols, comprising different combinations of MRI sequences, was assessed to determine which sequences were necessary for evaluation of patients with CC intended for primary surgical treatment, and whether any sequences could be excluded without impairing the assessment of local tumour extension.

The sensitivity and specificity for tumour visualization using a basic protocol including T2-weighted sagittal and transaxial sequences, T1-weighted transaxial sequences of the pelvis, and fat suppressed T1-weighted sequences from the diaphragm to the promontory, were not improved, by adding oblique or contrast-enhanced sequences. In patients without conization prior to MRI, the inter-observer agreement increased from ƙ 0.69 “good” to ƙ 0.77 “good” by including oblique sequences. In patients with prior conization, the inter-observer agreement for mrT was ƙ 0.58 “moderate” for protocol A and ƙ 0.61 “good” for protocol A+B. The sensitivity for detecting tumour was 57% for patients having undergone conization and 43 % in patients without prior conization, while the corresponding specificity was 94% and 100% respectively. The low sensitivity may possibly be due to misinterpreting post-biopsy changes as small tumours, since these are difficult to discriminate [120].

The detection of lymph node metastases remained unchanged, regardless of additional MRI protocols including oblique and contrast-enhanced sequences, with 33% sensitivity and 98% specificity. The low sensitivity for detection of lymph node metastases is at least partly reflected by micrometastases undetectable with MRI but demonstrated at histopathology. The inter-observer agreement for mrN stage was moderate, ƙ 0.55.

In patients with clinical FIGO-stage ≤IIA, addition of contrast-enhanced sequences to a basic standard protocol including transaxial and sagittal T2-weighted images, and transaxial T1-weighted sequences was not justified, which agrees with the ESUR guidelines from 2011[83], at the time of the study, and with current guidelines from 2019 [144].

Study II In patients with early-stage CC, who were followed for ten years the long-term outcome/ prognosis was similar in those with visible versus non-visible tumours on pretreatment MRI. However, previous conization had a significant positive impact on the outcome. The outcome was also better, however not significant, for small visible tumours <2cm, than for non-visible tumours, indicating a lack of information in non-visible tumours. Our results agree with those of Roh et al. [117] who found underestimation of non-visible tumours, and similar long-term outcome in visible and non-visible tumours. The RFS in our study was 82% for visible tumours and 83% for non-visible tumours, and the 5-year-survival was 88%, the latter being similar to the 90% 5-year survival reported by both Park [145] and Roh [117].

Study III assessed interobserver agreement among experienced and non-experienced observers for MRI and TVS regarding primary tumour extension in patients with all stages of CC.

The interobserver agreement was "good" for both experienced and non-experienced MRI observers regarding stromal invasion and parametrial invasion and "moderate" for less experienced observers regarding tumour detection, compared to "moderate" agreement among all TVS observers regarding tumour detection, stromal invasion and parametrial invasion. The similarity in interobserver agreement for both experienced and less experienced observers was unexpected. Level of experience was thought to have an impact on agreement with less experience having lower agreement, due to uncertainty. The only difference between experienced and non-experienced observers was regarding parametrial invasion for TVS, with significantly better agreement among the experienced observers. Also, similar sensitivity and specificity for tumour detection and stromal invasion was seen, regardless of level of experience, which supports the similar levels of agreement. Interobserver agreement was higher for MRI than for TVS, fortifying that TVS is dependent on the person performing the ultrasound. Also, the image reading setting for the gynaecologists, reviewing other examiners' images, and deprived of their customary simultaneous clinical interaction with the patient, further complicated their interpretation of the review.

Study IV The potential role of T2- and diffusion-weighted MRI was explored to predict treatment outcome in patients with locally advanced CC, and the optimal early time point in relation to CRT was established.

Among the early time points studied, identifying patients with poor prognosis i.e., residual/recurrent disease, the most optimal time point was found to be 5 weeks after the start of CRT. In the logistic regression analysis, the AUC was further improved by combining remaining signal on high b-value DWI at 5weeks with tumour size at baseline 0.83. Other combinations did not improve the results in the ROC analyses. Other studies have suggested that DWI at 2 weeks can be used as a potential biomarker for tumour response [133, 134], however, outcome cannot be compared as these patients were only followed during the treatment period i.e., up to three months, while the time from diagnosis to relapse in our study reached 38 months. It is also difficult to compare our results with those only evaluating response mid-treatment i.e., about 30 days after treatment start [129, 130]. The GP group could not be separated from the PP group with any of the studied variables; size, Δ size, mean ADC or Δ ADC. When therapy response can be predicted early during therapy, the treatment plan can be individualized and changed accordingly, potentially improving outcome and reducing morbidity. The results in this pilot study need to be validated in larger studies.

7 CONCLUSIONS

Adding oblique sequences and/or contrast-enhanced sequences to a basic protocol for preoperative staging does not improve agreement among mrT stage compared to pT stage, nor does it improve inter-observer agreement among reviewers. In small CC tumours, i.e., unequivocally without PMI, oblique and contrast-enhanced sequences are unnecessary. When interpreting pre-treatment MRI, information on previous cone biopsy is essential.

Patients assigned clinical stage IA1-IIA with non-visible and visible tumours on baseline MRI, experienced similar RFS, indicating a risk for underestimation of stage in non-visible tumours. RFS was longer for patients having undergone cone biopsy than for those who had not. Thus, tumour visibility versus non-visibility on baseline MRI has no impact on the long-term outcome, whereas pretreatment cone biopsy is a favourable prognostic parameter.

Interobserver agreement was higher for MRI than for TVS in patients with all stages of CC. Experience was only associated with agreement for evaluation of parametrial invasion among TVS observers. Acceptable interobserver agreement seems achievable for both experienced and less experienced observers, after attending a short basic MRI and TVS training session on evaluation of cervical tumours.

In patients scheduled for CRT, visible tumour on high b-value DWI at 5 weeks after treatment start, combined with a large tumour at baseline MRI, seems to predict disease recurrence. To confirm these results, further studies in larger cohorts are warranted.

8 POINTS OF PERSPECTIVE

In studies I – III, it is evident that information on tumour size and visibility is affected by prior conization. As conization may cause edema and hemorrhage [146, 147] and mimic small tumours, this probably led to false positive observations in all three studies.

There are numerous studies trying to improve visualization of small tumours by using transvaginal coils and dynamic contrast-enhanced imaging [115, 116]. However, one can question this ambition considering the patient's similar long-term outcome regardless of tumour visibility. Radiologists tend to show and describe all image findings, but when the imaging results do not affect the outcome, there is little clinical value in being able to confirm the presence of small biopsy verified tumours. This is not the case when fertility sparing treatment, i.e., trachelectomy, is considered.

For study I and II, we were unable to recruit a pathologist for review according to a standardized histopathological reporting protocol. Some histopathological reports described depth of stromal invasion in millimeters, some in "halves", and some in "thirds", which made direct comparison to MRI findings impossible. In all four studies, evaluation regarding depth of stromal invasion was successful, but could not be validated, except in study III. At the time the study started, we did not realize that almost half of the tumours would turn out to be non-visible, nor that so many patients had undergone conization prior to MRI.

Study II was initiated to identify prognostic factors on MRI. However, long after data collection, and review, i.e., during analysis, it became evident that half of the data was missing, due to non-visible tumours, partly because of patients having performed conization prior to MRI

Pretreatment staging is essential to select the best possible treatment for every individual patient. During the last 15 years the MR techniques have developed, and previously recommended protocols have changed. The first studies include images from when MRI of the pelvis was introduced as part of the routine work-up of patients with CC at Karolinska University Hospital. At that time, for a resident without MR experience, high resolution MR images with very detailed anatomy were fascinating, but it was also frustrating to realize that the information provided by MRI was not allowed to be implemented by the gynaecologic surgeons and oncologists in staging of the patients.

TVS is less costly in relation to MRI, readily available and can easily be customized during examination and focused on the area of interest. Biopsies can be performed with great accuracy if a suspected lesion is identified. However, it is difficult for someone who is not used to perform ultrasound to interpret the images and get a good overview of the pelvis and the exact location of lesions in relation to adjacent structures. Both TVS and MRI are affected by the patients' habitual state.

Comparing MRI with TVS is difficult, as one method consists of still images according to predefined protocols, and the other is a dynamic examination in collaboration with the patient who can express discomfort or pain, or just get tense indicating discomfort in a specific location. Also, the gynaecologist can distinguish between soft elastic tissue and irremissible tissue during the examination. Advantages of MRI are that the entire small pelvis is depicted, and lesions can easily be described in relation to adjacent organs, the images can be read by radiologists, surgeons, or oncologists, and can be used for treatment planning. Direct comparison of images pre- and post-treatment are of utmost importance. As TVS has not proven satisfactory regarding evaluation of treatment response, it is difficult to justify its use in the routine work-up.

In study III we had a workshop for all reviewers, partly because the non-experienced reviewers had to become familiar with definitions of PMI, how to measure maximum length and so on, but also because the experienced reviewers were not used to evaluate depth of stromal invasion, as that is not part of the routine work up, and not included in staging. We were surprised that a short training session led to such good interpretation of the images, even among the residents (non-experienced observers). This is important in so many aspects. We must share our knowledge, educate each other, and be prepared to learn new things all the time to benefit our patients.

In study IV, we initially intended to also include measurements of intravoxel incoherent motion (IVIM) in our therapy response assessment. Acquisition of multiple b-values for analysis of IVIM parameters, however, requires a long time in the scanner, which was not compatible with the patients´ poor health. Further, the challenges with DWI and IVIM, related to the signal-to-noise ratio, became evident in our patients, affected by side effects from CRT with increased bowel movement and oedema. Despite our best efforts, noise in the acquired data could not be overcome, leading to cross-contaminated parametric maps and overall poor quality in the resulting images.

In the future, one would need larger patient cohorts to draw more extensive conclusions. To collect a larger cohort validating the results from study IV, one might be able to retrospectively use the repetitive MRIs performed at each brachytherapy during CRT. It would also be interesting to study MRI in comparison with tissue samples, to learn more about molecular biological changes in the tumour during treatment, and why treatment is successful in some cases, but not in others. The more we know, the better we can tailor examination standards in staging and in relation to administered treatment.

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