Plan-of-the-day radiotherapy for patients with locally advanced cervical cancer - a prospective randomized controlled trial (the POD-protocol)

SPONSOR: **Oslo University Hospital**

Department of Oncology

Ullernchausseen 70

0379 Oslo, Norway

PRINCIPAL INVESTIGATOR: **Kjersti Bruheim, MD, PhD**

Department of Oncology

Tel: + 47 22 93 42 00

E-mail: UXKJUH@ous-hf.no

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PROJECT PARTNERS

Silje Skjelsvik Os	Dep. of Oncology, Oslo University Hospital
Esten Søndrol Nakken	Dep. of Oncology, Oslo University Hospital
Thea Hetland Falkenthal	Dep. of Oncology, Oslo University Hospital
Elisabeth Wang Areklett	Dep. of Oncology, Oslo University Hospital
Cecilie Delphin Amdal	PROMiNET/Dep. of Oncology, Oslo University Hospital
Cecilie Kiserud	Dep. of Oncology, Oslo University Hospital
Monica Eidem	Dep. of Oncology, St.Olavs Hospital
Ragnhild Sørum Falk	Oslo Centre for Biostatistics and Epidemiology
Taran Paulsen Hellebust	Dep. of Medical Physics, Oslo University Hospital
Linda Holth Djupvik	Dep. of Medical Physics, Oslo University Hospital
Francisca B. Correas Vidaurre	Dep. of Medical Physics, Oslo University Hospital
Anne Beate L. Marthinsen	Dep. of Radiotherapy, St.Olavs Hospital
Trine Martens	Dep. of Oncology, Oslo University Hospital
Irene Berntsen	Dep. of Oncology, Oslo University Hospital

SIGNATURE PAGE

Title: Plan-of-the-day radiotherapy for patients with locally advanced cervical cancer - a prospective randomized controlled trial (POD-protocol)

I hereby declare that I will conduct the study in compliance with the Protocol, ICH GCP and the applicable regulatory requirements (Helseforskningsloven).

Name	Title	Role	Signature	Date
Stein Kaasa				
Kjersti Bruheim				

CLINICAL STUDY SUMMARY

Title:	Plan-of-the-day radiotherapy for patients with locally advanced cervical cancer - a prospective randomized controlled trial (POD-protocol)
Study objectives:	The study objectives are to improve the treatment of LACC patients and to increase knowledge of the potential benefit of the plan-of-the-day concept on side effects during and after radiotherapy.
Clinical study design:	The study is a single blinded randomized controlled trial. In the control arm standard radiochemotherapy is delivered using one single treatment plan where safety margins takes into account possible movements of the target volume. In the intervention arm several treatment plans are prepared and the appropriate plan is used at each treatment session.
Inclusion / exclusion criteria:	**Inclusion criteria:** • Histologically confirmed cervical cancer eligible for definitive radiochemotherapy • FIGO stage Ib-IVa • Over 18 years • Speaks and understands Norwegian or English. • ECOG 0-2 • Histology: Squamous cell carcinoma, adenocarcinoma, adenosquamous carcinoma • Ability to understand and willing to sign a written informed consent • Large movers (LM), fundus movement ≥2,5 cm. **Exclusion criteria:** • Evidence of distant metastasis. Suspicious paraaortic lymphnodes below the renal vessels is allowed if they are covered by the radiation field • Patients with previous surgery for cervical cancer • Uncontrolled intercurrent somatic illness. • Psychiatric illness /social situations limiting study compliance • Prior radiotherapy to the pelvis • Patients who are pregnant or breastfeeding is excluded due to risk of teratogenic and abortifacient effects of radiotherapy and cisplatin, and the potential risk of adverse effect of nursing infants • Patients that have received treatment for other invasive malignancies the last 3 years, except non-melanoma skin cancers • Nephrostomy • Patients with inflammatory bowel disease

Primary endpoint:	• To compare the incidence of patient reported acute diarrhea during (week 4) and at the end of radiotherapy
Secondary endpoints:	• To compare patient reported diarrhea at 2 and 5 years follow up • To compare other items in EORTC QLQ-C30, QLQ-CX24 and EN24 (6 items) during, at the end and at 2 and 5 years after radiotherapy. • To compare physician reported morbidity grade 3 and 4 (CTCAE v.5.0) bowel and bladder toxicity during, at the end and at 2 and 5 years after radiotherapy. • To quantify extra workload for the plan-of-the-day concept by register man hours for treatment planning, plan verification and patient set-up procedure. • To estimate and compare the accumulated radiation dose to the bowel, bladder and target volume in the two groups
Duration of study:	The inclusion will be finalized within 4 years. With a follow up period of 5 years the time from start-up to last visit will be 9 years.

LIST OF ABBREVIATIONS

CBCT	**Cone Beam CT**
CRF	**Case Report File**
CT	**Computed Tomography**
EBRT	**External beam radiotherapy**
ECOG	**Eastern Cooperative Oncology Group**
EORTC	**European Organisation for Research and Treatment of Cancer**
FIGO	**The International Federation of Gynaecology and Obstetrics**
HRQoL	**Health Related Quality of Life**
IMRT	**Intensity-modulated radiation therapy**
LACC	**Locally advanced cervical cancer**
LM	**Large mover**
MRI	**Magnetic Resonance Imaging**
OUH	**Oslo University Hospital**
PET-CT	**Positron Emission Tomography-computed tomography**
PROM	**Patient reported outcome measurements**
REC	**Regional Ethics Committee**
RT	**Radiotherapy**
SOH	**St. Olavs Hospital**
VMAT	**Volumetric modulated arc therapy**
QoL	**Quality of Life**

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1 INTRODUCTION

Cervical cancer primarily affects young females and is the third most frequent cancer incident in the age group 25-49 in Norway (peak incidence at 35-39 years). In Norway approximately 300 women are affected each year with an 80 % overall survival for all stages (1).

The patients are staged according to the FIGO-system and TNM-system, and the treatment decision is made based on clinical staging, imaging, histology and patient fitness.

The locally advanced cases are treated with curative radiochemotherapy, and approximately 150 patients undergo this treatment in Norway every year.

The prognosis is good with a 5-year overall survival of 80%. Advanced radiotherapy techniques have been implemented the last decade, but still a large volume of healthy tissue is irradiated during the treatment. Irradiated volume of bowel is closely related to the probability of developing bowel toxicity (2-4). Many of these patients experience acute severe diarrhea, chronic diarrhea, bowel obstruction, incontinence and/or cystitis (5-9). Such toxicity will severely influence the quality of life and several patients report that their social life is nearly non-existing. Therefore, strategies reducing such toxicity are warranted. One of the suggested strategies is the plan-of-the-day strategy.

Patient reported outcome measurements (PROMs) are increasingly regarded as important endpoints and indicators of treatment success (10). The European Organization For Research and Treatment of Cancer (EORTC) Quality-of-life Questionnaire-Core (QLQ-C30), QLQ-CX24 and QLQ-EN24(11-13) are used in both EMBRACE I and II and in daily use in our department. In the wake of the EMBRACE studies several publications on toxicity with patient reported outcomes have been published (5, 8, 14, 15). Patient reported outcome measurements (PROMs) will be used as primary and secondary endpoints in this study. Previous studies (7-10) have shown that diarrhea is the most frequent single bowel symptom, and is therefore chosen as the primary endpoint in our study.

2 STUDY DESCRIPTION

2.1 Standard treatment

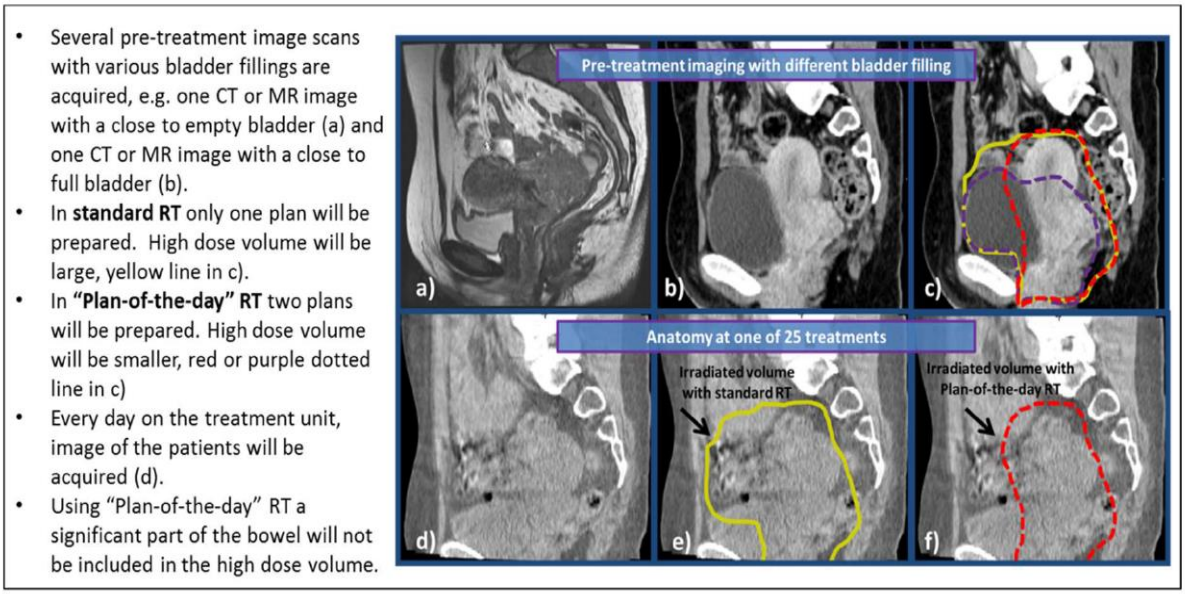
Concurrent cisplatin-based chemotherapy and radiation is the standard treatment for locally advanced cervical cancer (LACC). Concurrent chemotherapy has provided a 6 % improvement in 5-year overall survival compared to radiotherapy alone, shown in a Cochrane meta-analysis from 2010 (16). A more recent meta-analysis from 2017 showed an even greater survival benefit with an improved overall survival of 7.5 % (17).

Radiotherapy is given as 1,8 Gy x 25 to elective areas in the pelvis/abdomen, 2,2-2,3 Gy x 25 as simultaneous integrated boost to pathological lymph nodes and brachytherapy to the cervix 7,8 Gy x 4. Treatment is given according to the Embrace II protocol (appendix 1), and is in accordance with National treatment guidelines (18) .

2.2 Background plan-of-the-day

Computed tomography (CT) is a key component of the treatment planning process in radiotherapy. The primary purpose of CT scanning in radiotherapy is to enable delineation of the target volume(s) and organs at risk, and to facilitate an accurate calculation of the radiotherapy dose distribution in each individual patient. To be able to deliver an adequate dose to the tumour within the tolerance of surrounding normal tissue fractionated radiotherapy is required. Twenty-five external and 4 internal radiotherapy fractions are delivered within a maximum treatment time of 50 days. Day-to-day variation in size and position of bowel and bladder may induce displacement of the cervix and uterus which leads to a risk of missing the target volume during treatment. To mitigate the effect of such variations a safety margin is applied around the target during the treatment planning. The margins should be as small as possible to minimize the probability of treatment related morbidity, but at the same time large enough to guarantee that the requested dose is delivered to the target volume. In practise the therapeutic dose will be delivered to a volume which is larger than the target volume and this volume will inevitable include some healthy tissue.

One novel approach to reduce radiotherapy related toxicity is the plan-of-the-day concept (19). This concept utilizes improved imaging techniques on the radiotherapy treatment unit to control and take into consideration a day-to-day variation in patient anatomy. The plan-of-the-day concept and potential benefit compared to standard radiotherapy is illustrated in figure 1:



During the last two decades, advanced planning and radiotherapy delivery techniques such as intensity modulated radiotherapy (IMRT) or volumetric modulated arc therapy (VMAT) have been developed. These techniques improve conformity of the high dose area to the target volume compared to conventional radiotherapy (20, 21), and enables a smaller volume of healthy tissue to be irradiated to high dose levels. However, if the safety margin, described above, is increased, the

benefit of these conformal techniques will recede. Several studies have demonstrated large organ and target displacement (e.g. due to variations in the bladder filling) throughout the course of cervical cancer treatment (22). Large variations of margins to account for such uncertainties are suggested, varying from of 1 to 3 cm (23). Additionally, it seems that the required margin varies extensively from patient to patient (19, 24). A drinking protocol is suggested for standardization of the bladder volume, e.g. the patients should drink 300 ml water one hour prior to the treatment planning CT and prior to all the treatments. Such approach is implemented in many radiotherapy centers. However, a study by Ahmad et al showed the mean bladder volume for 24 patients reduced from 378 ml at planning to 109 ml in week 6 of the treatment, showing large inter- fraction time trend despite constant drinking protocol instructions (25). Also a large inter-patient variation was seen. By using population based safety margins some patients may receive unnecessary high radiation dose to the healthy tissue.

2.3 Rationale

In standard treatment one radiotherapy (RT) plan is prepared with robust margins to cover movement of the cervix and uterus. In this project we will make several plans to take into account daily anatomical variations. To control that the radiation beams are delivered according to the treatment plan, a verification of the patient set-up on the treatment couch is crucial. Such verification is usually performed by x-ray imaging utilizing an x-ray device mounted on the treatment machine. Images acquired during a complete rotation of the treatment around the patient are used to create a 3D reconstruction of the patient's anatomy. This is called Cone Beam CT (CBCT), since the principle of creating an image is corresponding to a CT. By comparing the CBCT images to the CT images used for planning, the position of the target can be verified.

Until recently it has not been possible to detect and thereby correct for soft tissue displacement and alteration due to inferior soft tissue contrast on the CBCT images. Lately, this contrast has improved and image registration based on soft tissue may be possible. This development is instrumental and makes it possible to study the magnitude of changes in the patient anatomy and further enhance the precision in the delivered dose.

The risk of missing the target volume could be significantly reduced by utilizing CBCT acquired prior to each treatment session and elaborates a new session specific plan every day. Such approach is time-consuming and requires tools that are not available for clinical use today. Alternatively, an adaptation of the original treatment plan may be performed.

In this study we will utilize improved imaging techniques and take into account daily anatomical variations. With the plan-of-the-day concept, plan libraries for patients with large bladder-induced cervix-uterus motion consisting of two IMRT plans (for relatively empty and full bladders, respectively) and a robust backup plan will be prepared. The backup plan will take into account most possible positions of the target. For patients in the intervention group this will mean that the total volume receiving high dose, including organs at risk will be lower. Whether it will be translated into lower toxicity is not known.

The plan-of-the-day technique is very resource-consuming. Buschmann et al estimated that the total average workload per patient increased by factor 3 compared to standard radiotherapy (26). Heijkoop et al (27) have showed less patient-reported diarrhea at the end of radiotherapy when such technique is compared to standard radiotherapy (9). This was a non-randomized study and to our knowledge no randomized study exists. With this study we will fill this knowledge gap and establish evidence of the clinical effect of the costly procedure for plan of the day radiotherapy.

3 OBJECTIVES AND HYPOTHESIS

3.1 Clinical study – objectives

The overall aim of this project is to improve the treatment of LACC patients and to increase knowledge of the potential benefit of the plan-of-the-day concept on side effects during and after radiotherapy.

3.1.1 Primary objective

The primary objective of this study is to investigate whether implementation of plan-of-the-day results in less acute gastrointestinal toxicity.

3.1.2 Secondary objectives

The secondary objectives are

- To investigate whether implementation of the plan-of-the-day concept results in less acute effects on bladder and Health Related Quality of Life(HQoL)
- To investigate whether implementation of the plan-of-the-day concept results in less late effects on bladder, bowel and HQoL.
- To investigate the extra workload for the plan-of –the-day concept.

3.2 Hypothesis

Null hypothesis (H0): Plan-of-the-day radiotherapy is **equal** to standard radiotherapy in patients with large internal movements during radiotherapy for LACC, regarding the change in patient reported **acute diarrhea** from baseline to the end of external beam radiotherapy.

Alternative hypothesis (H1): Plan-of-the-day radiotherapy is **superior** to standard radiotherapy in patients with large internal movements during radiotherapy for LACC, regarding the change in patient reported **acute diarrhea** from baseline to the end of external beam radiotherapy.

3.3 Risks and anticipated adverse events that are to be assessed

For the patients that will have inserted a bladder catheter during planning CT there will be a risk for catching a urinary tract infection. Adverse events otherwise are expected to be similar or less compared to standard treatment. The most common adverse events from radiochemotherapy of cervical cancer are fatigue, nausea and vomiting, urinary frequency, urgency and cystitis, diarrhea, difficulties controlling bowel and sexual dysfunction (7-9, 28).

4 PROM

In this study the primary endpoint will be change in patient-reported diarrhea from baseline to the end of radiotherapy. Secondary endpoints include change in patient and physician reported bowel and bladder toxicity. The PROMs will be measured using EORTC QLQ-C30, the EORTC QLQ-CX24 and 6 items from the QLQ-EN24 (appendix 2). The QLQ-C30 was developed to assess HQoL in cancer patients and has been validated and tested in different cultures and various cancer populations. The questionnaire includes 30 questions forming five function scales (physical, emotional, social, role, cognitive), three symptom scales (fatigue, nausea/vomiting and pain) and six single items (constipation, diarrhea, insomnia, dyspnea, and appetite loss), as well as global health/quality-of-life scale and a single item on financial impact. The two questions constituting the global HQoL scale are scored on a 7 point Likert scale ranging from 1 (very poor) to 7 (excellent). The remaining 28 questions have four point Likert scales with response categories: "not at all", "a little", "quite a bit" or "very much". Most items use a "past week" recall period. Raw scores are linearly converted to a 0-100 scale with higher scores reflecting higher levels of function and a higher level of symptom burden (11, 14).

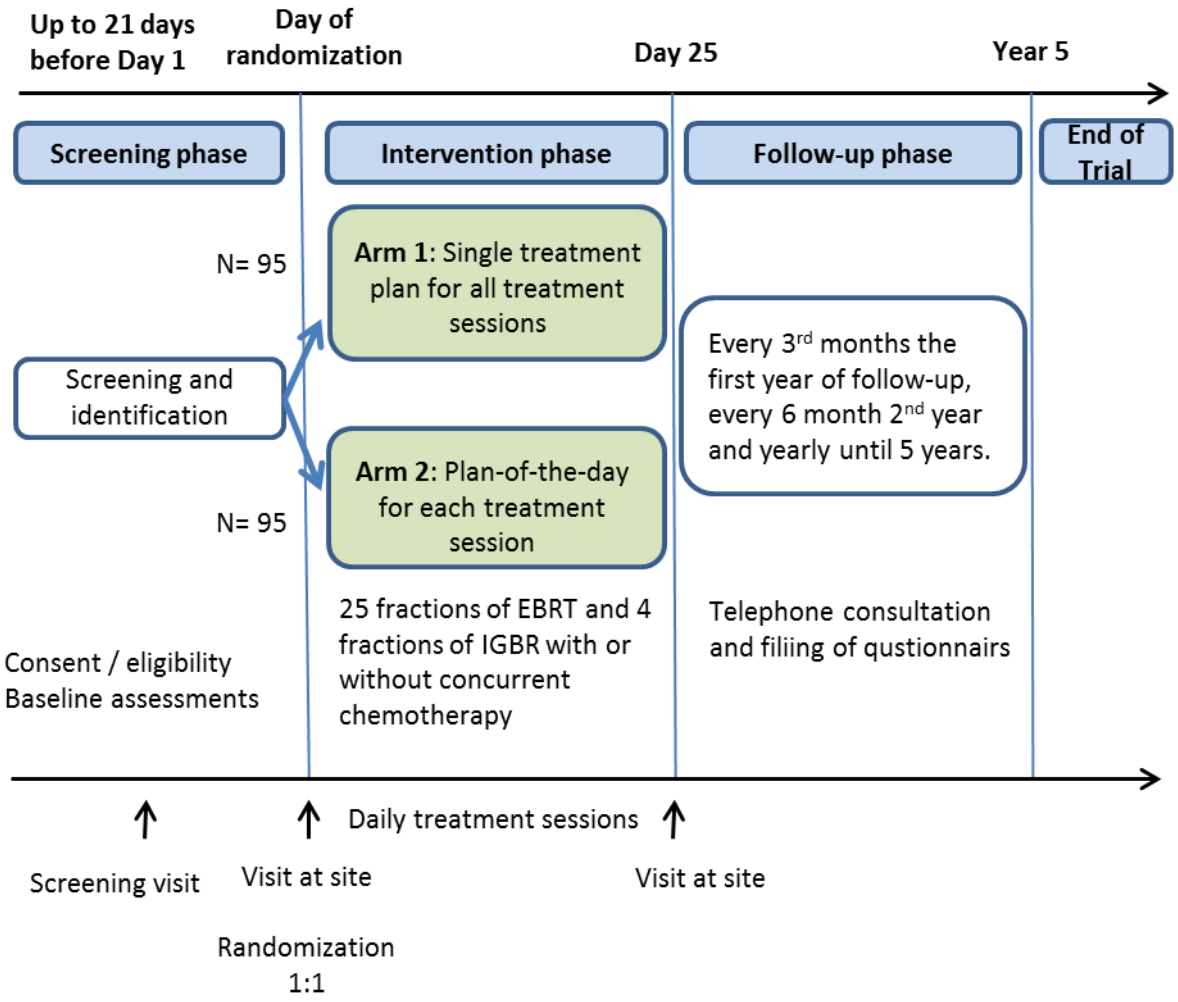
The EORTC QLQ-CX24 is a specific module for cervical cancer and consists of 3 multi-item scales and 5 single-item scales (13). In addition, six items are included from the endometrial cancer module, EORTC QLQ-EN24 (item 34, 38-40, 42 and 49). These are questions about bowel, bladder and sexual function not addressed in the QLQ-C30 or in the CX24 modules.

For every HQoL scale the mean and standard deviation will be calculated. All answers will be converted mathematicaly to a 0-100 scale where high scores represents a high degree of function or or a high degree of symptoms. For the EORTC scales, a difference of ≥10 is regarded as clinically significant(29).

In this study we will use the electronic data capture ViedocMe which includes an electronic module that lets patients report their PROMs via their smart-phones, tablets or computer. We will use automatic reminders via sms or e-mail. During treatment filling of the PROM questionnaires will be checked at the weekly visit for the outpatients, and the questionnaires filled in the eCRF can be reviewed by the key personnel. In the follow-up period we will send two reminders and accept response in a time window of +30 days. The patients preferring to fill the PROMs on paper will receive this by mail together with pre-stamped envelope. A key person will be responsible for reviewing the questionnaire data in the eCRF-system. If the patient prefers questionnaires in paper the nurse should follow-up the patient with phone calls.

5 STUDY DESIGN

5.1 General



5.1.1 Description

This is a national prospective, blinded, randomized controlled clinical trial with two radiotherapy centers participating in Norway. The trial is designed to compare the incidence of patient reported, acute diarrhea during and at the end of radiotherapy in patients treated with plan-of-the-day radiotherapy and standard radiotherapy. 190 patients will be enrolled in this study.

5.1.2 Primary and secondary endpoints

Primary endpoint

To compare the change in patient reported acute diarrhea from baseline to the end of radiotherapy

in patients treated with plan-of-the-day radiotherapy and standard radiotherapy. PROMs will be measured with item 17 in the EORTC QLQ-C30.

Secondary endpoints

- To compare the change between the two groups in patient reported diarrhea from baseline to 2 and 5 years follow up
- To compare the change between the two groups in other items in EORTC QLQ-C30, QLQ-CX24 and EN24 (6 items) from baseline to time points at 4 weeks of radiotherapy, at the end of the treatment and at 2 and 5 years after radiotherapy
- To compare the change between the two groups in the physician reported morbidity grade 3 and 4 (CTCAE version 5, appendix 3) bowel and bladder toxicity from baseline to time point at 4 weeks of radiotherapy, at the end of the treatment and at 2 and 5 years after radiotherapy
- To quantify extra workload for the plan-of-the-day concept by register man hours for treatment planning, plan verification and patient set-up procedure for both groups
- To estimate and compare the accumulated radiation dose to the bowel, bladder and target volume in the two groups

Exploratory objectives

- To assess time from treatment completed to progressive disease and overall survival at 2 and 5 years after end of treatment. Progressive disease or relapse is confirmed by either biopsy or radiological findings, is defined as local (in the cervix, parametria, vagina or uterine corpus), pelvic (within the irradiated pelvic, para-aortal or inguinal field) or distant (outside the external radiation field), either solitary or in combination.

Objectives	**Endpoints**	**Assessment**
Primary: To investigate whether implementation of the plan of the day concept results in less gastro-intestinal toxicity.	To compare the change in patient reported acute diarrhea from baseline to week 4 from start of the treatment and to the end of external radiotherapy	Item 17 in EORTC QLQ-C30
Secondary:		
To investigate whether implementation of the plan of the day concept results in less acute effects on bladder, bowel and QoL.	To compare the change in patient and physician reported radiation toxicity from baseline to week 4 from start of the treatment and to the end of external radiotherapy	EORTC QLQ-C30, QLQ-CX24 and item 34, 38-40 41 and 49 in QLQ-EN24. CTCAE v.5.0
To investigate whether implementation of the	To compare the change in patient reported diarrhea from baseline to 2	Same as above

plan of the day concept results in less late effects on bladder, bowel and QoL.	and 5 years follow up as well as other items in EORTC QLQ-C30, QLQ-CX24 and EN24	
	To compare the change in physician reported morbidity grade 3 and 4 (CTCAE v.5.0) bowel and bladder toxicity from baseline to 2 and 5 years after radiotherapy.	
To investigate the extra workload for the plan of the day concept.	To quantify extra workload for the plan of the day concept by register man hours for treatment planning, plan verification and patient set-up procedure.	
Exploratory:		
Efficacy	Disease free survival (DFS)	
Efficacy	Overall survival (OS)	

5.1.3 Equipment

The study will be performed at The Radium hospital, OUH and St. Olavs Hospital (SOH). A treatment planning systems enabling treatment planning of advanced radiotherapy RayStation® (RaySearch, Stockholm, Sweden) will be used. This system is especially developed to handle modern adaptive radiotherapy strategies where evaluation of daily CBCT is facilitated.

5.1.4 Methodology

Patients with locally advanced cervical cancer FIGO stages Ib1-IVa suitable for curatively intended radiochemotherapy will be considered for inclusion. See section 2.2 for description of standard treatment. Only patients with a potential gain of the plan-of-the-day concept will be included, the patients categorized as Large Movers (LM). These patients will be identified by quantifying the movement of the fundus uteri on two pre-treatment image sets with different bladder filling. Fundus movement ≥ 2.5 cm will be categorized as LM (26). Patients will be electronically randomized (1:1) in VieDoc to either radiotherapy with plan-of-the-day concept (intervention arm) or to standard radiotherapy (standard arm).

All patients will undergo diagnostic work up and treatment decision according to standard clinical practice.

In patients willingly to participate, a bladder catheter will be inserted prior to PET-CT scan. The PET-CT will be performed with open catheter and empty bladder. The CT taken with the PET will be a low-dose CT to avoid unnecessary radiation of the patient. Thereafter the bladder will be filled through the catheter with 300 ml of water and full-dose CT will be acquired. The catheter will be removed

after the CT procedure. The fundus movement between the filled and empty bladder will be measured in the two CT scans, and the large movers fulfilling the inclusion criteria described under 6.3.1 will be asked to participate in the study. In some patients the CT-scans will be captured with full and empty bladder without inserting a catheter.

For the patients in the intervention arm anatomical movement model (uterus, bladder, and cervix) will be created using a non-rigid image registration procedure between the empty and full bladder scan. Two target volumes (Internal Target Volumes – ITVs) will be created from this model: 1) $ITV_{empt\_to\_half\_way}$ covering the target movement from the empty bladder scan to the predicted halv way position and 2) $ITV_{half\_way\_to\_full}$ covering the target movement from the predicted half way position to the empty bladder scan. A library of two plans based upon these two ITVs will be prepared. Additionally a robust backup plan will be prepared based on an ITV that covers the whole movement from the empty to the full bladder scan.

Patients who are randomized to standard radiotherapy will be treated according to standard clinical procedure of radiochemotherapy using simultaneous integrated boost technique with VMAT described in the EMBRACE-II protocol. Patients who are randomized to plan-of-the-day treatment will also be given radiochemotherapy as describes in section 2.1, but the radiotherapy planning and delivery procedure is different. For two pre-treatment image sets with different bladder filling a patient-specific motion model will be created. Two VMAT plans with smaller than standard safety margin will be prepared. One plan for a situation of full to half-full bladder and one for the situation of half-full to empty bladder and the additional back-up plan. In both the standard and intervention arm the patients will follow a standardized drinking protocol prior to each treatment). At the treatment unit the patient will be imaged with CBCT in the treatment position and these images will be registered to the planning CT scan. For the patients in the intervention arm the status of the bladder and the position of the uterus and cervix will be evaluated and the appropriate plan will be chosen for treatment. If it is not possible to evaluate the position of the cervix and uterus due to bad quality of the images, the robust plan should be used. In the standard arm there will be only one treatment plan with safety margin around the target large enough to take into account day-to-day variation in size of the target volumes.

For the first 50 patient the workload in terms of man hour for treatment planning (including CT acquisitions), plan verification and patient set-up procedure at the treatment unit will be recorded and compared between the two groups as described in Kong et al [23].

Patient will be scored in the out-patient clinic at baseline, week 4 and at end of external radiotherapy. Follow up scoring will be performed as described in section 1.1.1.

5.2 Measures to minimize bias

Measures to be taken to minimize bias in this study include consecutive inclusion of patients, the use of both patients and physician reported outcomes and keeping the patients blinded to the randomization. The treatment planning in both arms will be performed by specially trained staff at the treatment planning unit. This will prevent a bias due to difference in the planner's skills between

the two arms. All the patients will be treated in a limited numbers of units from the same vendor with specially trained staff with regard to evaluating information in CBCT images. Such approach will prevent that a potential difference between the arms will be due to the skills of the technicians on the treatment unit. In addition to Norwegian speaking patients we will also include patients able to speak and read English. We are aware that nuances may be lost for patients with another mother tongue than English, but we assume that the randomization will take this into account.

During the screening period participants will be assigned a unique identity number from the eCRF in ascending numerical order at each study site. At randomization on Day 1 participants will be assigned a unique randomization number from the eCRF. The randomization number encodes the participant's assignment to one of the two arms of the study, according to the randomization schedule. Each participant will be dispensed blinded study intervention, labeled with her unique randomization number, throughout the study. Patients will be randomly assigned in a 1:1 ratio to receive study intervention.

6 RISKS AND BENEFITS

This is a new interventional procedure and the likelihood of complications is not known at this time. Complications that can occur are thought to be similar to standard treatment. The oncologist will inform the patient about possible risks and side effects connected to the involved treatment. At present the standard treatment for patients with LACC is EBRT, concurrent chemotherapy with cisplatin and brachytherapy.

6.1 Anticipated clinical benefits

Patients receiving RT with the plan-of-the-day concept have tighter safety margins reducing the radiation dose to organs at risk, especially bowel and bladder. Anticipated clinical benefits are less acute and chronic toxicity from bowel and bladder.

6.2 Anticipated adverse events

The patients willing to participate in the study will have a bladder catheter inserted for a few hours on the day of planning CT. With this procedure there is a small risk for contracting a urinary tract infection.

6.3 Subjects

6.3.1 Inclusion Criteria

- Histologically confirmed cervical cancer eligible for definitve radiochemotherapy
- FIGO stage IB1-IVa
- Over 18 years

- Speaks and understands Norwegian or English.
- ECOG 0-2
- Histology: Squamous cell carcinoma, adenocarcinoma, adenosquamous carcinoma
- Ability to understand and fill in patient questionnaires, and willing to sign a written informed consent
- Large movers (LM), fundus movement ≥2,5 cm.

6.3.2 Exclusion Criteria

- Evidence of distant metastasis. Suspicious paraaortic lymphnodes below the renal vessels is allowed if they are covered by the radiation field
- Patients with previous surgery for their cervical cancer
- Uncontrolled intercurrent somatic illness.
- Psychiatric illness /social situations limiting study compliance
- Prior radiotherapy to the pelvis
- Patients who are pregnant or breastfeeding is excluded due to risk of teratogenic and abortifacient effects of radiotherapy and cisplatin, and the potential risk of adverse effect of nursing infants
- Patients that have received treatment for other invasive malignancies the last 3 years except non-melanoma skin cancers
- Nephrostomy
- Patients with inflammatory bowel disease

6.3.3 Criteria for withdrawal or discontinuation

Patients may be discontinued from study treatment and assessments at any time. Specific reasons for discontinuing a patient for this study are:

- Voluntary discontinuation by the patient who is at any time free to discontinue her participation in the study, without prejudice to further treatment. Patients will however be kindly asked to give a reason for discontinuation since the information can be valuable for the further conduction of the study
- Safety reason as judged by the Principal Investigator
- Major protocol deviation
- Incorrect enrolment i.e., the patient does not meet the required inclusion/exclusion criteria for the study
- Patients lost to follow-up
- Disease progression

Patients who are withdrawn from study treatment will be followed up according to national guidelines for patients with uterine cervical cancer.

If possible, a final assessment shall be made (end of study visit). The reason for discontinuation shall be recorded. The investigator is obliged to follow up any significant adverse events until the outcome either is recovered or resolved, recovering/resolving, not recovered/not resolved, recovered/resolved with sequelae, fatal or unknown.

All patients randomized will be included in the study population.

Patients who withdraw or are withdrawn from the study after randomization cannot be replaced.

6.3.4 Enrolment

Subjects with LACC are candidates for enrolment into this clinical study. Following review of the inclusion and exclusion criteria, eligible subjects will be invited to participate in this clinical study. Written and oral information on the clinical study, the fact that it involves research, the purpose of the clinical study, potential risks/benefits, etc. will be given to the subject. All subjects must give written informed consent prior to any study procedures being carried out. Once the subject has given written informed consent, they can be enrolled into the clinical study.

The patients will be given oral and written information about the study at the first consultation with oncologist. At this moment it is not know yet whether the patient is a LM or not. The patients will decide, and if willingly to participate sign the consent sheet, before returning for the planning (PET)-CT. Immediately after the planning (PET)-CT the LM will be identified and can be included in the study and randomized. Those who are not large movers will be registered as screening failures.

The subject's participation in this clinical study is completely voluntary. If the subject decides not to participate in the clinical study, their decision will have no impact on any services or treatment the subject are currently receiving and will also not affect their relationship with their clinician. Subjects are allowed to withdraw their participation at any time during the study without sacrificing their rights as a patient or compromising their quality of medical care.

6.3.5 Duration clinical study

OUS and SOH treat 120 LACC patients per year and the number has been stable for the last years. We estimate that 50 patients will be categorized as LM in our cohort. This is based on results from Bushmann et al and Heijkoop et al who respectively found 56% and 28% LM in their cohorts (26, 30). If we anticipate that 90% of the LM will be eligible for the study, it will be feasible to finalize inclusion within 4 years. With a follow up after treatment of 5 years the time from start-up to last visit will be 9 years.

6.3.6 Expected subject duration

The time from enrolment to final follow up for a patient will be the treatment time of 6-7 weeks plus the follow up period of 5 years.

6.3.7 Number of subject

A total of 190 patients will be included in this study; 95 patients in each arm.

6.3.8 Time to select all subjects

The study will remain open for enrolment until the planned total number is reached. Estimated time required to select this number of subjects is 4 years.

6.4 Procedures

6.4.1 Standard diagnostic work up

Clinical status
Medical history (including disease history and corresponding treatment details), physical examination (cor/pulm/abdomen and peripheral lymph node status), vital signs (weight, height, blood pressure, temperature and pulse) and ECOG performance status will be evaluated at baseline.

During treatment patients will be followed weekly by a physician, and toxicities will be registered.

Imaging
Multiparametric MRI of the pelvis/abdomen and CT scan of the thorax/abdomen/pelvis performed within 4 weeks before inclusion.

T2-weighted- and diffusion-weighted-MRI will be repeated at brachytherapy.

Laboratory analysis
Laboratory tests will be performed at baseline and weekly during treatment, and include hematological parameters, electrolytes, creatinine, albumin, CRP.

Gynecological examination under general anesthesia
Patients will be examined under general anesthesia for assessment of FIGO-stage and measurement of tumor size. Tumor biopsies will be performed for verification of diagnosis.

Radiotherapy planning The treatment planning will be performed according to the EMBRACE II protocol (appendix 1) and local procedures (E-håndbok).

6.4.2 Study specific procedures

Informed consent
Informed consent must have been given voluntarily by each subject before any study specific procedures are initiated. See section 12.

Concomitant medication
All concomitant medication (incl. vitamins, herbal preparation and other “over-the-counter” drugs) used by the subject within 28 days of treatment start must be recorded in the CRF.

Evaluation of safety Acute and long-term toxicity will be graded using the CTCAE version 5.0. Frequency data for selected treatment-related Adverse Events (AEs), grade 3 or 4, and Serious Adverse Events (SAEs) will be reported, see section 13.Late toxicity will be registered and reported, and the incidence will be compared between study arms.

PROM-questionnaires and CTCEA scoring

QLQ-C30, QLQ-CX24 and QLQ-EN24 and a selection of CTCAE early and late morbidity v. 5.0 -scoring will be performed at baseline, at week 4 of treatment, at end of external radiotherapy and every 3rd months the first year, every 6 months 2nd year and yearly until 5 years.

Baseline PROMs and CTCAE scoring will be controlled and performed at the first weekly visit in the outpatient clinic. This visit will be scheduled prior to the first treatment. Further filling of PROMs will be done electronically for most patients as described in section 4. For those preferring paper filling this will be done at weekly visits with key personnel keeping control of the time schedule. CTCAE scoring will be done at weekly visit or at ward if patient is admitted. Follow-up scoring of CTCEA will be done by telephone. A time window of +30 days will be accepted.

Image acquisition

Patients will have a CT scanning with or without a PET as a standard component of the treatment planning process. Before imaging the patient will have inserted a bladder catheter. First one scan is acquired with empty bladder and thereafter the bladder is filled and a new scan is acquired, both in treatment position. This is described in detail in section 5.1.4

Radiotherapy planning

The full-bladder CT will always be used for treatment planning, and a physician will perform the contouring. The planning procedure is described in detail in 5.1.4 and 6.4.1

At the treatment unit

CBCT scans will be acquired daily and registered to the planning CT scan. For the patients in the intervention arm the procedure is described in section 5.1.4.

6.4.3 Follow-up

After end of treatment patients will have follow-up according to guidelines at their local hospitals. We will perform telephone consultations every 3rd months the first year of follow-up, every 6 month 2nd year and yearly until 5 years and to fill in the CTCEA-scores v.5.0. At the same time interval the patients will receive the QLQ-C30, QLQ-CX24, and QLQ-EN24 electronically or in paper format by mail. CT of the thorax, abdomen and pelvis is always performed 3 months after end of treatment. MRI will be assessed in each individual case. Further imaging will be assessed by follow-up doctor.

6.4.4 Schedule of Activities

Procedure	**Screening period**		**Intervention Period**				**End of external radiotherapy**	**Follow-up 1st year)**	**Follow-up 2nd to 5th year**	**Notes**
	(up to 21 days before Day 1)	**Day of randomization**	**Week 1** (Day 1)	**Week 2** (± 2 days)	**Week 3** (± 2 days)	**Week 4** (± 2 days)	**Fraction 25** (± 2 days)	**Every 3 months** (+ 30 days)	**Every 6 months** (+ 30 days)	
Standard diagnostic procedures:										
Demography	X									
Full physical examination including height and weight	X									
Medical history	X									
Past and current medical conditions	X									
Radiological assessments within 4 weeks before inclusion	X									
Diagnostic gynecological examination under general anesthesia	X									

Procedure	Screening period		Intervention Period				End of external radiotherapy	Follow-up 1st year)	Follow-up 2nd to 5th year	Notes
	(up to 21 days before Day 1)	**Day of randomization**	**Week 1** (Day 1)	**Week 2** (± 2 days)	**Week 3** (± 2 days)	**Week 4** (± 2 days)	**Fraction 25** (± 2 days)	**Every 3 months** (+ 30 days)	**Every 6 months** (+ 30 days)	
Laboratory tests (weekly)	X	X*	X	X	X	X				See section 6.4.1 *only creatinine on day of randomization
Vital signs	X									
Standard arm only: standard radiotherapy (daily)			X	X	X	X	X			
ECOG performance status	X									
Study specific procedures:										
Informed consent	X									
Inclusion and exclusion criteria	X									
Randomization		X								
Radiotherapy planning		X								
CT scanning with or without PET as a standard component of the treatment planning process.		X								Scanning will be performed with a bladder catheter inserted, see section 5.1.4
Study intervention arm only: Radiotherapy with plan-of-the-day-concept (daily)			X	X	X	X	X			

Procedure	Screening period		Intervention Period				End of external radiotherapy	Follow-up 1st year)	Follow-up 2nd to 5th year	Notes
	(up to 21 days before Day 1)	**Day of randomization**	**Week 1** (Day 1)	**Week 2** (± 2 days)	**Week 3** (± 2 days)	**Week 4** (± 2 days)	**Fraction 25** (± 2 days)	**Every 3 months** (+ 30 days)	**Every 6 months** (+ 30 days)	
CTCAE early morbidity						X	X			
CTCAE late morbidity			X					X	X	
Protocol defined AE review		X	←==========→				X			
Concomitant medication review		X	←==========→				X			
Patient reported outcomes:										
EORTC QLQ C30-questionnaire			X*				X	X	X	*baseline questionnaire filled in before start of treatment
CX24-Questionnaire			X*				X	X	X	*baseline questionnaire filled in before start of treatment
EN24-questinnaire			X*				X	X	X	*baseline questionnaire filled in before start of treatment

7 STATISTICAL CONCIDERATIONS

7.1 Statistical design

This is a single blinded randomized controlled trial. In the control arm standard radiochemotherapy is delivered using one single treatment plan where safety margins takes into account possible movements of the target volume. In the intervention arm several treatment plans are prepared and the appropriate plan is used at each treatment session.

The primary trial objective is to test the null hypothesis (H0) of no difference in change in patient reported diarrhea from baseline to the end of radiotherapy between the two groups.

7.2 Sample size, significance and power of the clinical study

The sample size was calculated as for a superiority study, based on the null hypothesis that patient reported quality of life following plan-of-the-day treatment is equal to patient reported quality of life following standard treatment. The primary outcome, reported acute diarrhea, was used for the sample size calculation.

Based on Kirchheiner et al (9) we calculated a mean score of 65 at the end of conformal radiotherapy for LACC. Based on data presented in the EMBRACE-II protocol (31) a small reduction of 5 in the EORTC-score can be anticipated when VMAT technique is used, i.e. a mean score of 60 for diarrhea at the end of radiotherapy can be expected in our standard arm. After plan-of-the-day treatment, representing the intervention arm in our study, Heijkoop et al found a score of 49 (28). Such a difference in change, 60 vs. 49, is considered clinical important.

The standard deviation (SD) for diarrhea at the end of radiotherapy was assumed to be 29 (27). It is expected that the standard deviated is similar in the two arms. Further, based on data from 56 patients included the EMBRACE I protocol at OUS showed a correlation of 0.41 between diarrhea at baseline and the end of treatment. A similar correlation can be expected in the present study.

With equal allocation in both arms, a power of 80% and two-sided significance level of 0.05, the sample size was calculated to be 95 patients in each treatment arm, and 190 patients in total.

7.3 Statistical analysis

The primary endpoint, **the diarrhea single item score**, will be analyzed with a linear mixed model with treatment, time point (baseline, 4 weeks, at the end of radiotherapy), and treatment x time point interaction as fixed effects. A random intercept will be used. Based on the fitted model, we will estimate the mean baseline, 4 weeks, and at the end of radiotherapy values (with 95% CIs) for each treatment, and the between-treatment difference in changes from baseline to the end of radiotherapy (with 95% CI and a p-value for the null hypothesis of no difference).

The secondary endpoints will be analyzed in the same way using the time points at baseline, 2 and 5 years after treatment.

Descriptive statistics will be presented for the two treatment arms. Non-parametric tests (Mann-Whitney U test) will be used for comparison between the two groups of patients when data are non-normally distributed.

8 DATA MANAGEMENT

8.1 Case report forms (CRFs)

The designated investigative staff will enter the data required by the protocol, including the PROM questionnaires completed by the patients, into the database. The study will use an electronic Case Report Form (CRF) system provided by VieDoc.

The Principal Investigator is responsible for assuring that data entered into the database is complete, accurate, and that entry is performed in a timely manner. The signature of the Investigator will attest the accuracy of the data on each CRF. If any assessments are omitted, the reason for such omissions will be noted on the CRFs. Corrections, with the reason for the corrections will also be recorded.

After database lock, the information will be stored on a dedicated and access controlled directory at K\:Sensitivt.

8.2 Source Data

The medical records for each patient should contain information which is important for patient safety and continued care and to fulfill the requirement that critical study data should be verifiable.

To achieve this, the medical records of each patient should clearly describe at least:

• That the patient is participating in the study, e.g., by including the enrollment number and the study code or other study identification;

• Date when Informed Consent was obtained from the patient and statement that patient received a copy of the signed and dated Informed Consent;

• Results of all assessments confirming a patient's eligibility for the study;

• Diseases (past and current; both the disease studied and others, as relevant);

• Surgical history, as relevant;

• Treatments withdrawn/withheld due to participation in the study;

• Results of assessments performed during the study;

• ECOG performance status

• Treatments given, changes in treatments during the study and the time points for the changes;

• Visits to the clinic / telephone contacts during the study, including those for study purposes only;

• Non-Serious Adverse Events and Serious Adverse Events (if any) including causality assessments;

• Date of, and reason for, discontinuation from study treatment;

• Date of, and reason for, withdrawal from study;

• Date of death and cause of death, if available;

• Additional information according to local regulations and practice;

If source data for any of the above listed data is not captured in the medical records, the location must be clearly identified in a source data list and filed in the Investigator Site File.

Confidentiality

The investigator shall arrange for the secure retention of the patient identification and the code list. Patient files shall be kept for the maximum period of time permitted by each hospital. The study documentation (CRFs, Site File etc) shall be retained and stored during the study and for 15 years after study closure. All information concerning the study will be stored in a locked cabinet inaccessible to unauthorized personnel.

9 AMENDMENTS TO THE RESEARCH PROTOCOL

The Research Protocol may be requiring to be amended during the conduct of the clinical study. Any amendments to the Research Protocol will be agreed upon between the representative for the research responsible institution and the principle investigator. The amendments will be approved by the ethics committee (REC).

10 DEVIATIONS FROM THE RESEARCH PROTOCOL

10.1 Statement that investigator is not allowed to deviate from the research protocol

Investigators ascertain they will apply due diligence to avoid protocol deviations. All significant protocol deviations will be recorded and reported in the Clinical Study Report.

10.2 Procedures for recording deviations for the research protocol

Authorized representatives of a Competent Authority and Ethics Committee may visit the investigational site to perform inspections, including source data verification. Likewise, the representatives from sponsor may visit the center to perform an audit. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP) (unless other specified in the protocol), and any applicable regulatory requirements. The study PI will ensure that the inspectors and auditors will be provided with access to source data/documents.

11 STATEMENTS OF COMPLIANCE

11.1 Statement of compliance with ethics principles

The study will be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with GCP (unless other specified in the protocol) and applicable regulatory requirements. Registration of patient data will be carried out in accordance with national personal data laws.

11.2 Statement regarding ethical approval

The study protocol, including the patient information and informed consent form to be used, must be approved by the regional ethics committee before enrolment of any patients into the study. The study PI is responsible for informing the ethics committee of any serious and unexpected adverse events and/or major amendments to the protocol as per national requirements.

11.3 Additional requirement from ethics committee

The clinical study performance will include any additional requirements by the REC.

12 INFORMED CONSENT PROCESS

The Investigator is responsible for giving the patients full and adequate verbal and written information about the nature, purpose, possible risk, and benefit of the study. They will be informed as to the strict confidentiality of their patient data, but that their medical records may be reviewed for trial 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 prejudice the patient's subsequent care. Documented informed consent must be obtained for all patients included in the study before they are registered in the study. This will be done in accordance with the national and local regulatory requirements. The Investigator is responsible for obtaining signed informed consent.

A copy of the patient information and consent will be given to the patients. The signed and dated patient consent forms will be filed in the Investigator Site File binder and a note will be made in the patient's electronic medical record at the hospital.

13 ADVERSE EFFECTS

13.1 Protocol defined Adverse Events

In accordance with ICH GCP an adverse event (AE) is any untoward medical occurrence, unintended disease or injury, or any untoward medical occurrence, unintended disease or injury, or any untoward clinical sign (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the study treatment.

IMPORTANT, NOTE: Due to the study design and study intervention in this academically radiotherapy trial it is decided to not collect all AEs and SAEs as specified in ICH GCP-guidelines. In this trial only two conditions will be collected:

- Diarrhea
- Electrolyte disturbances

This is because the study intervention consists of expansion of an already implemented procedure (dose plan), not a comparison of two different interventions. The trial consists of more frequent assessment of the dose planning for radiotherapy than in standard care, the patients in the exploratory arm are not expected to experience increased frequency of side effects; in contrast it is expected to decrease side effects of the radiotherapy. The efficacy of the study intervention will be assessed as described in chapter 5.

13.2 Protocol defined Serious Adverse Events (SAE)

Serious Adverse Events (SAE) is diarrhea or electrolyte disturbances that:

1. Results in death
2. Led to serious deterioration in the health of the subject, that either resulted in
    a) Life threatening illness or injury, or
    b) A permanent impairment of body structure or body function, or
    c) In-patient or prolonged hospitalization, or
    d) Need of medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or body function

NOTE: This includes events that might have led to a serious adverse event if

a) suitable action had not been taken or
b) intervention had not been made or,
c) the circumstances had been less fortunate

These are handled under the SAE reporting system in the eCRF.

13.3 Assessment and reporting of protocol defined AEs and SAEs

All protocol defined AEs and SAEs will be graded using CTCAE version 5.0.

Reporting of AEs

Only protocol defined AEs grade 3 or more should be reported in the eCRF in timely manner.

Reporting of SAEs

Protocol defined SAEs must be reported by the Investigator to the sponsor, Oslo University Hospital within 24 hours after the site has gained knowledge of the SAE. Every SAE must be documented by the Investigator on the SAE pages in the eCRF. The initial report shall promptly be followed by detailed, written reports if necessary. The initial and follow-up reports shall identify the trial subjects by unique code numbers assigned to the latter.

The sponsor keeps detailed records of all SAEs reported by the Investigators and performs an evaluation with respect to seriousness, causality and expectedness.

13.4 Reporting of serious undesirable unexpected medical events

By Norwegian regulations (The Norwegian Health Research Act §23) the project leader shall report serious undesirable unexpected medical events judged to be caused by the research project. Such events can be sent to the health authority in writing. Please contact Kjersti Bruheim at UXKJUH@ous-hf.no as soon as possible, if you suspect such an event.

13.5 List of foreseeable events, anticipated adverse treatment/ intervention effects

Radiotherapy

Radiotherapy is the primary therapeutic modality, and delays or dose modifications of the planned course of radiotherapy will only be performed in exceptional circumstances were acute, severe toxicity persists after relevant measures. Any interruptions in radiotherapy treatment will be recorded in the CRF including the reason for treatment break.

14 SUSPENSION OR PREMATURE TERMINATION OF THE CLINICAL STUDY

The whole trial may be discontinued at the discretion of the PI or the sponsor in the event of any of the following:

- Occurrence of AEs unknown to date in respect of their nature, severity and duration
- Medical or ethical reasons affecting the continued performance of the trial
- Difficulties in the recruitment of patients

The sponsor and principal investigator will inform all investigators, the relevant Competent Authorities and Ethics Committees of the termination of the trial along with the reasons for such action. If the study is terminated early on grounds of safety, the Competent Authorities and Ethics Committees will be informed within 15 days.

15 PUBLICATION POLICY

Upon study completion and finalization of the study report the results of this study will either be submitted for publication and/or posted in a publicly assessable database of clinical study results.

The results of this study will also be submitted to the Competent Authority and the Ethics Committee according to EU and national regulations.

All personnel who have contributed significantly with the planning and performance of the study (Vancouver convention 1988) may be included in the list of authors.

16 TRIAL INSURANCE

The principal Investigator has insurance coverage for this study thorough membership of “Norsk Pasientskadeerstatning”.

17 BIBLIOGRAPHY

1. registry Nc. 2019 [Available from: https://www.kreftregisteret.no/Registrene/Kreftstatistikk/.

2. Chopra S, Krishnatry R, Dora T, Kannan S, Thomas B, Sonawone S, et al. Predictors of late bowel toxicity using three different methods of contouring in patients undergoing post-operative radiation for cervical cancer. 2015;88(1055):20150054.

3. Isohashi F, Yoshioka Y, Mabuchi S, Konishi K, Koizumi M, Takahashi Y, et al. Dose-Volume Histogram Predictors of Chronic Gastrointestinal Complications After Radical Hysterectomy and Postoperative Concurrent Nedaplatin-Based Chemoradiation Therapy for Early-Stage Cervical Cancer. International Journal of Radiation Oncology*Biology*Physics. 2013;85(3):728-34.

4. Sini C, Noris Chiorda B, Gabriele P, Sanguineti G, Morlino S, Badenchini F, et al. Patient-reported intestinal toxicity from whole pelvis intensity-modulated radiotherapy: First quantification of bowel dose–volume effects. Radiotherapy and Oncology. 2017;124(2):296-301.

5. Fokdal L, Pötter R, Kirchheiner K, Lindegaard JC, Jensen NBK, Kirisits C, et al. Physician assessed and patient reported urinary morbidity after radio-chemotherapy and image guided adaptive brachytherapy for locally advanced cervical cancer. Radiotherapy and Oncology. 2018;127(3):423-30.

6. Fokdal L, Tanderup K, Pötter R, Sturdza A, Kirchheiner K, Chargari C, et al. Risk Factors for Ureteral Stricture After Radiochemotherapy Including Image Guided Adaptive Brachytherapy in Cervical Cancer: Results From the EMBRACE Studies. International Journal of Radiation Oncology*Biology*Physics. 2019;103(4):887-94.

7. Jensen NBK, Pötter R, Kirchheiner K, Fokdal L, Lindegaard JC, Kirisits C, et al. Bowel morbidity following radiochemotherapy and image-guided adaptive brachytherapy for cervical cancer: Physician- and patient reported outcome from the EMBRACE study. Radiotherapy and Oncology. 2018;127(3):431-9.

8. Kirchheiner K, Pötter R, Tanderup K, Lindegaard JC, Haie-Meder C, Petrič P, et al. Health-Related Quality of Life in Locally Advanced Cervical Cancer Patients After Definitive Chemoradiation Therapy Including Image Guided Adaptive Brachytherapy: An Analysis From the EMBRACE Study. International Journal of Radiation Oncology*Biology*Physics. 2016;94(5):1088-98.

9. Kirchheiner K, Nout RA, Czajka-Pepl A, Ponocny-Seliger E, Sturdza AE, Dimopoulos JC, et al. Health related quality of life and patient reported symptoms before and during definitive radio(chemo)therapy using image-guided adaptive brachytherapy for locally advanced cervical cancer and early recovery — A mono-institutional prospective study. Gynecologic Oncology. 2015;136(3):415-23.

10. Kirchheiner K, Pötter R, Nout RA, Schwartz-Vittrup A, Holzner B, Bentzen SM, et al. Late, Persistent, Substantial, Treatment-Related Symptoms After Radiation Therapy (LAPERS): A New Method for Longitudinal Analysis of Late Morbidity-Applied in the EMBRACE Study. International journal of radiation oncology, biology, physics. 2020;106(2):300-9.

11. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: A Quality-of-Life Instrument for Use in International Clinical Trials in Oncology. JNCI: Journal of the National Cancer Institute. 1993;85(5):365-76.

12. Greimel E, Nordin A, Lanceley A, Creutzberg CL, van de Poll-Franse LV, Radisic VB, et al. Psychometric validation of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Endometrial Cancer Module (EORTC QLQ-EN24). European Journal of Cancer. 2011;47(2):183-90.

13. Greimel ER, Kuljanic Vlasic K, Waldenstrom A-C, Duric VM, Jensen PT, Singer S, et al. The European Organization for Research and Treatment of Cancer (EORTC) Quality-of-Life questionnaire cervical cancer module. 2006;107(8):1812-22.

14. Kirchheiner K, Nout R, Lindegaard J, Petrič P, Limbergen EV, Jürgenliemk-Schulz IM, et al. Do clinicians and patients agree regarding symptoms? A comparison after definitive radiochemotherapy in 223 uterine cervical cancer patients. Strahlentherapie und Onkologie : Organ der Deutschen Rontgengesellschaft [et al]. 2012;188(10):933-9.

15. Najjari Jamal D, Pötter R, Haie-Meder C, Lindegaard JC, Juergenliemk-Schulz IM, Mahantshetty U, et al. Physician assessed and patient reported lower limb edema after definitive radio(chemo)therapy and image-guided adaptive brachytherapy for locally advanced cervical cancer: A report from the EMBRACE study. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology. 2018;127(3):449-55.

16. Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: individual patient data meta-analysis. The Cochrane database of systematic reviews. 2010;2010(1):Cd008285.

17. Datta NR, Stutz E, Liu M, Rogers S, Klingbiel D, Siebenhüner A, et al. Concurrent chemoradiotherapy vs. radiotherapy alone in locally advanced cervix cancer: A systematic review and meta-analysis. Gynecol Oncol. 2017;145(2):374-85.

18. Helsedirektoratet. Nasjonalt handlingsprogram med retningslinjer for gynekologisk kreft 2020 [Available from: https://www.helsedirektoratet.no/retningslinjer/gynekologisk-kreft-handlingsprogram.

19. Bondar ML, Hoogeman MS, Mens JW, Quint S, Ahmad R, Dhawtal G, et al. Individualized nonadaptive and online-adaptive intensity-modulated radiotherapy treatment strategies for cervical cancer patients based on pretreatment acquired variable bladder filling computed tomography scans. International journal of radiation oncology, biology, physics. 2012;83(5):1617-23.

20. van de Bunt L, van der Heide UA, Ketelaars M, de Kort GAP, Jürgenliemk-Schulz IM. Conventional, conformal, and intensity-modulated radiation therapy treatment planning of external beam radiotherapy for cervical cancer: The impact of tumor regression. International Journal of Radiation Oncology*Biology*Physics. 2006;64(1):189-96.

21. Veldeman L, Madani I, Hulstaert F, De Meerleer G, Mareel M, De Neve W. Evidence behind use of intensity-modulated radiotherapy: a systematic review of comparative clinical studies. The Lancet Oncology. 2008;9(4):367-75.

22. Jadon R, Pembroke CA, Hanna CL, Palaniappan N, Evans M, Cleves AE, et al. A Systematic Review of Organ Motion and Image-guided Strategies in External Beam Radiotherapy for Cervical Cancer. Clinical Oncology. 2014;26(4):185-96.

23. Lim K, Small W, Portelance L, Creutzberg C, Jürgenliemk-Schulz IM, Mundt A, et al. Consensus Guidelines for Delineation of Clinical Target Volume for Intensity-Modulated Pelvic Radiotherapy for the Definitive Treatment of Cervix Cancer. International Journal of Radiation Oncology*Biology*Physics. 2011;79(2):348-55.

24. Ahmad R, Bondar L, Voet P, Mens J-W, Quint S, Dhawtal G, et al. A margin-of-the-day online adaptive intensity-modulated radiotherapy strategy for cervical cancer provides superior treatment

accuracy compared to clinically recommended margins: A dosimetric evaluation. Acta Oncologica. 2013;52(7):1430-6.

25. Ahmad R, Hoogeman MS, Quint S, Mens JW, de Pree I, Heijmen BJM. Inter-fraction bladder filling variations and time trends for cervical cancer patients assessed with a portable 3-dimensional ultrasound bladder scanner. Radiotherapy and Oncology. 2008;89(2):172-9.

26. Buschmann M, Majercakova K, Sturdza A, Smet S, Najjari D, Daniel M, et al. Image guided adaptive external beam radiation therapy for cervix cancer: Evaluation of a clinically implemented plan-of-the-day technique. Zeitschrift für Medizinische Physik. 2018;28(3):184-95.

27. Heijkoop ST, Nout RA, Quint S, Mens JWM, Heijmen BJM, Hoogeman MS. Dynamics of patient reported quality of life and symptoms in the acute phase of online adaptive external beam radiation therapy for locally advanced cervical cancer. Gynecologic Oncology. 2017;147(2):439-49.

28. Kirchheiner K, Pötter R, Nout RA, Schwartz-Vittrup A, Holzner B, Bentzen SM, et al. Late, Persistent, Substantial, Treatment-Related Symptoms After Radiation Therapy (LAPERS): A New Method for Longitudinal Analysis of Late Morbidity—Applied in the EMBRACE Study. International Journal of Radiation Oncology*Biology*Physics. 2020;106(2):300-9.

29. Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. 1998;16(1):139-44.

30. Heijkoop ST, Langerak TR, Quint S, Mens JWM, Zolnay AG, Heijmen BJM, et al. Quantification of intra-fraction changes during radiotherapy of cervical cancer assessed with pre- and post-fraction Cone Beam CT scans. Radiotherapy and Oncology. 2015;117(3):536-41.

31. www.embracestudy.dk. 2020 [

LIST OF APPENDICES

Appendix 1 Embrace II protocol

Appendix 2 EORTC QLQ-C30, QLQ-CX24 and QLQ-EN24 QoL questionnaires

Appendix 3 CTCAE early and late morbidity