IQ-EMBRACE

Quantitative MR Imaging in Locally Advanced Cervical Cancer

Sub-study under the EMBRACE II protocol

(version 001, 27032017)

PROTOCOL TITLE: Quantitative MR Imaging in Locally Advanced Cervical Cancer

Protocol ID	**Not applicable**
Short title	**Quantitative MRI in Cervical Cancer**
Version	**001**
Date	
Project leader	
Principal investigator(s) ***Project coordinators:*** ***Kari Tanderup, Aarhus University Hospital, Denmark*** ***Uulke van der Heide, The Netherlands Cancer Institute, The Netherlands*** ***<Multicentre research: per site>***	
Sponsor: Aarhus University Hospital	

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

2D	**2-dimensional**
3D	**3-dimensional**
BT	**Brachytherapy**
CRF	**Case Record Form**
CTV	**Clinical Target Volume**
DCE-MRI	**Dynamic Contrast Enhanced – Magnetic Resonance Imaging**
DWI	**Diffusion Weighted Imaging**
EBRT	**External Beam Radiotherapy**
EORTC	**European Organisation for Research and Treatment of Cancer**
ESTRO	**European Society for Therapeutic Radiology and Oncology**
FIGO	**The International Federation of Gynaecology and Obstetrics**
MRI	**Magnetic Resonance Imaging**
OAR	**Organs at Risk**
PDR	**Pulsed Dose Rate**
HDR	**High Dose Rate**
PET-CT	**Positron Emission Tomography – Computed Tomography**
SUV	**Standard Uptake Value**
T/M	**Tumour Muscle Ratio**
MREC	**Medical research ethics committee**

SUMMARY

Title of the study	Quantitative MR Imaging in Locally Advanced Cervical Cancer
Name of study coordinators	Kari Tanderup, Aarhus University Hospital Uulke van der Heide, Netherlands Cancer Institute
Objectives	*Primary:* To evaluate the sensitivity and specificity of dynamic contrast enhanced (DCE-MRI) to identify patients who have increased risk of disease recurrence (local, nodal, systemic) after radio-chemotherapy of cervix cancer. *Secondary:* To apply radiomics for identification of patients who have increased risk of disease recurrence (local, nodal, systemic) after radio-chemotherapy of cervix cancer. Radiomics analysis will include features from DCE-MRI, DWI and quantitative T2 imaging. *Secondary:* To correlate MR imaging parameters with biomarkers based on pathology (immunohistochemistry, genomic analysis), in a subgroup of patients *Secondary:* To evaluate the implementation of quantitative imaging in a multicentre setting.
Rationale	Hypoxic tumour cells within the primary tumour have shown prognostic importance for local and metastatic disease control in several cancer sites. Radioresistant hypoxic cells diminish the rate of local control, and the hypoxia driven increase in metastatic potential of the tumour and lowers the rate of distant disease control. DCE MR imaging has been used to quantify the extent of poor perfusion regions within cervical tumours and it has been shown to be a surrogate of hypoxia. Furthermore, a number of studies have demonstrated that DCE MR is predictive of disease failure in cervix cancer. The EMBRACE II study will implement an imaging sub-study, which will evaluate the value of quantitative MR imaging to identify patients at increased risk of disease recurrence (local, nodal and systemic).
Methodology	Patients will undergo MRI before initiation of external beam radiotherapy. The sequences include T1W and T2W sequences as well as DWI and DCE-MRI with contrast administration. Kinetic modelling will be applied in DCE-MRI images to assess quantitative kinetic parameters in the gross tumour volume related to blood volume, interstitial

	volume, flow and permeability. It will be tested whether different thresholds of haemodynamic parameters can predict disease free survival. Extra quantitative MR sequences can be added (optional) when the patient is MR scanned for brachytherapy treatment planning. This will allow for longitudinal evaluation of treatment response and correlation to outcome (disease free survival).
Number of patients	At least 8 centres in the EMBRACE II consortium will offer EMBRACE II patients the possibility to participate in the imaging study. Assuming that 70% of the patients will accept participation and that 8 centres each accrue 10-20 patients, there will be a total accrual of around 80 patients per year amounting to 320 patients over the 4-year study period.
Major inclusion criteria	• Patients included in the EMBRACE study (see inclusion criteria in the EMBRACE protocol) • Patients without previous record of allergic reaction to infusion of protocol related contrast media (Gadolinium-based) • Patients with sufficient kidney function according to local regulations • Patient informed consent
Major exclusion criteria	• According to EMBRACE II protocol • Patients with active infection or severe medical condition
Study design	Registration study
Study duration	4 years
Hypothesis	It is hypothesised that low perfusion in the primary tumour - as determined from DCE-MRI - is a risk factor for persistent and recurrent disease (local, nodal and systemic): All patients: Current retroEMBRACE 3/5y cancer specific survival: 81/74% Hypothesis 3y disease free survival: - Well perfused 89% - Poorly perfused: 73% N+ or stage III+IV: Current retroEMBRACE 3/5y cancer specific survival: 69/57% Hypothesis 3y disease free survival: - Well perfused: 81%

	- Poorly perfused: 57%
Safety	For the standard DCE-MRI exam, 0.1mmol/kg of the contrast agent Dotarem (Gadoteric Acid, concentration 0.5M) is administered i.v. where minor patient discomfort may occur
Quality of Life	Not applicable
Pharmakinetics (PK)	Not applicable
Translational research (TR)	Not applicable

1. INTRODUCTION AND RATIONALE

Radiotherapy is an important treatment modality in the management of cancers of the uterine cervix. About half of patients with cervical cancer receive definitive radiotherapy in the course of their disease. Radiotherapy is most often administered as a combination of external beam radiotherapy (EBRT) and brachytherapy (BT). In the late 90's a major breakthrough in cervical cancer radiotherapy took place with the introduction of MR image guidance of BT. By performing MR imaging before each BT implant it is possible adapt the dose given by BT to the anatomy of each individual patient taking into account not only the position of organs at risk (bladder, rectum and sigmoid) but also the tumour regression induced by the preceding EBRT and chemotherapy.

Functional imaging that reflects hypoxia, metabolism, heamodynamics and tissue structure have been applied to locally advanced cervical cancer with the goal to identify imaging markers that may predict outcome early on and improve tissue classification. DCE-MRI may be the most investigated so far for locally advanced cervical cancer. A comprehensive literature review including papers investigating the prognostic value of DCE-MRI in patients with locally advanced cervical cancer identified 20 papers from 10 research groups, with a median number of 30 patients (range 7-102 patients). A total number of 17 papers publish a positive association between pre-treatment DCE-MRI and outcome in terms of local control or disease free survival (1–17). However, not all studies present independent cohorts of patients. Three papers show no effect (18–20) The studies on cervical cancer points in the direction that DCE-MRI has the capability to identify aggressive forms of cervical cancer, and that the pre-treatment measurements may serve as, predictive markers for outcome after chemo-radiotherapy. The largest studies indicate that in particular the tumour fraction with the lowest signal enhancement is an important parameter, though the diversity in methodology is significant.

Diffusion weighted MRI (DWI-MRI) has to a lesser extent than DCE-MRI been investigated in locally advanced cervical cancer. Most studies using DWI-MRI in cervical cancer have investigated its diagnostic capabilities (21–28) all concluding high sensitivity and specificity (review by Kundu et al. (29)). The Toronto group; McVeight et al. (26) and later Gladwish et

al. (30) found prior to the onset of treatment that the highest 90th % ADC value correlated with response, similar finding was found by the group in Tianjin; Liu et al. (22). Both groups found that higher ADC value insides the tumour was predictive of poor response to treatment and suggest the higher ADC to be connected to tumour necrosis. When tumour necrosis, occur there is loss of cell membrane integrity and therefore an increase in the extracellular volume and a decrease in intracellular volume effectively increasing the ADC. Conversely, the group from London UK; Harry et al. (31) and Somoye et al. (32) showed no correlation to treatment response at the time prior to treatment. Instead the ADC at 2 weeks (and the change in ADC) into treatment was predictive of treatment response and prognostic of patient outcome. Finally, Marconi et al. (33) found a relation between minimum ADC in the tumour and both DSS and DFS.

Publication	Imaging marker	Endpoint	# patients
DCE-MRI			
Mayr (2012) (1)	FRV	LC, DSS	102
Mayr (2010) (2)	SI(10%)	LC, DSS, OS	98
Andersen (2012) (3)	nRSI(0.5min)	LRC	81
Loncaster (2002) (4)	median SI-I (Brix model)	DSS	50
Takayama (2009) (5)	R_{down}	TVRR	42
Semple (2009) (6)	K^{trans}	TVRR	20
Mayr (1998) (7)	RSI	LC	20
Mayr (1996) (8)	RSI	LC	17
Mayr (2000) (9)	RSI	LC	16
Mannelli (2010) (10)	NE_F	TVRR	13
Zahra (2009) (11)	K^{trans}, k_{ep}	TVRR	13
Gong (1999) (12)	ΔME, ΔPE	TVRR	7
Andersen (2011) (13)	CVF (K^{trans}, v_e)	LC	81
Mayr (2009) (14)	SI(10%)	LC, DSS, OS	88
Huang (2014) (15)	SI	LC, DSS	102
Torheim (2014) (16)	texture features from GLCMs of A_{Brix}	PFS	81
Donaldson (2010) (17)	E_F(25 sec)	DFS	50
Mayr (2010) (18)	SI(10%)	No effect (for preRT alone)	62
Kim (2012) (19)	K^{trans}, v_e	No effect	35
Boss (2001) (20)	TTP, BAT	No effect	10
DWI-MRI			
McVeight (2008) (26)	ADC_{pre}(90%)	TVRR	47
Liu (2009) (22)	Mean ADC_{pre}	TVRR	17
Somoye (2012) (32)	ADC_{wk2}, $\Delta ADC_{pre\text{-}wk2}$	OS, PFS	20
Harry (2008) (31)	ADC_{wk2}, $\Delta ADC_{pre\text{-}wk2}$	TVRR	20
Marconi (2016) (33)	ADC_{min}	DSS	66
Gladwish (2015) (30)	ADC_{95}, $nADC_{95}$	DFS	85

Imaging marker abbreviation

FRV: Function Risk Volume, R_{down}: the ratio of the number of down-sloped pixels to that of all selected pixels, SI:

Signal Intensity, SI-I: signal intensity increase over baseline, RSI: Relative Signal Intensity, nRSI: normalized Relative Signal Intensity, E_F: Enhancing Fraction, NE_F: Non-Enhancing Fraction. ∆ME: change in Mean Enhancement, ∆PE: change in Peak Enhancement, CVF: Cluster Volume Fraction. TTP: Time To Peak, BAT: Bolus Arrival Time, GLCM: Gray Level Co-occurence Matrix,ADC: Apparent Diffusion Coefficient, nADC: ADC normalized to diffusion in urine, A_{Brix}:Amplitude in the Brix model, K^{trans}: forward volume transfer constant, k_{ep}: reverse volume transfer constant.

Endpoint abbreviation
DSS: Disease Specific Survival, OS: Overall Survival, LC: Local Control, LRC: LocoRegional Control, TVRR: Tumor Volume Reduction Rate, PFS: Progression Free Surviva, DFS: Disease Free Survival

2. OBJECTIVES

Primary: To evaluate the sensitivity and specificity of dynamic contrast enhanced (DCE-MRI) to identify patients who have increased risk of disease recurrence (local, nodal, systemic) after radio-chemotherapy of cervix cancer.

Secondary: To apply radiomics for identification of patients who have increased risk of disease recurrence (local, nodal, systemic) after radio-chemotherapy of cervix cancer. Radiomics will include features from DCE-MRI, DWI and quantitative T2 imaging.

Secondary: To correlate functional imaging parameters with pathology, in a subgroup of patients

Secondary: To evaluate the implementation of quantitative imaging in a multicentre setting.

3. STUDY DESIGN

This is an observational prospective, non-randomized study in which patients with locally advanced cervical cancer included in the EMBRACE II study can enrol. The study will be carried out in 8-15 EMBRACE centres.
MRI will be carried out prior to radiotherapy. The details of the MRI exams will differ from standard clinical practice in the centres, but will be consistent with international guidelines for cervix MRI. The exam will include T1, T2, diffusion, and dynamic contrast-enhanced imaging. At time of brachytherapy, the treatment planning MRI will additionally include DWI and qT2.
Patients will be followed up according to the EMBRACE II follow-up schedule.

4. STUDY POPULATION

4.1 Population (base)

Yearly, each EMBRACE II centre is expected to enrol 10-20 patients. The inclusion for the imaging protocol in a given centre is expected to be 70% of patients enrolled in EMBRACE II. We expect that at least 8 institutions will enrol 10 patients per year, which will result in minimum 80 patients per year, and thereby at least 320 patients within the 4-year study period. This number is sufficient to meet the required number of patients for the hypotheses in the overall patient population (sample size 196 patients – see sample size calculation below) and in the high-risk patients (sample size 248 patients – see sample size calculation below).

4.2 Inclusion criteria

- Patient included in the EMBRACE II study
- Patients without previous record of allergic reaction to Gadolinium-based contrast media
- Patients with sufficient kidney function according to local regulations for intravenous Gadolinium-based contrast media administration
- Patient informed consent

4.3 Exclusion criteria

- According to EMBRACE II protocol
- Patients with contra indications to MRI
- Patients with active infection or severe medical condition

4.4 Sample size calculation

It is expected to accrue at least 320 patients (section 4.1). With this sample size it is possible to identify a significant difference with a power of at least 80% in the entire cohort as well as in a subgroup analysis in high risk patients:

All patients:
Current retroEMBRACE 3/5y cancer specific survival: 81/74%
Hypothesis 3y disease free survival:

- Well perfused (50% of patients): 89%
- Poorly perfused (50% of patients): 73%

Sample size (log-rank test, 80% power 5% significance): 196 pts

N- and stage I+II:

Current retroEMBRACE 3/5y cancer specific survival: 90/87%
Hypothesis 3y disease free survival:

- Well perfused (50% of patients): 95%
- Poorly perfused (50% of patients): 85%

Sample size (log-rank test, 80% power 5% significance): 292 pts

N+ or stage III+IV:
Current retroEMBRACE 3/5y cancer specific survival: 69/57%
Hypothesis 3y disease free survival:

- Well perfused (50% of patients): 81%
- Poorly perfused (50% of patients): 57%

Sample size (log-rank test, 80% power 5% significance): 124 pts

Background for estimations of disease free survival and differences:
In the entire patient cohort of Halle et al, 28% difference was found in progression-free survival with 40% and 75% progression free survival in poorly and well perfused tumours, respectively.
In the entire patient cohort of Mayr et al, 20% difference was found in disease free survival (3 years) with 60% and 80% disease free survival in poorly and well perfused tumours, respectively.
Assumptions for this study: We assume a 24% difference in cancer specific survival in the high risk group (N+ or stage III+IV), which is the mean of the difference found by Halle et al and Mayr et al. The reason that the difference is assumed in a high risk group and not in the entire group, is that disease free survival is significantly higher in retroEMBRACE than in the cohorts of Halle et al and Mayr et al. The survival reported by Halle and Mayr is more similar to the retroEMBRACE survival in the high risk group. For the low risk group (N- and stage I+II), 10% difference is assumed, and for the entire cohort 17% difference which is mean of 10% and 24%. The distribution between high and low risk patients is 50%-50%. We assume a selection of perfusion cut-point which divides the cohort into 50% well perfused and 50% poorly perfused, as was also the case in the study from Halle et al. With an overall sample size calculation based on the overall population, a number of 196 patients need to be enrolled. Sample size calculations in the high risk group indicate that with a sample size of 248 patients (2x124 patients), it is furthermore possible to observe a difference in the high risk group. It is not expected, that it is possible to perform a sub-group analysis in the low risk group with a sample size of 248 patients (a subgroup analysis in the low-risk group would require 2x292=584 patients).

5. TREATMENT OF SUBJECTS

This study does not contain any interventions.

6. INVESTIGATIONAL PRODUCT

Not applicable.

7. NON-INVESTIGATIONAL PRODUCT

7.1 Name and description of non-investigational product(s)

For the perfusion imaging part of each MRI exam, 0.1 mmol/kg of Dotarem or similar Gadolinium based contrast agent is administered intravenously.

7.2 Summary of findings from non-clinical studies

Not applicable

7.3 Summary of findings from clinical studies

Not applicable

7.4 Summary of known and potential risks and benefits

Not applicable

7.5 Description and justification of route of administration and dosage

Not applicable

7.6 Dosages, dosage modifications and method of administration

Not applicable.

7.7 Preparation and labelling of Non Investigational Medicinal Product

Not applicable.

7.8 Drug accountability

Not applicable

8. METHODS

8.1 Study parameters/endpoints

8.1.1 Main study parameter

DCE-MRI
Kinetic modelling (10) will be applied in DCE-MRI images to assess quantitative kinetic parameters in the gross tumour volume related to blood volume, interstitial volume, flow and permeability. It will be tested whether different thresholds of haemodynamic parameters can predict disease free survival.

8.1.2 Secondary study parameters

Potential bias between centres will be evaluated for quantitative T2, quantitative DWI and DCE MRI parameters using ANOVA analysis. For DWI: the ADC (median tumour values) will be evaluated for assessment of any centre-effect.

We will investigate the use of machine learning techniques such as radiomics and deep learning in computer aided detection (CAD) of the primary lesion. The features used for this task will comprise of the full set and subsets of the functional and textural parameters extracted from DWI, DCE and qT2. The accuracy of the learned algorithm will be evaluated on a separate validation set with expert delineated primary lesion or a leave-one-out-cross validation.

Furthermore the DWI and qT2 will be tested whether they may predict disease free survival separately. The combination of all extracted functional (DCE, DWI, qT2) and textural features will be used to train a machine learning algorithm separating the classes: patients with and without disease free survival.

8.2 Study procedures

8.2.1 QA

Participating centres will have different scanning platforms, with different vendors and different generation of scanners providing more or less advanced sequences. Therefore the sequences for this study need to be optimized for each scanning platform to exploit its full potential. To ensure consistent quantification between the participating centres, a quality assurance procedure will be followed prior to inclusion of the first patient. This procedure consists of imaging of calibration phantoms with the proposed sequences for the study. The quantitative values will be compared to the ground truth phantom values. In addition, a set of benchmark sequences will be scanned. These consist of robust techniques that are available on each platform, but that typically are too slow for clinical use. Comparison of the obtained

values with the proposed study sequences and ground truth values will be done to assess the origin of potential differences in values so as to facilitate optimization of the study sequences. The results will be sent to the trial coordinators for analysis. Upon approval of the sequences specific for the centre by the trial coordinators, inclusion in the study in a participating centre can start.

8.2.2 Patient recruitment

Patients who are eligible for inclusion in the study are informed by their physician about the study. After respite according to national guidelines, the patients will be contacted to ask whether they are willing to participate. The patients are then asked to sign informed consent.

8.2.3 MRI exam

Each patient will undergo MRI before initiation of external beam radiotherapy. The MRI should be within 4 weeks before first EBRT fraction.

The MRI exam will consist of the following sequences, all axially sliced:

- Quantitative T2 mapping
- B0 mapping
- Diffusion-weighted MRI
- B1 mapping (for patients scanned on 3T MRI platforms)
- Quantitative T1 mapping
- DCE-MRI

MRI at time of first brachytherapy fraction is optional and will consist of the following sequences:

- Quantitative T2 mapping (axially sliced)
- B0 mapping
- Diffusion-weighted MRI

8.2.4 Recording and reporting

Reporting of clinical status at diagnosis, and treatment parameters are to EMBRACE CRFs

8.2.5 Follow-up investigations

Follow-up is according to EMBRACE II follow-up schedule.

8.3 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

8.4 Replacement of individual subjects after withdrawal

If a participant withdraws from the study, an extra patient will be included.

8.5 Follow-up of subjects withdrawn from treatment

Patients who have withdrawn from the imaging study will continue their enrolment into EMBRACE II

8.6 Premature termination of the study

No measures need to be taken if the study is terminated prematurely.

SAFETY REPORTING

8.7 Adverse and Serious Adverse Events

Adverse events are defined as any undesirable experience occurring to a subject during the Study which are related to administration of contrast and imaging. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

A serious adverse event is any untoward medical occurrence or effect that at any dose

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect;
- is a new event of the trial likely to affect the safety of the subjects, such as an unexpected outcome of an adverse reaction, lack of efficacy of an IMP used for the treatment of a life threatening disease, major safety finding from a newly completed animal study, etc. All SAEs will be reported to the accredited MREC that approved the protocol, according to the requirements of that MREC.

8.7.1 Suspected unexpected serious adverse reactions (SUSARs)

Not applicable

8.7.2 Annual safety report

Not applicable

8.8 Follow-up of adverse events

All adverse events will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow - up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

9. IMAGE ANALYSIS

The MRI exam will result in a T1 and a T2 scan, DWI-MRI, and DCE-MRI.
Imaging data will be uploaded on a secure server, and centralised data analysis will be performed at Aarhus University Hospital (AUH) and Netherlands Cancer Institute (NKI).

Tumour volume delineation

Delineation of GTV on T2 weighted images will be performed by the institution treating the patient.

DCE-MRI

The image analysis of the dynamic contrast enhanced scans will be done at Aarhus University Hospital by using a number of in-house scripts to determine the functional parameters; blood-flow, surface permeability, plasma volume fraction and barrier transport constant. From the complex image the arterial input function (AIF) will be extracted in the major feeding arteries using the work by Simonis et al. (34). Baseline T1 measurements derived from the prescans will be used to convert the signal measured in dynamic scan into contrast agent concentration. The measured AIF will be used in the convolution of the monoexponential impulse response function minimizing the difference to the measured tissue concentration curves, thus allowing the extraction of haemodynamic parameters (35,36).

DWI

The diffusion weighted imaging data will be used to calculate ADC maps (37). This sequence will acquire a set of different diffusion sensitive gradients (b-values). Excluding low b-values (<100-200 s/mm^2) the signal at higher b-values will be fitted using a monoexponential decay to extract the relevant diffusion coefficient (38). At higher field strength (≈3T) local frequency shifts due an inhomogeneous background magnetic field (B0) may be observed. This will be corrected by an initial measurement of the B0-field (39).

T1 quantitative

The longitudinal relaxation rate is integral part of the DCE-MRI analysis and may be determined using a set of SPoiled Gradient Recalled echo (SPGR) sequences with varying nutation angles. This technique is known as the Variable Flip Angle (VFA) approach. By distributing the flip angles around the Ernst angle a reliable estimation of the longitudinal relaxation time may be performed.

T2 quantitative

The transverse relaxation may be estimated using a set of T2-weighted sequences with different echo-times (TE). The decay in signal with increasing TE may be approximated to a single exponential with the characteristic decay constant being the transversal relaxation

rate. Compressed sensing techniques such as k-T SPARSE may be used to accelerate the data acquisition.

Machine Learning.

For cervix tissue classification we will explore machine learning techniques like support vector machines (SVM), artificial neural networks (ANN) and convolutional neural networks (CNN)(40,41). We will combine both supervised and un-supervised classification techniques. An important step in both methods will be to eliminate the parameters that are not useful in distinguishing healthy and tumorous tissue ("feature selection"), since redundant parameters then can be avoided in future prospective designs. The output classification will be a set of probabilistic maps that will reflect the likelihood of tumour presence.

For the outcome measure training the use of SVM's will likely be the most successful approach (16,42). The result will in this case be a probability of disease free survival for an unseen case. The validation of this training will be performed using a leave-one-out cross validation.

10. ETHICAL CONSIDERATIONS

10.1 Regulation statement

The collection of all data will be performed with written informed consent and according to national legislation concerning ethical requirements. Patient data will be stored and processed in the Department in accordance with applicable requirements. Transfer of anonymised patient data material between participating institutions will be performed with informed consent according to national and European law.

10.2 Recruitment and consent

Informed consent

Specific patient information folders for the study will be produced. All patients will be informed of the purpose of the investigation, the possible side-effects, procedures and potential hazards to which she will be exposed.

Patients will be informed as to the strict confidentiality of their patient data, but that their medical records may be reviewed for study purposes by authorized individuals other than their treating physician.

It will be emphasized that the participation is voluntary and that the patient is allowed to refuse further participation in the protocol whenever she wants. This will not influence the patient's subsequent care. Documented informed consent must be obtained for all patients

included in the study before they are registered at the Study Office. This must be done in accordance with the national and local regulatory requirements.
For European Union member states, the informed consent procedure must conform to the ICH guidelines on Good Clinical Practice. This implies that “the written informed consent form should be signed and personally dated by the patient or by the patient’s legally acceptable representative”.

Patients will be asked by the radiation oncologist about their interest in participating in the study. Written and oral information will be given by the doctor filling in the patient record and informing the patients about the forthcoming treatment.

10.3 Objection by minors or incapacitated subjects (if applicable)

Not applicable

10.4 Benefits and risks assessment, group relatedness

At present, the standard treatment for patients with locally advanced cervical cancer is EBRT, concurrent chemotherapy with Cisplatin and intracavitary BT. This treatment will also be used in the present protocol. The patients will be informed of the possible risks and side effects involved with the extra scan and contrast administration. If they do not wish to participate, this will not prevent them from obtaining the standard treatment. On this background it seems reasonable to conduct the investigation.

10.5 Compensation for injury

Health damage caused by trial participation is covered by the trial Insurance of the hospital, which is in accordance with the Legal requirements. The Insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

10.6 Incentives

Not applicable

11. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

11.1 Handling and storage of data and documents

The investigators will ensure that this study is conducted in agreement with either the Declaration of Helsinki (Tokyo, Venice, Hong Kong, Somerset West and Edinburgh amendments) or the laws and regulations of the country, whichever provides the greatest protection of the patient. The patients will be anonymized. Clinical data will be entered in a web-based database where each enrolled patient is automatically assigned a sequential study patient ID number. The key between study ID number and patient identity is safeguarded in the enrolling institution according to local regulations for management of patient data. Imaging data will be anonymised and exchanged on a secure server.

The protocol has been written, and the study will be conducted according to the ICH Harmonized Tripartite Guideline for Good Clinical Practice. The protocol has been approved by the local Research Ethics Committee in accordance with national guidelines and legislation in the participating centres. The data will be kept 15 years.

11.2 Monitoring and Quality Assurance

Not applicable

11.3 Amendments

Amendments are changes made to the research after approval from local Research Ethics Committee. All substantial amendments will be notified to the local Research Ethics Committee. Non-substantial amendments will not be notified to the ethics committee, but will be recorded and filed by the sponsor.

11.4 Annual progress report

Not applicable

11.5 End of study report

Not applicable

11.6 Public disclosure and publication policy

The results, regardless of positive or negative, will be published in the form of one or more articles in recognized international scientific journals in accordance to the Vancouver rules.

11.7 Authorship

At least one author from each recruiting department will co-author publications based on the study.

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