EMBRAVE

IntErnational observational study on primary (chemo)radiotherapy and iMage-based adaptive BRAchytherapy for Vaginal cancEr

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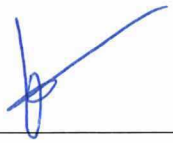
Principal Investigator: Prof. Dr. R.A. Nout, Radiation Oncologist		11-2-2025

TABLE OF CONTENTS

1. LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

^{18}F-FDG	Fluorine 18 - Fluorodeoxyglucose
2/3/4D	Two/Three/Four-dimensional
ABS	American Brachytherapy Society
ACT	Addenbrooke's Contouring Tool
ATRAB	Applied and Translational Radiobiology (Medical University Vienna)
AUC	Area Under the Curve
BL	Baseline
BT	Brachytherapy
CBG	Canadian Brachytherapy Group
CBCT	Cone beam computed tomography
CHT	Chemotherapy
COP	Coverage Probability
CR	Complete Remission
CRF	Case Report Form
CRT	Conformal Radiotherapy
CSS	Cancer Specific Survival
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTV	Clinical Target Volume
CTVHR	High risk clinical target volume
CTVIR	Intermediate risk clinical target volume
CuSO4	Copper sulphate
D90	The isodose that includes 90% of the target
D100	The isodose that includes 100% of the target
$D2cm_3$	Minimum dose in the most exposed 2 cm3 of an OAR
DFS	Disease Free Survival
DNA	Deoxyribonucleic acid
DVH	Dose Volume Histogram
EANM	European Association of Nuclear Medicine
EBRT	External Beam Radiotherapy
EMBRACE	The European and International study on MRI-guided Brachytherapy in locally Advanced Cervical Cancer
EORTC	European Organisation for Research and Treatment of Cancer
EoT	End of Treatment
EPID	Electronic Portal Imaging Device
ER	Oestrogen Receptor
ESTRO	European SocieTy for Radiotherapy and Oncology
EQD2	Equivalent dose in 2 Gy fractions
FIGO	Fédération Internationale de Gynécologie et d' Obstétrique
FTE	Full Time Equivalent
Fx	Fraction
G	(Morbidity) Grade
GEC	Groupe Européen de Curiethérapie
GFR	Glomerula Filtration rate
GI	Gastro-Intestinal
GTV	Gross Tumour Volume
Gy	Gray
HDR	High Dose Rate
HPV	Human Papilloma Virus
HR	High Risk
IC	Intracavitary
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICRU	International Commission on Radiation Units and Measurements

IGABT	Image-guided Adaptive Radiotherapy
IGRT	Image Guided Radiotherapy
IMRT	Intensity Modulated Radiotherapy
IR	Intermediate Risk
IS	Interstitial
ITV	Internal Target Volume
IV	Intravenous
kV	Kilovoltage
LACC	Locally Advanced Cervical Cancer
LC	Local Control
LN	Lymph Nodes
LR	Low Risk
MMRd	Mismatch repair deficiency
MRI	Magnetic Resonance Imaging
MVCT	Megavoltage Computed Tomography
N0/N-	Lymph Node Negative
N1/N+	Lymph Node Positive
OAR	Organs at Risk
OS	Overall Survival
OTT	Overall Treatment Time
p53abn	p53 abnormal
PAN	Para-Aortic Lymph Nodes
PDR	Pulsed Dose Rate
PET-CT	Positron Emission Tomography- Computed Tomography
PFS	Progression Free Survival
PI	Principal Investigator
PIBS	Posterior-Inferior Border of Symphysis
POLE	DNA polymerase epsilon
PTV	Planning Target Volume
QoL	Quality of Life
RT	Radiotherapy
SD	Standard Deviation
SIB	Simultaneous Integrated Boost
SPSS	Statistical Package for Social Sciences
SUV_{max}	Maximum Standardized Uptake Value
TNM	Tumour (Lymph)Nodes Metastasis
TPS	Treatment Planning System
TRAK	Total Reference Air Kerma
uCR	Uncomplete Remission
US	Ultrasound
VMAT	Volumetric Modulated Arc Therapy
WHO	World Health Organization

2. SUMMARY

Background/Rationale

Primary vaginal cancer is a rare gynaecologic cancer, constituting approximately 3% of gynaecological malignancies, with the vast majority being of squamous or adeno(-squamous) histology. Due to its rareness, the optimal treatment strategy for vaginal cancer is mainly based on experience from the treatment of locally advanced cervical cancer with which it shares many similarities. Radio(chemo)therapy with image-guided adaptive brachytherapy (IGABT) is the current standard treatment for locally advanced cervical cancer. The first clinical experiences in limited numbers of patients showed that IGABT for vaginal cancer was feasible, and promising clinical results were reported. However, there were distinct differences with cervical cancer, in particular with regard to anatomy and brachytherapy applicator systems, and a common concept for brachytherapy target volume and dose reporting was lacking. For this purpose, the GYN GEC-ESTRO task-group developed a target concept for primary vaginal cancer, in which different target volumes were defined for brachytherapy.

While the majority of primary vaginal cancers has a squamous or adeno(-squamous) histology, there are few rare histological subtypes (e.g. clear cell carcinoma, neuroendocrine carcinoma of the vagina) that may be treated in accordance to the aforementioned target concept. In addition, there are rare clinical scenarios (primary vaginal cancer stage I <2cm; vaginal carcinoma in situ), that in selected cases may be treated with IGABT alone. Contemporary clinical evidence to guide treatment decision making in these situations is sparse. This study, offers a parallel registration cohort for these rare histological subtypes and treatment with IGABT alone, with the aim to gather prospective clinical outcomes in a multicentre setting.

The clinical management of vaginal recurrences from other cancers of the female genital tract (e.g. endometrial cancer, cervical cancer) with IGABT is also considered an appealing approach. For this reason, a consensus target concept for treatment with radio(chemo)therapy and IGABT for vaginal recurrences of other cancers of the female genital tract (e.g. endometrial cancer, cervical cancer) was developed by a joint effort of GYN GEC-ESTRO, ABS and CBG. This target concept shows great similarity to that of primary vaginal cancer.

The target concepts for primary vaginal cancer and vaginal recurrences need clinical validation as the uptake, feasibility and oncological outcomes including morbidity and quality of life are yet unknown. The rationale for this study is the need for an evidence-based treatment for primary and recurrent vaginal cancer. Now targets concept have been developed, they should be implemented and evaluated in a multicentre setting to advance treatment.

Objective and hypothesis

The general aim is to improve clinical outcomes of patients with vaginal cancer treated with definitive radio(chemo)therapy and IGABT. Specific aims are to develop evidence-based recommendations for IGABT and to identify prognostic parameters for oncological outcomes, morbidity and quality of life. Parallel registration cohorts for rare histological subtypes and treatment with IGABT alone are aimed to provide contemporary multicentre prospective clinical outcomes in these rare conditions. Furthermore, the study aims to create possibilities for future fundamental and/or translational studies by asking study participants permission for the storage and use of tumour tissue, imaging and treatment plans.

Study design:

The study is a prospective, observational, international multi-centre cohort study on the treatment of vaginal cancer with radio(chemo)therapy and IGABT. This design offers parallel registration of cohorts for rare histological subtypes and treatment with IGABT alone. This cohort study is designed as a continuous international registry, since vaginal tumours are rare malignancies for which international prospective data collection is needed.

Study population:
Adult patients with primary vaginal cancer (FIGO stage I-IVA) or vaginal recurrences (without distant metastases) who are treated with curative intent by primary radio(chemo)therapy and MRI based image-guided adaptive brachytherapy according to the abovementioned target concept for vaginal cancer are eligible to participate in this study. Rare histological subtypes including carcinoma in situ and treatment with IGABT alone are eligible for registration in a parallel cohort within this study.

Treatment of study population:
Patients included in this registration study receive the same treatment and have the same follow-up as patients who do not participate. Study participants will give informed consent for the prospective collection of their clinical and treatment data (including DICOM imaging and DICOM-RT treatment data). Furthermore, they will have the opportunity to participate in the observational morbidity and quality of life study, for which questionnaires will need to be filled out on a regular basis. Finally, they will have the opportunity to give permission for the storage and use of tumour material for future fundamental or translational studies.

Quality assurance:
This study will have two study phases: in the first phase only 6 institutions (Aarhus University Hospital, Amsterdam UMC, Leiden UMC, Erasmus MC, Medical University of Vienna and Gustave Roussy) will open for inclusion. These institutions were involved in the development of the GEC-ESTRO target concept for vaginal cancer and already treat vaginal cancer with the most up-to-date treatment equipment and techniques. Based on the experience of these 6 centres during the first year, accreditation and quality assessment procedures are refined for new centres. New centres should already be experienced with the treatment of cervical cancer by MRI-based IGABT and should complete a dummy run (to ensure adherence to the target concept, methodology for dose reporting, and study logistics) to obtain accreditation. In addition, quality assessment (QA) procedures will be performed for every participating centre after the first year to ensure continuous adherence to the protocol. Centres will be given feedback on their performance, and additional QA's will be planned if necessary.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness:
The current study is a longitudinal observational study with registration of clinical outcomes after standard care with radio(chemo)therapy and IGABT for vaginal cancer. As such, there are no experimental interventions performed in this study. Hence, there is no potential benefit or risk for the patients participating in this study. The aim of this study is to collect data in order to optimize and improve treatment of vaginal cancer.

Main study outcome measures:
This study is an observational, prospective registration study, wherein neither an experimental treatment is compared to the standard treatment, nor groups of patients are compared. As a result, this study has no classical primary study endpoint.
Nonetheless, the following endpoints are defined to ascertain proper effectuation:

1) Oncological events (disease control; disease-free, disease-specific and overall survival) at 2 and 5 years of follow-up.
2) Acute and late morbidity events (urogenital, gastrointestinal, bone and general toxicity) at 2 and 5 years of follow-up.
3) Uptake of the target concept recommendations.
4) Feasibility of concurrent systemic therapy (% completion, prevalence of reasons for non-completion).

Sample size and data maturity:
This observational cohort study is designed as a registry for vaginal cancer. As such there is no predefined maximal number of patients that can be included in the registry. At the inclusion of 100 patients, the overall incidence of the clinical outcomes (oncological evens and morbidity) can be

estimated. Furthermore, a descriptive analysis of prescribed doses and a validation of the target concept can be conducted.
At the inclusion of 300 patients, multivariable analyses can be performed to determine the independent effect of predictors on clinical outcomes. However, estimates will become more accurate and conclusions more reliable, if more patients can be included.
It is expected that the first 100 patients with vaginal tumours will be included during the first 3 years and the first 300 patients during the first 8 years. Henceforth, the first analyses which require 100 patients, and that don't require follow-up after treatment could be done in the 3rd year. First analyses using oncological outcomes will require a follow-up and are expected to be performed in the 6th year. The analyses that require at least 300 patients and use clinical outcomes could be performed at earliest in the 11th year of the study.

3. BACKGROUND AND RATIONALE

3.1 Background

3.1.1 Primary vaginal cancer

Primary vaginal cancer is a rare gynaecologic cancer, constituting approximately 3% of gynaecological malignancies, with the vast majority being of squamous or adeno(-squamous) histology. [1] Radiotherapy including brachytherapy is the treatment of choice for the majority of patients as organ-sparing surgery with negative resection margins is difficult to achieve.[2] Due to its rareness, the treatment strategy for primary vaginal cancer has been based on experience from the treatment of locally advanced cervical cancer with which it shares many similarities. Therefore, a combination of external beam radiotherapy (EBRT) (45-50Gy with 1.8-2Gy per fraction) and a brachytherapy-boost up to a total dose of 70-80Gy in combination with concomitant weekly cisplatin-based chemotherapy is currently considered standard of care.[3-7]

Due to the anatomy, primary vaginal cancer is an optimal target for brachytherapy. Traditionally vaginal cylinders or vaginal mould applicators allowing for a stable geometry within the vagina were used as intracavitary applicators for the brachytherapy sources. In case of more extensive residual disease after EBRT combined intracavitary/interstitial techniques were considered. First conceptual ideas on a target volume concepts for vaginal cancer brachytherapy date back from the era before the use of volumetric 3-dimensional imaging. These concepts were related to the application technique and dose prescription according to institutional experience. The concepts included: (1) in small well-defined superficial tumours: the gross tumour volume (GTV) with 1-2 cm margin; (2) in larger tumours after EBRT: either the initial tumour volume with a safety margin (mainly related to the tradition of prescribing to the cumulative 60Gy reference isodose), or alternatively the GTV at time of brachytherapy with a safety margin to prescribe a higher dose (>60Gy).[8] Treatment planning and reporting was based on the clinical experience using mainly applicator related points, and systems (e.g. the Paris system) in case of interstitial techniques. Dose reporting followed the ICRU reports 38 and 58.[9,10] Several large institutional radiograph-based brachytherapy experiences report local/pelvic control rates ranging from 44-87% (~75%). Pelvic control was good for stage I-II (~90%) compared to 40-80% (~60%) for stage III and 0-69% (~45%) for stage IV, while severe morbidity was mainly described for the GU and GI tract.[3-5,9-18]

3.1.2 Vaginal recurrences

Primary endometrial or cervical cancer can result in recurrences in the vagina. Endometrial cancer recurrences commonly arise in the post-hysterectomy surgical scar, but can also develop at other sites in the vaginal wall.[19-23] Multifocal spread can also be observed in case of extensive lymph vascular space involvement (LVSI) or more aggressive histologies.[24] The prognosis is associated with the original risk-group classification.[19] Evidence suggests to consider also molecular risk factors (i.e. p53 or mismatch repair deficient).[25] Central recurrences for cervical cancer are observed after radical hysterectomy with risk factors including size of the primary tumour, depth of invasion, presence of LVSI, and nonsquamous histologies.[20,21]

Clinical management of vaginal recurrences is challenging, as the location in central pelvis can result in significant symptoms and treatment-related toxicities. Organ-preserving approaches combining EBRT with BT represent an attractive option, especially with the advent of image-guided brachytherapy (IGABT).

Small institutional studies reported favourable local control and acceptable toxicity levels in treating vaginal recurrences with primary radiotherapy including IGABT. While local control rates range from 80% to 90%, there is considerable variability in disease-free and overall survival and toxicity outcomes because of the heterogeneity of patients, variations in dose specification, treatment volumes, and total dose [26-37].

3.2 Current evidence

Recent developments in the field IGABT for cervical cancer appear also attractive for vaginal cancer. The principle of IGABT for cervical cancer is to apply repetitive three-dimensional (3D) volumetric imaging to visualize both the targets and organs at risk in relation to the applicator. During dose planning the dose is shaped according to the individual target volumes, taking tumour regression during radio(chemo)therapy into account. Due to the superior soft tissue contrast, MRI is the recommended imaging modality for target delineation. Various steps within the treatment chain of IGABT for cervical cancer has been elaborated and published as recommendations (target volume delineation, dose reporting, applicator reconstruction, imaging) by the GYN GEC-ESTRO working group.[38-41] Standardization of target volume and dose reporting has greatly facilitated multicentre evaluation of these concepts. Subsequent studies have demonstrated the superiority of IGABT in comparison to conventional point-A based treatment planning; showing improved local control with a simultaneous reduction of treatment related morbidity.[42-46] Finally, these concepts have now been implemented in the most recent ICRU report 89, which in addition includes concepts and terminology for EBRT.[47]

Due to the similarities between cervical cancer and vaginal cancer, IGABT was a logical next step. Indeed, first clinical experiences in a limited number of patients showed the feasibility of IGABT for vaginal cancer and promising clinical results were reported.[7,37,48-50] However, there are also distinct differences with cervical cancer, in particular in regard to anatomy and applicator systems, and a common concept for target volume and dose reporting was lacking.

To address this issue, two parallel international efforts provided new recommendations for IGABT target definitions for primary vaginal cancer and vaginal recurrences. These target concepts needs clinical validation. The uptake, feasibility and oncological outcomes including morbidity and quality of life are yet unknown. Moreover, there is in general lack of good evidence regarding the optimal treatment of vaginal cancer.

3.2.1 Primary vaginal cancer

In 2013 a task group within the Gynaecological Groupe Européen de Curiethérapie and the European Society for Radiotherapy & Oncology (GYN GEC-ESTRO) was established with the aim to introduce IGABT concepts. The report published in 2020 summarizes the GYN GEC-ESTRO concepts and recommendations for target volume definition in IGABT for primary vaginal cancer.[51] While the majority of primary vaginal cancers have a squamous or, adeno(-squamous) histology, there are few rare histological subtypes (e.g. clear cell carcinoma, neuroendocrine carcinoma of the vagina) that may be treated in accordance to the aforementioned target concept. In addition, there are rare clinical scenarios (primary vaginal cancer stage I <2cm; vaginal carcinoma in situ), that may be treated with IGABT alone[13,52]. Contemporary clinical evidence to guide treatment decision making in these situations is sparse. This study, offers a parallel registration cohort for these rare histological subtypes and treatment with IGABT alone, with the aim to gather prospective clinical outcomes in a multicentre setting.

3.2.2 Vaginal recurrences

To develop international consensus recommendations, representative members from GEC-ESTRO, American Brachytherapy Society (ABS), and the Canadian Brachytherapy Group (CBG) convened to establish definition for IGABT clinical target volumes at the time of brachytherapy for recurrent endometrial/ cervical cancers in the vagina[53]. This international effort addressed the variability in target volume definition found in literature, and the specific considerations that should be considered for vaginal recurrences compared with primary vaginal cancer. There are some differences between primary vaginal and recurrent endometrial/cervical vaginal lesions: 1) histology, with different natural histories and related patterns of infiltration and spread, 2) and post-hysterectomy issues associated with the surgical scar and bowel sitting superior to the vaginal cuff.[54]

3.3 Rationale

The rationale for this study is the need for an evidence-based treatment for vaginal cancer. Now a target concept has been developed, it should be implemented and evaluated to advance treatment. This should be done in the setting of a carefully designed prospective study. More specifically, in a prospective registration study of state-of-the-art treatment for vaginal cancer. This will ensure systematic prospective data collection of treatment and outcome parameters and minimize registration bias. With the data that this study will generate, evidence-based recommendations for planning aims & constraints for radiotherapy targets and OAR can be developed. This will further harmonize treatment delivery across different centres, optimize oncological outcomes and limit morbidity.

4. STUDY AIMS

The general aim of this study is to improve clinical outcomes of patients with primary vaginal cancer or vaginal recurrences treated with definitive chemoradiation and MRI based IGABT. Specific aims of this study are to develop evidence-based recommendations for the treatment of vaginal cancer and to identify prognostic parameters for oncological outcomes, morbidity and QoL. Parallel registration cohorts for rare histological subtypes and treatment with IGABT alone within this study are aimed to provide contemporary multicentre prospective clinical outcomes in these rare conditions. Furthermore, the study aims to create possibilities for future fundamental and/or translational research of this rare cancer by asking study participants permission for the storage and use of tumour tissue, imaging and treatment planning data.

1. Establishing a reference for clinical outcomes with state-of-the-art treatment of vaginal cancer

- Estimate the incidence of treatment failure
- Estimate the incidence of acute and late treatment-related morbidity
- Estimate the impact of treatment on patient reported symptoms and quality of life

2. Identification of prognostic parameters for clinical outcomes

- Identification of risk factors for disease recurrence and death
- Identification of risk factors for morbidity and reduced quality of life

3. Development of evidence-based recommendations for radiotherapy treatment

- Evaluation of the uptake of the target concepts for vaginal cancer
- Evaluation of the variation in radiation doses delivered to treatment targets and organs at risk
- Determining the relation between radiation dose in the OAR and morbidity and quality of life
- Determining the relation between radiation doses in the targets and oncological outcomes
- Developing radiotherapy planning aims & constraints for dose to targets and OAR

4. Evaluation of the use of concurrent systemic therapy

- Evaluation of the feasibility of completing systemic therapy
- Evaluate the impact of chemotherapy reduction or withholding of chemotherapy on clinical outcomes

5. Creating possibilities for future fundamental or translational research

- Informed consent for the storage and use of FFPE tumour material, imaging and treatment planning data

5. STUDY DESIGN

5.1 Design

The proposed study is a prospective, observational international multi-centre cohort study on the treatment of vaginal cancer by radio(chemo)therapy and MRI-based IGABT. This design offers parallel registration of cohorts for rare histological subtypes and treatment with IGABT alone. This cohort study is designed as a continuous international registry, since vaginal cancer is a rare malignancy for which no international prospective data collections exist yet.

The study has first opened first for inclusion in a limited number of institutions; based in Aarhus, Amsterdam, Leiden, Rotterdam, Vienna and Villejuif. These institutions were involved in the development of the GEC-ESTRO target concept for vaginal cancer and already treat vaginal cancer with the most up-to-date treatment equipment and techniques, and have initiated this study. Based on the experience of these 6 centres during the first year, the study procedures and data collection were further optimized. In addition, accreditation and quality assessment procedures have been refined for other centres that will start including after the first year.

Patients who will be included in this registration study will receive the same treatment and have the same follow-up as patients who do not participate in the study. However, patients that participate will give informed consent for the prospective collection of their clinical and treatment data (including DICOM imaging and DICOM-RT treatment data). Furthermore, they will have the opportunity to participate in the observational patient reported morbidity and quality of life study, for which questionnaires will need to be filled out on a regular basis. Finally, they will have the opportunity to give permission for the storage and use of tumour material in future fundamental or translational studies.

After inclusion, patients' baseline data (clinical characteristics, pre-treatment morbidity and QoL) will be registered before the start of treatment. Treatment will be performed according to the local treatment protocols. However, the treatment targets and OAR will have to be defined according to the common MRI-based target concepts for vaginal cancer as defined in the published recommendations[51,53] and the doses delivered to targets and OAR will have to be registered in a uniform way. At the end of treatment (EoT) morbidity will be assessed and patients who consented to participate in the morbidity and quality of life study will be invited to fill out the respective questionnaires. According to the standard of care, after treatment, patients are normally invited for follow-up assessments at the hospital at a regular basis by their treating radiation oncologist for at least 5 years. The follow-up assessments are expected to be scheduled around 3, 6, 12, 18, 24, 36, 48 and 60 months after end of treatment and will be performed according to the local standard practice. At each follow-up visit, the treating physician will perform a detailed anamnesis and physical and gynaecological examination to assess the disease status and morbidity. Radiological tumour evaluations (MRI pelvis and 3D imaging of thorax/abdomen) will be performed according to local standard practice, at a minimum MRI pelvis should be performed at 3 months. At the follow-up visits patients who consented to participate in the morbidity and quality of life study will be invited to fill out the respective questionnaires. An overview of the different assessments at baseline and during follow-up is provide in **Table 5.1**.

Table 5.1. Overview of assessments at baseline and during follow-up

Follow-up (months):	baseline	EoT morbidity	3	6	12	18	24	36	48	60	At recurrence
Clinical assessments											
Physical exam	x		x	x	x	x	x	x	x	x	x
Gynaecological exam	x		x	x	x	x	x	x	x	x	x
Pelvic MRI	x		x								x
3D imaging chest/abd	x										x
Morbidity and QoL assessments											
CTCAE v5.0	x	x	x	x	x	x	x	x	x	x	no
EORTC QLQ*	x	x	x	x	x	x	x	x	x	x	no
Permission for storage and use of:											
FFPE material	x										optional

* EORTC QLQ-C30 and selection of questions from the CX24, EN24 and the VU34 modules. Collection of questionnaires is optional at all the time points.

5.2 Data

Patient and tumour characteristics

Assessment of the baseline parameters must take place before the start of radiation therapy. A detailed description of the baseline variables are provided in chapter 13. In short, relevant patient and tumour characteristics, such as age and performance status at diagnosis, tumour histology (according to WHO classification[55], appendix 1) and stage (according to FIGO and TNM, appendix 2) will be registered.

Treatment parameters

Data on the different aspects of the treatment will be prospectively registered using dedicated web-based CRFs (detailed description in chapter 13). This concerns the following treatments:

- External beam radiotherapy
- Systemic treatment
- Brachytherapy
- Treatment of recurrences

Data collection of dose and treatment volume parameters will be extensive (including full DICOM imaging and DICOM-RT treatment data) as one of the study objectives is to develop a radiotherapy dose planning aims and constraints.

Oncological outcomes

If there is, at any time after inclusion, suspicion of disease recurrence or metastasis, a complete patient work-up should be performed. This includes a gynaecological examination (preferably under general anaesthesia), pelvic MRI, CT thorax-abdomen or a full-body (PET-)CT. Procedures to obtain material for pathological examination, such as biopsies of local recurrences or US-guided fine needle aspiration in case of suspected lymph nodes, are recommended.

The following events (definitions provided in chapter 10) will be registered at the date of diagnosis of the recurrence, which can be at any moment after inclusion in the study:

- *Local failure*
- *Lymph node failure*
- *Distant failure*
- *Disease-related death*

To be able to perform survival analysis of the oncological outcomes the following additional data will be registered if applicable:

- *Death due to any other cause(s)*
- *Date of last follow-up examination*
- *Date lost to follow-up*

If patients are diagnosed with a recurrence or metastasis, they will be treated at the discretion of their physician according to the local treatment practices. The primary salvage or palliative treatment will be registered in the study database.

Physician-reported morbidity

At baseline and every scheduled follow-up visit (**Table 5.1**) the absence or presence of physician-assessed treatment-related morbidity in the relevant organs at risk (definition in chapter 13) will be prospectively registered according to the CTCAE v5.0.[56] This entitles that the physician will register whether the morbidities are present or not; and will grade the severity of the toxicity according to predefined criteria. For this study a selection of CTCAE v5.0. Items has been made to cover all relevant morbidities of the treatment of vaginal cancer:

- Genital morbidity: vaginal haemorrhage, vaginal discharge, vaginal stricture, vaginal inflammation (this includes ulceration under grade 2 and 3), dyspareunia.
- Urinary morbidity: haematuria, urinary frequency, urinary urgency, urinary incontinence, urinary tract obstruction.
- Gastro-intestinal morbidity: abdominal pain, diarrhoea, faecal incontinence, rectal haemorrhage, proctitis, enterocolitis, small intestine stenosis.
- Skin morbidity: radiation dermatitis (this includes necrosis under grade 3)
- Bone morbidity: fracture
- Lymph oedema
- Fistula
- Fatigue

Patient-reported morbidity and quality of life

At baseline and every scheduled follow-up visit (Table 5.1) quality of life will be scored by the patient herself using validated questionnaires of the EORTC.[57] As there is no specific QLQ vaginal cancer module, questions from the modules for cervical cancer, endometrial cancer and vulvar cancer have been selected with permission from the EORTC item bank to cover all relevant disease- and treatment-related morbidities and problems surrounding sexual activity. The following items of the EORTC QLQ modules[1] will be used (the complete questionnaire can be found in Appendix 3):

- EORTC QLQ-C30, which is of general use for all cancer sites and consists of five functional scales (physical, emotional, social, role and cognitive functioning), a global health status/QoL scale and several symptom scales commonly reported by cancer patients.[40] All questions of the C30 module are used in this study.

[1] The Item Library is an online platform comprised of more than 900 individual items from over 60 EORTC questionnaires, some of which have been translated into over 100 languages. The item bank can be used to create custom-made item lists (https://www.eortc.be/itemlibrary/)

- EORTC QLQ-CX24, which is a cervical cancer module that covers typical disease and treatment-related symptoms and items regarding sexuality.[58] From this module a selection of 15 of the 24 questions has been made: 4 questions that constitute the sexual and vaginal functioning scale, 4 single items on urinary morbidity, 1 single item on rectal haemorrhage, 1 single item on leg oedema, 1 single item on hot flushes, 1 single item on peripheral neuropathy and 3 questions on sexual activity and enjoyment.
- EORTC QLQ-EN24, which is an endometrial cancer module that covers typical disease and treatment-related symptoms and items regarding sexuality.[59] From this module a selection of 5 questions has been made from the gastro-intestinal symptom scale.
- EORTC QLQ-VU34, which is a vulvar cancer module that covers disease and treatment-related symptoms and items regarding sexuality. From this module a selection of 4 questions has been made: 1 single item on vaginal discharge, 1 single item on genital pain, 1 single item on irritated genital skin and 1 single item on genital oedema.

Creating possibilities for future fundamental or translational research

There is increasing knowledge of the impact of biomarkers and molecular classification in the context of primary endometrial (e.g. POLE, MMRd, p53abn and ER status) and cervical cancer (PDL-1, p16 status) and their potential impact on patient managment (refs TCGA endometrial and cervical cancer; ESGO ESTRO ESP endometrial cancer; BioEMBRACE and Keynote A18). However, knowledge of the impact and role in recurrent disease is limited. C A small number of studies have been conducted on retrospective series (no. of included patients 7 to 77). These small series hint that there a probably a number of biomarkers relevant for the patient's prognosis: HPV[60,61], MIB-1 index[62], p16[63] and p53.[63,64] Due to the rarity of vaginal cancer none of these single centre studies could include sufficient number of patients, which resulted in underpowered comparisons in all studies.

The EMBRAVE registry study is an unique opportunity to ask informed consent for the use of tissue in a cohort that is homogenous for treatment and prospectively registers data on oncological outcomes. Hence, the EMBRAVE study could yield the data and the tissue to finally have sufficient events to discover and validate biomarkers related to disease recurrence.

Summarizing, translational research on tumour material of vaginal cancers collected in this cohort may have an impact on the treatment of vaginal cancer in the future. Therefore, all patients of this study will be asked to consent for the storage and use of tumour material. This will concern rest-material of the biopsies (as formalin-fixated, paraffin-embedded tumour block(s)) that were obtained to diagnose and classify vaginal cancer. The choice of the patient, whether or not they give permission will be stored in the database. No physical tissue repository will be built until a meaningful number (>150) of patients have given informed consent for the storage of tissue. At that time, a separate research proposal for a translational study with this tissue will be written and presented to the involved medical-ethical committees.

5.3 Endpoints

This study is an observational, prospective registration study, wherein neither an experimental treatment is compared to the standard treatment, nor groups of patients are compared. As a result, this study has no classical primary study endpoint. Nonetheless, endpoints are defined for the first 3 aims of this study to ascertain proper effectuation.

Aim 1: Establishing a reference for clinical outcomes with optimized treatment of vaginal cancer

Oncological events

The following oncological outcomes will be evaluated at 2 and 5 years after treatment:

- Local control
- Regional control
- Distant control

- Disease-free survival
- Disease-specific survival
- Overall survival

Definitions of these oncological events are provided in chapter 10.

Acute morbidity

All acute treatment-related morbidities (<3 months after treatment) will be evaluated, both for the scoring by the physician and by the patient at EoT and the 3-month follow-up visit. Acute treatment-related toxicities of the following types are considered most relevant as endpoints:

- Genital
- Urological
- Gastro-intestinal
- Skin
- Lymph oedema
- Fatigue

Late morbidity

All selected late treatment-related morbidities (≥3 months after treatment) will be evaluated at 2 and 5 years after treatment; both for the scoring by the physician and by the patient. Late treatment-related morbidities of the following types at risk are considered most relevant as endpoints:

- Genital
- Urological
- Gastro-intestinal
- Bone
- Lymph oedema
- Fatigue

Aim 3: Development of evidence-based recommendations for radiotherapy treatment

After the treatment of the first 50 and 100 patients has been completed, the uptake of the target concepts recommendations will be evaluated, based on available information on clinical tumour extension, available MRI imaging and DICOM structures. Results of this evaluation will be reported back to the GYN GEC-ESTRO to discuss and promote further development of the target concept if applicable.

Once sufficient data on oncological outcomes and morbidity to the organs at risk has accrued, the study group will develop recommendations for dose planning priorities, aims and constraints to optimize local tumour control and aims and constraints for organs at risk to limit treatment morbidity.

Aim 4: Evaluation of the use of systemic therapy

- Percentage of patients that completed the scheduled systemic therapy
- Prevalence of reasons for not completing systemic therapy
- Prevalence of disease recurrences with and without systemic therapy

6. STUDY POPULATION

6.1 Population (base)

This study is conducted within the GEC-ESTRO GYN network (Groupe Européen de Curiethérapie and the European Society for Radiation Therapy and Oncology) by the established EMBRACE research group. The EMBRACE research group has been initiated in 2008 with the aim to improve the clinical outcomes of cervical cancer (www.embracestudy.dk). This study group consists of European institutions with pioneering technical and clinical experience in the radiotherapeutic treatment of gynaecological cancers. The EMBRACE group has successfully conducted the world's three largest international multi-centre cohort studies on cervical cancer; the RetroEMBRACE, EMBRACE, and EMBRACE II studies.[23] These studies have generated scientific output leading to improvement in the treatment of cervical cancer and adoption of IGABT as the state-of-the-art brachytherapy treatment as reflected by ICRU report 89.
Initially, six institutions (Aarhus, Amsterdam, Leiden, Rotterdam, Vienna and Villejuif) were involved in developing the target concept for vaginal cancer, and the initiation of this study. After a start-up phase, other centres are expected to obtain accreditation (procedure described in chapter 11.3) and start including patients as well.

6.2 Inclusion and exclusion criteria

Patients who are suspected of having primary or recurrent vaginal cancer should undergo the following diagnostic procedures before the start of treatment:

- Gynaecological examination (preferably under general anaesthesia), including a schematic drawing (appendix x).
- Histological biopsy of the tumour
- Pelvic MRI (preferably with intravaginal gel)
- 3D imaging of abdomen and chest (CT, MRI or PET-CT); in patients with (suspicion of) nodal involvement or those presenting with recurrent disease PET-CT is suggested.
- For primary vaginal cancer: staging according to the FIGO 2018 and TNM (IUCC 8th Edition) classification systems, appendix 2

Patients who fulfil all of the inclusion criteria and have none of the exclusion criteria are eligible for participation in this study and should be asked informed consent.

Inclusion criteria

- Age ≥ 18 years
- Histologically proven primary vaginal cancer, vaginal carcinoma in situ (VAIN) or vaginal recurrence, per WHO classification[38] (appendix 1)
- Histological proven primary vaginal cancer:
  - squamous cell carcinoma, adenocarcinoma or adenosquamous carcinoma of the vagina
  - other epithelial carcinoma's and carcinoma in situ
- Histological proven vaginal recurrence from any gynaecological cancer for whom curative treatment is envisioned that includes image guided adaptive brachytherapy according to the target concept.
- Primary vaginal cancer: stage I-IVA
- Para-aortic lymph node metastasis below L1-L2 interspace are allowed
- Macroscopic visible tumour present on MRI and/or gynaecological examination at diagnosis.
- Planned IGABT treatment with MRI-guided adaptive brachytherapy (at least the 1st fraction contouring and planning on MRI; CT for later fractions is allowed):

  - External beam radio(chemo)therapy followed by IGABT
  - IGABT alone for stage I <2cm or carcinoma in situ
- Treatment with curative intent
- Written informed consent

Exclusion criteria

- Primary vaginal cancers with involvement of the ostium of the cervix or vulva (these should be classified as cervical cancer or vulvar cancer, respectively)
- Metastatic disease beyond para-aortic region L1-L2 interspace
- Sarcomas and melanomas.
- Treatment only by external beam radiotherapy without brachytherapy to boost the primary disease
- Primary vaginal cancer: treatment by primary surgery or debulking surgery
- Vaginal recurrences: treatment by primary surgery or debulking surgery
- Treatment with neo-adjuvant chemotherapy followed by surgery
- Treatment with radiotherapy followed by surgery
- Previous pelvic or abdominal radiotherapy
- Pregnancy

Treatment with concurrent systemic therapy is regarded standard care, but no concurrent therapy or concurrent hyperthermia instead of systemic therapy is allowed and not causing ineligibility for this observational study. Furthermore, use of (neo-)adjuvant systemic therapy is currently not recommended as standard of care in this patient population. In selected cases with very extensive disease this may be considered to render a patient suitable for curative radiotherapy. Given the ongoing research for optimal treatment strategies in locally advanced cervical cancer and endometrial cancer, additional systemic therapy may be considered in the near future in selected patients. For these reasons in this observational study this will not cause ineligibility, and we will register its use.

6.4 Sample size calculation

This observational cohort study is designed as a registry for vaginal cancer. As such there is no predefined maximal number of patients that can be included in the registry. The minimal number of patients required to answer the different research questions of this study will be estimated hereafter in order of increasing numbers. If the study is successful and includes substantially more than 100 patients, more advanced statistical analyses can be performed which will yield better understanding of the disease and its response patterns to treatment.

N ≈ 100

For study aim 1 (described in chapter 4), the incidence of the clinical outcomes (oncological events and morbidity) need to be estimated. This can be done by using estimated basic statistical methods, such as Kaplan-Meier analysis, and will give reasonably accurate estimations (95% confidence intervals ranging from -7.5% to +7.5% around the estimate) with approximately 100 patients. Of course, estimates will become more accurate with more patients, especially for subgroup analysis.

N ≥ 300

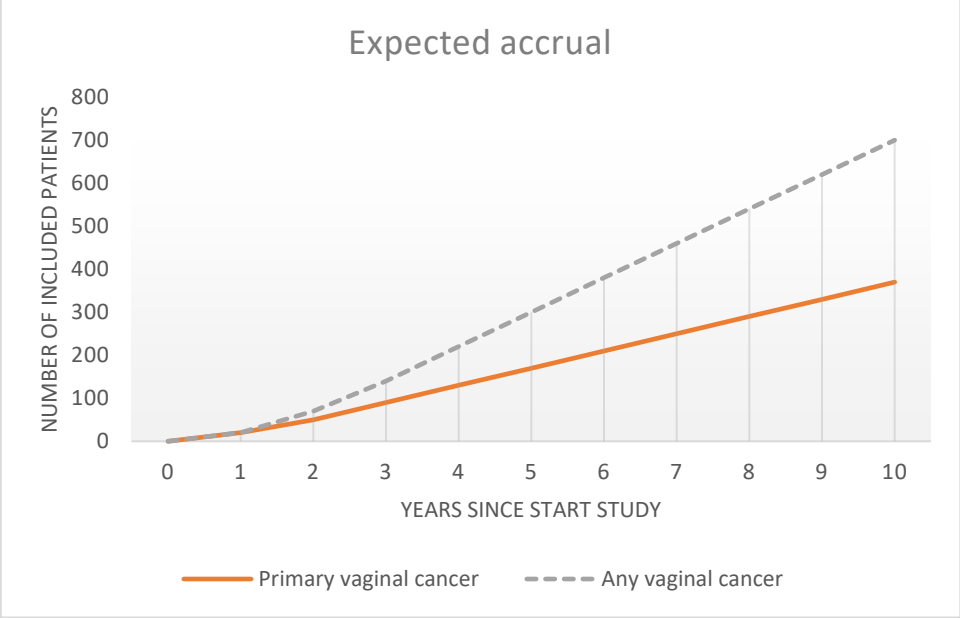
For study aim 2, 3 and 4 (described in chapter 4) multivariable analyses need to be performed to determine the independent effect of predictors (such as dose and tumour characteristics) on clinical outcomes (tumour recurrence, morbidity). For a meaningful multivariable regression

analysis at least 10 outcome events are required per predictor. The number of predictors in the analyses of all endpoints cannot be defined beforehand, as these will be determined by the predictive value to the candidate predictors in the univariable analyses (detailed description of statistical methods in chapter 10). It is common to have 3-6 predictors in a multivariable model.
This implies that at least 30-60 outcome events are required. The number of patients that is required for analyses will depend on the incidence of the different outcomes. For example, based on a retrospective study this study group conducted, the incidence of local tumour recurrence is estimated to be 20% at 3 years of follow-up.[67] For this example, this would imply that one would need 1/0.20*60 = 300 patients for this analysis. Again, for these types of analyses, estimates will become more accurate, and conclusions more reliable with more patients in the analyses.

6.5 Patient accrual and study period

The institutions of the EMBRACE research group have investigated how many primary vaginal cancer patients they have been treating with radio(chemo)therapy and IGABT on average per year; which was 5 or 5-10.[6]
During the first year of the study, only 6 institutions will open for inclusion, as described at 6.1. Based on the aforementioned data[6], about 40 patients are expected to be treated for primary and recurrent vaginal cancer in these centres during the first year. It is expected that half to two thirds of the patients will give informed consent for participation; based on the experience of the research group with the registration studies on cervical cancer. Besides, the majority of the patients who consent to participate are expected to consent for the morbidity and quality of life study and the storage and use of tumour tissue as well. Thus, inclusion of about 27 patients in the first year seems a realistic goal.
After the first year, the 6 centres will continue to include about 30 patients (primary and recurrent vaginal cancer) per year and the study will open for inclusion at other centres. It is expected that eventually at least 10 other centres will start including patients during the second and third year. Thus, the inclusion rate is expected to increase from 30 patients per year to 100 patients per year in the 3rd year of the study. The expected cumulative accrual over time is presented by the solid orange line in **Figure 6.1**.

Figure 6.1. Expected cumulative accrual over time



Based on these assumptions, it is expected that the first 100 patients will be included during the 3rd year and the first 300 patients during the 8th year.
Henceforth, the first analyses which requires only about 100 patients (see 6.4), and that doesn't require follow-up after treatment (such as analysis of variations in radiotherapy dose and volumes and feasibility of concurrent systemic therapy) could be done in the 3rd year. Analyses that require a follow-up of only 3 months (such as tumour response evaluations and analysis of acute morbidity) may also be performed in the 3rd year of the study. Analyses using oncological outcomes will require a follow-up of at least 3 years, because most of the disease recurrences are diagnosed in the first 2-3 years[68,69], and are expected to be performed in the 6th year. The analyses that require at least 300 patients (see 6.4) all use clinical outcomes and will therefore require a follow-up of at least 3 years. This would imply that these analyses could be performed at earliest in the 11th year of the study. The study period with this study design will be at least 11 years.

The analyses on the relation between the radiotherapy doses and morbidity and QoL for vaginal recurrences could be added to the group of patients with primary vaginal cancer. For the analyses on oncological outcomes, the groups will be analysed separately, as recurrences of other gynaecological cancers might behave different than primary vaginal cancers.

7. EXTERNAL BEAM RADIOTHERAPY TREATMENT

7.1 Introduction and aims

State of the art treatment for vaginal cancer consists of external beam radiotherapy (EBRT) with concurrent systemic therapy and a radiotherapy boost with MRI-based image-guided adaptive brachytherapy. In the participating centres, EBRT treatment is standardized and performed according to the protocol of the EMBRACE II study.[48]
Briefly, patients are treated with 45 Gy in 25 fractions of 1.8 Gy, 5 times per week. In case of endometrial vaginal recurrence, EBRT schedules of 23 fractions of 2.0 Gy or 27 fractions of 1.8 Gy, 5 times per week, are also allowed. Image guided Radiation Therapy (IGRT) with daily imaging (recommended cone beam CT) is delivered using intensity modulated radiation therapy (IMRT), volumetric modulated arc therapy (VMAT) or tomotherapy. Maximal overall treatment time including external beam radiotherapy, concurrent systemic therapy and brachytherapy is 50 days.

The aim of external beam radiotherapy is to obtain regional and nodal tumour control, and to achieve initial regression of the primary tumour. EBRT provides a homogenous dose to which the steep dose gradient of the brachytherapy boost dose is added to achieve the high dose that is needed to obtain local control of the primary tumour.

7.2 Preparation for treatment planning

A gynaecological examination, preferably under general anaesthesia, must be performed. Local tumour extension should be documented by using the specifically developed cartoons (see **Figures 8.1 and 8.2**).

Imaging should minimally consist of: 1) a diagnostic T2-weighted pelvic MRI (preferably in treatment position in three orthogonal planes; from the aortic bifurcation to the whole vulva with a slice thickness ≤ 5 mm and intra-vaginal gel); 2) a PET-CT is recommended, especially in node positive patients, but optional; and 3) a treatment planning CT in treatment position. Slice thickness of the treatment planning CT scan should be ≤ 3 mm. The use of intravenous and oral contrast media for the treatment planning CT is optional but use is recommended to ease identification of structures of interest. The choice for immobilization devices is according to the clinical routine of the individual institutes.

It is recommended, to perform an empty bladder scan on top of the comfortably filled bladder scan. Full and empty bladder scans give information about the range of internal motion of the target volumes, and this can be exploited when defining an individualized ITV. Bladder is intended to be comfortably filled on the treatment planning CT scan and throughout the treatment. Therefore, a drinking protocol is mandatory with specifications on 1) timing of voiding and 2) timing and volume of fluid intake. An acceptable drinking protocol would be that the patients are asked to void 1 hour before imaging and each EBRT fraction, then drink 300-500 ml of water/clear fluid and try not to void before treatment delivery.

The rectum and sigmoid should be as empty as possible. The patient is asked to empty the stools before scanning and treatment. If significant gas or filling is discovered while scanning for treatment planning (diameter of gas or filling in rectum > 4 cm maximum extension in any direction), the patient should be asked to empty the rectum or deflation with a catheter or postponing the treatment planning CT to another day could be considered.

7.3 Definition of EBRT target and fields

The definition of the EBRT targets, as defined by the GYN GEC-ESTRO Vaginal cancer working group, is provided in **Table 7.1**, and should be used in this study. The same definitions apply for vaginal recurrences.

Table 7.1 GEC-ESTRO definitions of EBRT targets for vaginal cancer[51]

GTV-T_{init}	The initial macroscopic (gross) tumour volume at time of diagnosis as described by clinical examination and/or imaging	Characterized by a hyperintense signal intensity on T2 weighted MRI. Due to the limited soft tissue contrast of CT in the lower pelvis, the GTV-T_{init} can only be adequately delineated using MRI in combination with information from clinical gynaecological examination.
CTV-T_{LR}	The low risk clinical target volume consists of the GTV-T_{init}, vagina, paravaginal space, paracolpia, parametria, and cervix.	It is generally recommended to include the whole vagina in the CTV-T_{LR}. For small (<2cm) stage I tumours located in the upper third, the upper two-thirds should be minimally included.
CTV-E	The elective clinical target volume contains lymph node regions according to the anatomical extension of the primary tumour and the presence of lymph node metastasis. See also PTV, any internal organ motion related to lymph node regions will be included in the CTV-E.	In patients with tumours in the upper two thirds of the vagina, delineation of nodal areas follows the same principle as in patients with cervical cancer (internal, external and common iliac, obturator and pre-sacral regions). In case of involvement of the lower third of the vagina the inguino-femoral nodes should be included in addition (as is done in vulvar cancer), however then omission of the common iliac area can be considered in node negative patients. In patients with multiple lymph node metastases including the common iliac region, the para-aortic lymph nodes (up to the renal vein)

		should be considered as part of the CTV-E. In case of para-aortic lymph node metastasis the para-aortic region with margin above the most cranial pathologic lymph node should be included in the CTV-E.
GTV-N_x / CTV-N_x	Nodal gross tumour volume / related clinical target volume, with 'x' specifying prescribed dose (e.g.) GTV-$N_{57.5}$	Additional sub volumes for EBRT by simultaneously boost to pathological lymph nodes if applicable.
ITV-T	Internal target volume related to the for the primary tumour volume	Further margins from CTV-T_{LR} to derive the ITV-T are based on available treatment planning imaging (e.g. planning-CT with full and empty bladder).
PTV	Planning target volume	The PTV margin needs to accommodate random and systematic geometrical errors that are among others caused by: internal organ motion (here accommodated in ITV-T for primary tumour and CTV-E for nodal regions) and geometrical errors in positioning during the course of EBRT for the tumour and lymph node related CTVs (set-up errors).

The definition of the elective nodal clinical target volume (CTV-E) depends on the location of the tumour in the vagina and the presence of pathological lymph nodes and risk of lymph node micro-metastasis.

Criteria for categorizing a lymph node as pathologic are:

- FDG-PET positive and/or
- Short axis ≥ 1 cm on CT or MRI and/or
- Short axis 0.5-1 cm on MRI with pathological morphology: irregular border, high signal intensity and/or round shape
- Histological / cytological proof of tumour spread to the lymph node(s)
- It is recommended to obtain cytological confirmation in case of suspicious inguinal lymph nodes.

Using these criteria, tumour location and **Table 7.2** allow to determine which lymph nodes areas should be included in the CTV-E.

In case the patient has already undergone a complete (diagnostic) lymph node dissection at baseline and none of the removed lymph nodes were involved with tumour, the definition of the CTV-E may be adjusted accordingly at the discretion of the treating radiation oncologist.

ITV-T

It is recommended to use an ITV-T that accommodates target motion and to use daily IGRT to evaluate whether the target is being treated adequately. Margins for ITV-T are based on the available (pre-)treatment planning imaging (e.g. planning-CT with full and empty bladder) and possibilities for image-guidance during EBRT (IGRT, e.g. daily cone beam CT).

PTV

The total CTV-T to PTV-T margin needs to accommodate random and systematic geometrical errors that are among others caused by: internal organ motion (ITV-T) (e.g. rectum, bladder filling status) and geometrical errors in positioning during the course of EBRT for the tumour and lymph node related CTVs (set-up errors).

The PTV margin is based on the available treatment planning imaging (e.g. planning-CT with full and empty bladder) and possibilities for image-guidance during EBRT (IGRT, e.g. daily cone beam CT). When daily soft tissue imaging (cone beam CT) is used (recommended) an isotropic of 5 mm margin from the combined ITV-T and CTV-E to PTV45 should be applied.

For the involved nodes, PTV-Nx is CTV-Nx with an isotropic margin of 5 mm. Each individual pathologic node will have an individual PTV-Nx, with the x specifying the total EBRT dose to the node.

Table 7.2 Definition of CTV-E

	CTV-E			
Lymph node involvement at baseline	**Inguino-femoral LN**	**int. iliac, ext. iliac, obturator, pre-sacral LN**	**com. iliac LN**	**PAO LN up to the renal vein**
Tumours involving only lower 1/3rd of the vagina				
Node negative	yes	yes	no	no
Inguinal	yes	yes	no	no
Pelvic below com. iliac	yes	yes	yes	no
Common iliac	yes	yes	yes	yes
Para-aortal	yes	yes	yes	yes, with ≥ 3 cm margin above most cranial pathological LN
Tumours involving only upper 2/3rd of the vagina				
Node negative	no	yes	yes	no
Pelvic below com. iliac	no	yes	yes	no
Common iliac	no	yes	yes	yes
Para-aortal	no	yes	yes	yes, with ≥ 3 cm margin above most cranial pathological LN
Tumours involving the lower 1.3rd and the upper 2/3rd of the vagina				
Node negative	yes	yes	yes	no
Inguinal	yes	yes	yes	no
Pelvic below com. iliac	yes	yes	yes	no

Common iliac	yes	yes	yes	yes
Para-aortal	yes	yes	yes	yes, with ≥ 3 cm margin above most cranial pathological LN

7.4 Organs at risk and reference points: definitions and contouring

The outer contour of the following organs should be delineated separately:

Bladder	Whole organ including the bladder neck
Urethra	From the bladder to the ostium urethra
Rectum	From the ano-rectal sphincter to the recto-sigmoid junction
Anal canal	From the external anal orifice to the ano-rectal junction
Sigmoid	From the recto-sigmoid junction to the left iliac fossa
Bowel	Bowel-bag: outer contour of bowel loops including the mesentery (no individual loops)
Femoral heads	Both femoral head and neck to the level of the trochanter minor

For para-aortic irradiation in addition:

Kidneys	Outer contour excluding renal pelvis
Spinal cord	Outer contour

Optional (if para-aortic RT above L1 is applied):

Duodenum	Whole organ
Pancreas	Whole organ
Liver	Whole organ

In case of ovarian transposition:

Ovary	Outer contour

7.5 Dose and fractionation

Standard fractionation involves 1 fraction per day, 5 fractions per week. Hyper-fractionation is not allowed. All beams and segments involved in a given part of the treatment must be treated at each fraction.
Unplanned treatment breaks (>2 consecutive treatment days) should be compensated by two daily EBRT fractions spaced by at least 6 hours. This compensation should only be performed once per week. To minimize the risk of consequential late damage the dose accumulation of EBRT it must not exceed 10.8-12 Gy per week.

PTV45

The planning aim dose and fractionation schedule for PTV45 is 45 Gy delivered in 25 fractions of 1.8Gy, 1 fraction per day and 5 fractions per week. In case of an endometrial vaginal recurrence, EBRT schedules of 23 fractions of 2.0 Gy or 27 fractions of 1.8 Gy with a simultaneous boost (SIB) of 2.2 Gy or 2.3 Gy, 5 times per week, are also allowed.

The dose to the PTV45, or PTV46 or PTV48.6, should be homogenous, with at least 95% of the PTV covered by the 95% prescription isodose, and dose maximum less than 107% of the prescribed dose.

Special attention is needed for the OAR irradiation in close proximity to the GTV-T_{init} where the high BT dose will be delivered. To ensure even less dose variation in this region, where summation of EBRT and BT dose is critical, a helper contour with a margin of 10 mm generated around the GTV-T_{init} (GTV-T_{init} +10mm) is recommended. The dose within this helper contour should be less than 103% of 45Gy to avoid hotspots in OAR walls which are likely to also receive considerable BT dose.

PTV-Nx

All pathological nodes are contoured (GTV-Nx, CTV-Nx). The 'x' denominates the boost dose level, e.g. PTV-N_{55Gy}. Nodal boosting of all pathological lymph nodes by use of a simultaneous integrated boost (SIB), with a total number of fractions of 25 is recommended to a dose of 55-60 Gy. In case of an endometrial vaginal recurrence, a SIB with a total number of fractions of 27 to a physical dose of 59.4-62.1 Gy is allowed. Biological equivalence calculations are performed by use of the linear-quadratic formulation assuming that the alpha/beta value is 10 Gy for tumour effects. Dose attribution from brachytherapy is to be taken in account.

Total dose to PTV-Ns of about 60 Gy EQD2 can be achieved with the following fractionation schedules:

- PTV-N_{55Gy} EBRT with SIB 25 x 2.2Gy = 55 Gy physical dose. This schedule is equivalent to 56 Gy EQD2 EBRT and should be use when an additional 3-4 Gy EQD2 is expected from brachytherapy which results in a total dose of ~60 Gy EQD2.
- PTV-$N_{57.5Gy}$ EBRT with SIB 25 x 2.3 Gy = 57.5 Gy physical dose. This schedule is equivalent to ~59 Gy EQD2 and BT dose contribution is negligible.

In the study database, the local investigators will register whether boosting for suspicious or positive lymph nodes has been applied and which dose level(s) has been used. More detailed information on the DVH parameters surrounding nodal boosting can be extracted from the separately collected DHV and imaging data.

7.6 Planning aims for targets and organs at risk

With a prescription dose of 45 Gy to PTV45, and 55-57.5 Gy to PTV-Nx(s) if applicable, delivered in 25 fractions, the dose volume constraints for organs at risk (OAR) summarized in **table 7.3** need to be met. In case of other EBRT schedules (23x2 Gy or 27x1.8 Gy with/without SIB), constraints should be recalculated in EQD2 according to the EBRT schedule used.

Table 7.3. Summary of planning aims for OAR and target

		Hard dose constraints	**Soft dose constraints**
Targets	PTV45	V95% > 95% Dmax<107%*	
	ITV45	Dmin> 95%	
	PTV-Nx	D98% > 90% of prescribed LN dose Dmax < 107% of prescribed LN dose	
	CTV-N		D50% > 102%
Help contour	GTV-T_{init} +10mm		Dmax < 103%
OAR	Bowel	Dmax < 105% (47.3Gy)*	When no lymph node boost: - V40Gy < 100cm^3** - V30Gy < 350cm^3**

			When lymph node boost or para-aortic irradiation: - V40Gy < 250cm^3** - V30Gy < 500cm^3** Dmax < 57.5Gy
	Sigmoid	Dmax < 105% (47.3Gy)*	Dmax < 57.5Gy
	Bladder	Dmax < 105% (47.3Gy)*	V40Gy < 75%** V30Gy < 85%** Dmax < 57.5Gy
	Rectum	Dmax < 105% (47.3Gy)*	V40Gy < 85%** V30Gy < 95%** Dmax < 57.5Gy
	Anal canal	Dmax < 105% (47.3Gy)*	V30Gy < 50%
	Urethra	Dmax < 105% (47.3Gy)*	
	Spinal cord	Dmax < 48Gy	
	Femoral heads	Dmax < 50Gy	
	Kidney	Dmean < 15Gy	Dmean < 10Gy
	Body	Dmax < 107%*	
Optional			
	Duodenum[48]		V55Gy<15cm^3

**In case that lymph nodes are not boosted*
***Soft constraints which can be used as optimization constraints as they are not based on clinical evidence. The constraints are not supposed to be fulfilled by all patients, but rather by ~70-80% of the patients.*

7.7 Technique and procedures for EBRT including daily image-guidance

IMRT, VMAT or tomotherapy based on inverse treatment plan optimization should be used to optimize EBRT dose distributions and to minimize the dose to OAR delivered with EBRT.

Irradiation is given with high-energy photons. As pointed out in the introduction the dose contribution from EBRT has to be homogenous within this study, at least for the volume representing the GTV-T_{init} and the CTV-T_{LR} and the small volumes in the adjacent OAR. If this homogeneity is not achieved it will compromise the evaluation of dose volume effects of BT on local control and on morbidity.

It is recommended to use coverage probability (CoP) dose planning principles for lymph node boosting as used in the EMBRACE-II study. With CoP planning principles it is assumed that the CTV-Nx is more often occupying the central region of the PTV-Nx than the edge region. According to this, it is aimed to generate a heterogeneous dose across the PTV-Nx in such a way that the central dose >100% and the edge dose is decreased down to 90%. In case of large lymph nodes, it is possible to escalate the central part of the GTV-Nx to e.g. D50 > 102%, while respecting an upper limit of 107%.

Daily 2D (MV or kV) or recommended 3D (CBCT or MVCT) IGRT is mandatory. The daily imaging is used for fusion and position verification on bony anatomy. Couch correction must be performed daily before treatment delivery according to the bony fusion between the on-board imaging and the treatment planning CT. Couch alignment should take soft tissue into account. Soft tissue verification (evaluation of the position of CTV-T_{LR}) based on CBCT can be performed, but is not

mandatory. With soft tissue verification it is possible to evaluate if the daily position is significantly different from expected and this knowledge can be used to decide that a new treatment plan would be beneficial.

In case that 3D soft tissue verification imaging and monitoring shows that significant parts of CTVs are repeatedly outside the 95% isodose volume, the following should be considered:

- Additional tattoos at the level of L2
- Additional planning CT scan for re-planning
- Redefining the ITV, taking the information acquired with CBCT into account.
- Adjustment of the PTV margin (see the section on angulation of the pelvis in relation to the lumbar spine.

Angulation of the pelvis in relation to the lumbar spine

With para-aortic radiation, flexing of the thoracolumbar spine in relation to the pelvis can be a concern considering the tight PTV margin. In case of repeated residual misalignment of more than 5mm despite daily correcting to match on bony anatomy the following procedures should be considered: check if immobilization device is used optimally; consider additional tattoos at the level of L2; consider an additional planning CT scan; a last step would be to consider to expand the PTV margin in the para-aortic region where the residual set-up error persists.

7.8 Dose and volume reporting

For clinical purposes the following dose and volume parameters are recorded.

Volume (nomenclature)	**Dose and volume parameters**
GTV-T_{init} (cm^3)	Volume
CTV-T_{LR} (cm^3)	Volume
ITV-T (cm^3, Gy)	Volume, D98
PTV45 (cm^3, Gy)	Volume, D98
GTV-Nx volume (cm^3)	Volume
CTV-Nx (Gy)	Volume, D98
PTV-Nx (Gy)	D98
Bowel (cm^3)	V15Gy
Bowel (cm^3)	V30Gy
Bowel (cm^3)	V40Gy
Bowel (cm^3)	V50Gy
Sigmoid (%)	V30Gy
Sigmoid (%)	V40Gy
Sigmoid (%)	V50Gy
Bladder (%)	V30Gy
Bladder (%)	V40Gy
Bladder (%)	V50Gy
Rectum (%)	V30Gy
Rectum (%)	V40Gy
Rectum (%)	V50Gy
Body (cm^3)*	V43Gy
Body (cm^3)*	V50Gy
Body (cm^3)*	2cc

** Total volume (including PTV and entire body). Depending on planning system a helper structure might be necessary (e.g. Monaco)*

For research purposes, full DHV data will be stored (DICOM imaging and treatment data).

8. BRACHYTHERAPY

8.1 Introduction

With the publication of the GEC-ESTRO recommendations for three-dimensional (3D) and adaptive (4D) target brachytherapy (BT) in locally advanced cervical cancer, IGABT has been introduced in gynaecological BT.[38,40,67] The GEC-ESTRO target concept has proven useful in cervical cancer and clinical studies have shown improvements in local control without additional late morbidity.[42-46]
Based on the results on IGABT in cervical cancer, small mono-institutional studies have been conducted on IGABT in primary vaginal cancer[37,50,70] and vaginal recurrences. When these studies are compared with previous studies using X-ray based BT there seem to be an improved local control rate associated with IGABT, especially in larger tumours.
So far, systematic MRI-based BT dose planning has been limited to single centre experience, but based on the initial promising monocentric results a cooperative group within the GEC-ESTRO was formed in 2013 aiming to explore and introduce (4D) adaptive BT in vaginal cancer. During the last years the group has held regular meetings and conducted a retrospective multicentre study on IGABT in vaginal cancer. This study included 148 patients treated in 5 European centres and showed that 4D IGABT in vaginal cancer was associated with a good local control rate and limited morbidity.[6] The group has introduced a new GYN GEC-ESTRO target concept for IGABT in primary vaginal cancer. This target concept has now been evaluated and accepted for publication.[51] Few years later, an aligned consensus for target definitions was also published for recurrent endometrial and cervical tumours in the vagina treated with IGABT[53]. Target definitions in this protocol are according to these concepts and recommendations.

8.2 Preparations for brachytherapy

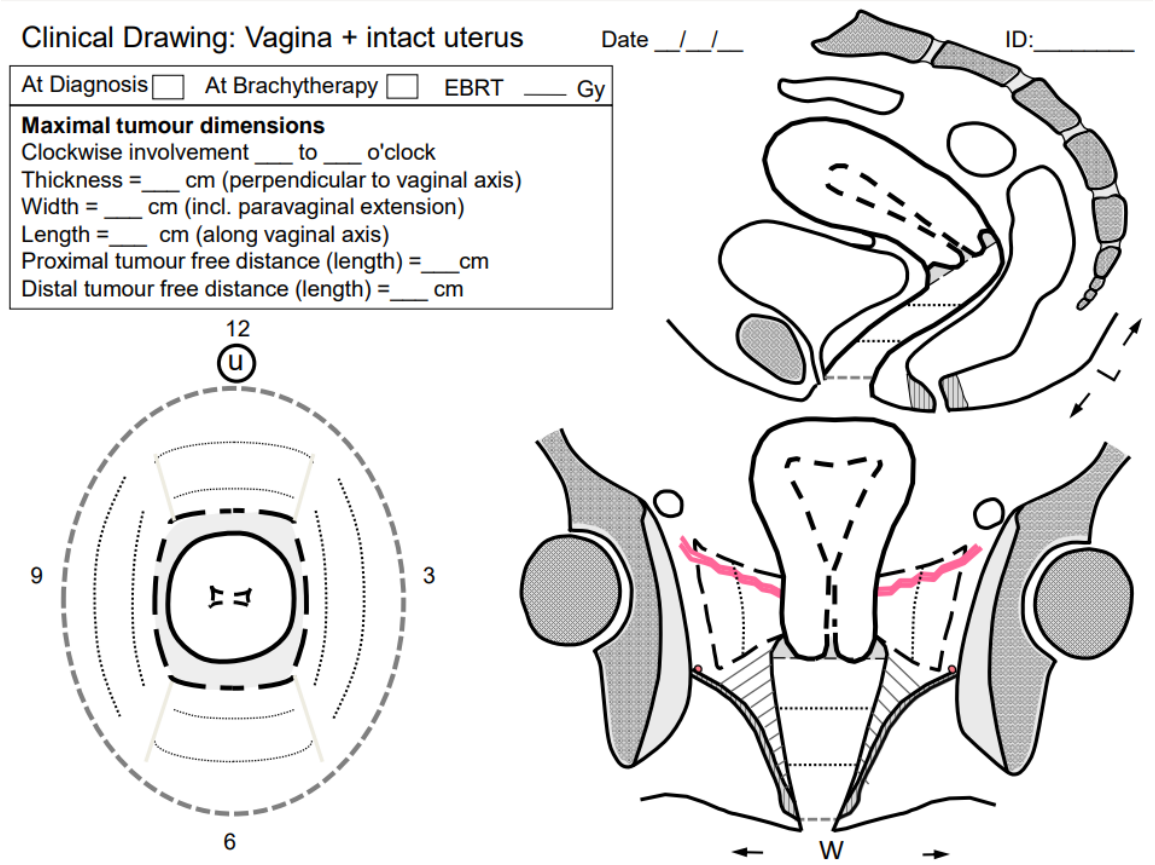
Treatment planning for BT is based on gynaecological examination and MRI performed with the BT applicator in place. This can be supported by CT, especially for the process of applicator reconstruction. Before placement of the BT applicator a clinical assessment of the tumour extension is performed describing tumour dimensions and possible paravaginal involvement, as well as involvement of OAR. The clinical examination is documented by drawings by use of standard cartoons (see **Figures 8.1 and 8.2 and Appendix 4**). Using these drawings a clockwise definition of the tumour spread at upper, middle and lower third, the length of the tumour along the vaginal axis, the thickness perpendicular to the vaginal axis and the left-right (laterolateral) width of the tumour including any paravaginal extension are recorded. Due to the potential deformation of the vagina by the tumour, the expected tumour regression during radio(chemo)therapy and the possibility to stretch the vagina during the examination, tumour-free distances from the apex to the cranial border of the tumour (proximal) and from the caudal border of the tumour to the level of the introitus should be systematically reported (both at time of diagnosis and at time of BT). The external urethral ostium, the posterior commissure, the portio, the fornices (if present) and the anus represent important anatomical landmark reference structures.

Bowel preparation should be used to ensure an empty rectum and sigmoid colon. Supportive treatment such as low molecular weight heparin, antibiotics and analgesics are given according to individual patient needs and institutional practice. A Foley catheter is placed in the bladder. Each participating department should define standard rules for bladder filling which should be followed both during MRI acquisition and the subsequent BT treatment.
The choice of MRI compatible applicator type and interstitial needles are up to the decision of each centre. Use of an individual mould or other customized procedures is allowed for fixation of the applicator according the practice of the participating institution.
For brachytherapy, the choice of applicator and implant procedures should follow the usual standard of the individual department. After applicator insertion, the patient is transferred to the MRI scanner to obtain appropriate images with the applicator in situ.

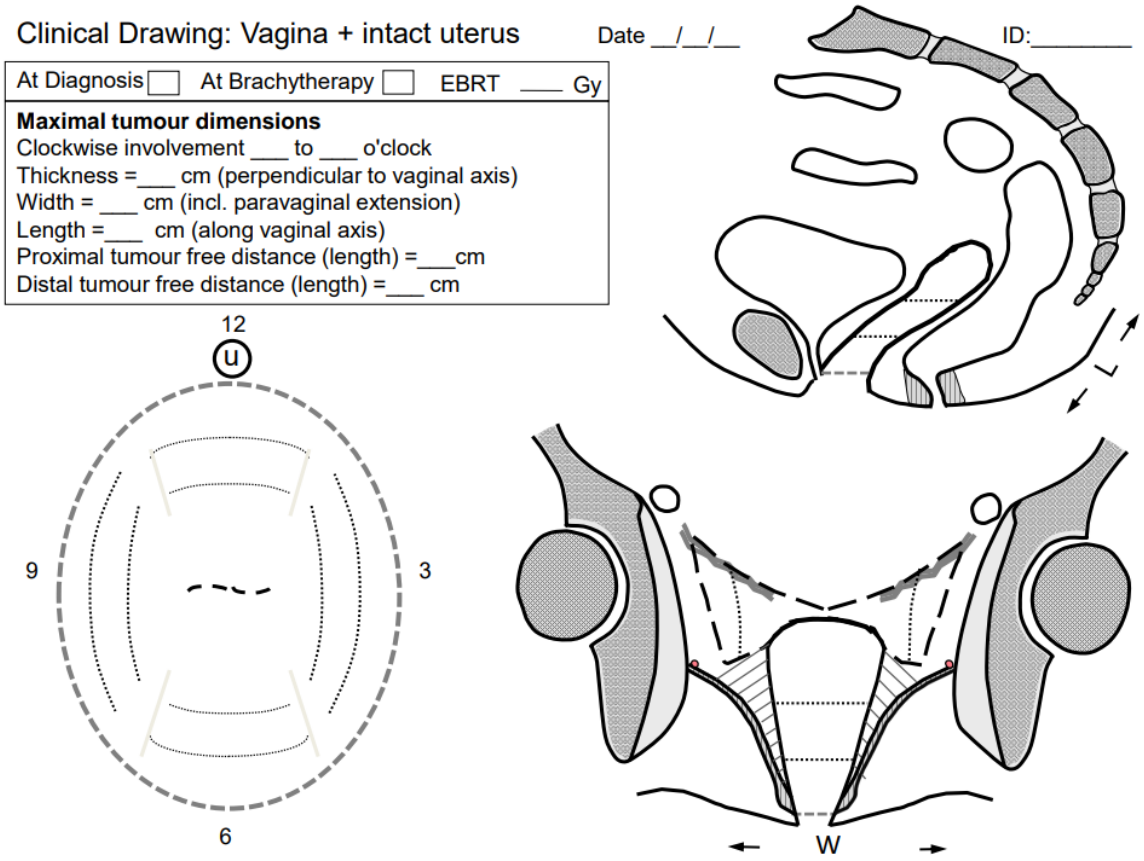
8.3 Imaging for brachytherapy

MR images should be obtained with applicator in situ and the patient in the supine treatment position. To ensure a reliable reconstruction of the applicator the slice thickness of MRI should be ≤ 5 mm (preferably ≤ 3 mm) with no interslice gap. For high field MRI (i.e. 1.5 Tesla) the reconstruction of the applicator can be eased by placing catheters containing water, oil, CuSO4 or other substances in the channels of the applicator. Transverse images perpendicular to the orientation of the vagina / applicator are recommended for optimal target volume / tumour depiction. The application of intravaginal gel should be considered for any MRI before or during EBRT (if no applicator is in place). An additional ("pre-planning") MRI before brachytherapy with a provisional applicator (e.g. vaginal cylinder only) can help to plan the type of application (combined intravaginal and interstitial vs intravaginal alone) and facilitate later contouring in case of an extensive interstitial component which may cause additional oedema and or haemorrhaging. These images can also be used to generate a full pre-plan, where the required needle positions in relation to the target volumes can be defined upfront.[71] The intraoperative use of a transrectal / transvaginal ultrasound can help to identify the target volume, correlate it with clinical findings and support the application and delineation.[72] MRI compatible markers might be used for the identification of the maximum tumour dimensions, and support applicator position verification.

Figure 8.1 Clinical drawing of vagina



a. With intact uterus



b. Without uterus

Left:
Speculum view: from centre to periphery: cervical os, portio, fornixes (grey area surrounded by thick dashed line), upper third, middle third, lower third (all separated by thin dotted lines), hymnal remnants marking the lower vaginal boundary (grey thick dashed line); u = urethra; for clockwise "3D" tumour delineation
Right:
Sagittal view (top) with reference structures including uterus, cervical os, portio, fornixes, upper third, middle third, lower third (all separated by thin dotted lines) of the vagina, ostium urethrae, anus; for longitudinal tumour delineation
Coronal view (below) with reference structures including uterus, cervical os, portio, fornices, upper third, middle third, lower third (all separated by thin dotted lines) of the vagina, parametria, paravaginal space; for longitudinal tumour delineation

8.4 Applicator reconstruction and dose points for OARs

Uncertainties of at least half the slice thickness can be present in applicator reconstruction. Great care should therefore be exercised when the applicator is reconstructed in the dose planning system. Each centre must ensure that the applicator reconstruction can be performed with an uncertainty of < 3 mm. Applicator reconstruction on MRI may be supported by additional CT.

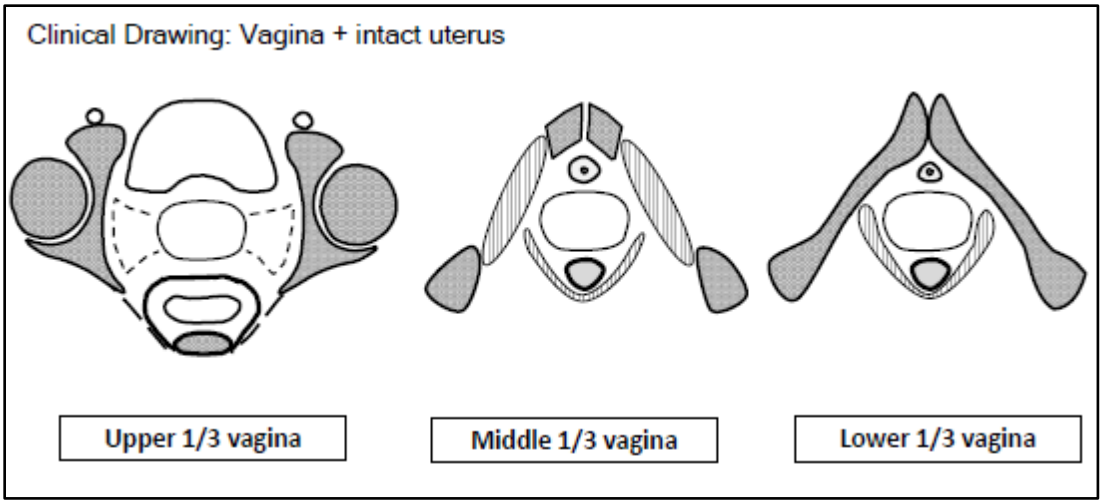


Figure 8.2 Clinical drawing axial view

Axial view in the upper third (left), middle third (middle) and lower third (right) of the vagina including parametria / paravaginal space; for clockwise tumour delineation

8.5 Contouring for brachytherapy

For each application, contouring for both tumour and OAR is performed on T2 weighted MRI sequences on transverse images perpendicular to the orientation of the vagina / applicator in a dedicated 3D brachytherapy dose-planning system. In case of fractionated HDR treatment with the applicator remaining in place, a CT with the applicator in situ may be used, aided by the MRI from the first fraction, to verify applicator position and target volume and OAR relation which may lead to adjustment of the treatment plan. However, full MRI-based IGABT is recommended.

Applicator movements may be observed in intravaginal brachytherapy, in particular if the uterus has been removed, and in combined intravaginal/interstitial (perineal) brachytherapy. Techniques using only an intravaginal component (e.g. vaginal cylinder) may show rotations and cranio-caudal shifts. In combined intravaginal/interstitial techniques the applicator is fixed to the target volume and rotations are less likely but there may be cranio-caudal shifts due to insufficient applicator fixation and/or swelling due to oedema/haemorrhage. A caudal shift of the applicator appears to be the most critical movement leading potentially to a substantial unplanned dose reduction in the respective cranial parts of the target volume (and to a significant dose increase in the adjacent caudal region). Therefore, strategies to reduce or outweigh applicator movements are essential and clinical monitoring and / or repetitive imaging is recommended. This is especially the case for patients undergoing multi-fractionated treatments within one application. Use of markers, re-imaging, re-positioning, re-planning and optimization of fixation should be prioritized, but uncertainties likely remain especially for PDR and fractionated HDR schedules lasting for a longer time period.

Vaginal cancer is associated with substantial shrinkage during radio(chemo)therapy in the majority of patients, which needs to be taken into account for brachytherapy boost treatment planning. This implies the definition of different (response-related) brachytherapy target volumes according to the expected different cancer cell densities. Based on the expected cancer cell densities (decreasing with distance from the GTV) and routes of microscopic tumour extension different target volumes can be defined and adapted according to regression during the course of treatment (**Figure 8.3**). For IGABT the target volumes are related to the vaginal tumour and are detailed in **table 8.1** (primary) and 8.2 (recurrences)

The following targets should be contoured according to target concept recommendations[51,53]:

Table 8.1 Target volume concept for IGABT in primary vaginal cancer.

GTV-T_{res}	The macroscopic gross residual tumour volume at the time of brachytherapy as described by clinical examination and/or imaging.	Clinically this is the remaining visible and palpable residual macroscopic tumour during gynaecological examination. On T2-weighted MRI this is visualised as a remaining mass with hyperintense to isointense signal intensity, within the initial tumour extension at diagnosis, GTV-T_{init}. There is usually considerable shrinkage of GTV-T_{init}, resulting in small GTV-T_{res}. This underlines the importance of proper documentation using clinical drawings of GTV-T_{init} at time of diagnosis and at time of BT.
CTV-T_{HR}	The high risk clinical target volume includes the GTV-T_{res} and areas of pathologic tissue	This includes the GTV-T_{res} and any abnormal thickened or irregular vaginal wall within the initial tumour extension before EBRT (GTV-T_{init}). On T2-weighted MRI the thickened or deformed wall typically has a more hypointense appearance. In case of tumours infiltrating the paravaginal or parametrial space at diagnosis, so called ‘‘grey zones” can be observed, and are included in the CTV-T_{HR}. In accordance to cervical cancer grey zones are considered as signs of tumour regression in terms of conversion of tumour cells into fibrotic tissue and are defined as areas with hypo-isointense signal intensity on T2-weighted MRI occurring within the initial tumour extension in the paravaginal or parametrial space.
CTV-T_{IR}	The intermediate risk clinical target volume should include all significant microscopic disease adjacent to the CTV-T_{HR}	The CTV-T_{IR} should minimally encompass the initial tumour extension at diagnosis (GTV-T_{init}), adapted to the anatomical situation at brachytherapy. At present, a safety margin of minimal 0.5 cm in tissue around the CTV-T_{HR} should be applied, limited by previously unaffected anatomical borders/compartments: e.g. pubic bone, pelvic wall, pelvic floor musculature, bladder, urethra, mesorectal fascia, rectum, anal sphincter.

Table 8.2 Target volume concept for IGABT in vaginal recurrences.

GTV-T_{res}	Macroscopic gross tumor that remains at the time of brachytherapy as documented by clinical examination and/or imaging	Has similar clinical and imaging characteristics as the initial GTV at diagnosis; on T2-weighted MRI this is the remaining mass with hyperintense to isointense signal intensity.
CTV-T_{HR}	Includes the GTV-T_{res} and areas on imaging and/or clinical examination that are concerning for harbouring macroscopic pathologic disease. On clinical examination this should include any abnormal thickened or irregular fibrotic vaginal mucosa/wall within the initial tumour extent.	Has different clinical and imaging characteristics compared with GTV-T_{res}. On T2-weighted MRI pathologic abnormalities of thickened or deformed vaginal walls have a more hypointense fibrotic appearance and should also be included. In cases where tumours infiltrated the paravaginal or parametrial space at the time of diagnosis, after some regression during external beam radiation these areas may appear as “grey zones” and should also be included in the CTV-THR target volume.
CTV-T_{IR}	Includes at a minimum the initial extent of disease at the time of diagnosis (GTV-T_{init}), and should encompass a minimal safety margin of 0.5 cm added	When including the original extent of disease at diagnosis or applying the minimal 0.5 cm safety margin in tissue, this expansion should be limited by the previously unaffected anatomic borders (eg, pubic bone, pelvic wall, pelvic floor

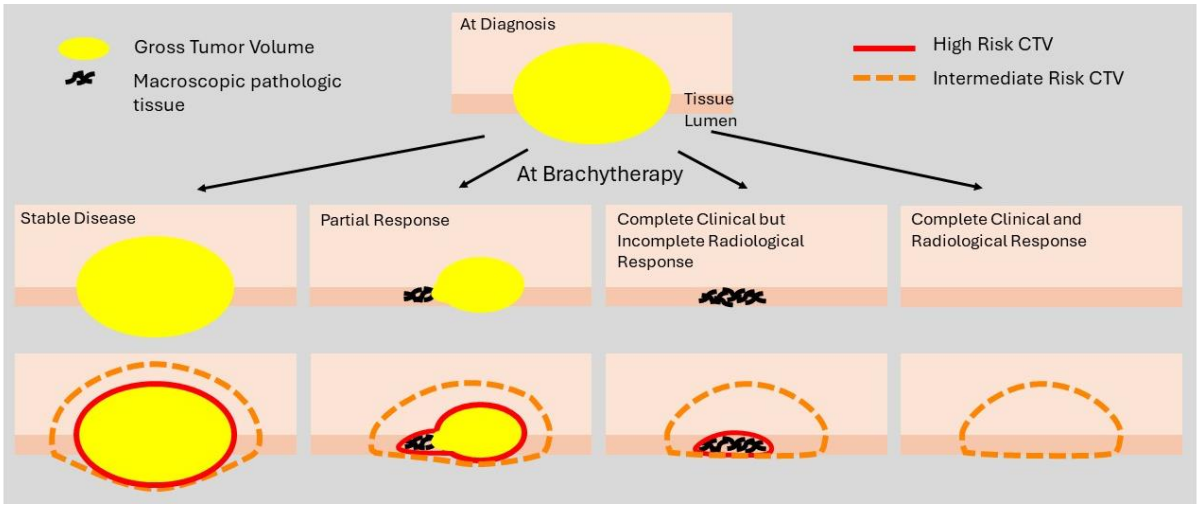
	to the CTV-T_{HR}. In cases of high-risk histologies (eg, serous cancer) known extensive LVSI, or multifocality, a larger margin can be added along the vaginal wall in the craniocaudal and circumferential directions. In the case of a complete response to EBRT both on imaging and clinical examination, only a CTV-T_{IR} is defined. This would include the original extent of disease in the superior and inferior direction and the full thickness of the vaginal wall to 0.5 cm tissue depth.	musculature, bladder, urethra, mesorectal fascia, rectum, and anal sphincter).

The macroscopically normal vagina is per definition part of the CTV-T_{LR} for EBRT but may be OAR at time of IGABT. Therefore, the dose to the vagina, excluding CTV-T_{HR}, will be evaluated both using α/β=10Gy and α/β=3Gy.

In case of partial involvement of cervix (but without involvement of the cervical ostium) the target delineation for IGABT should be based in addition on the recommendations for cervical cancer.[38] This implies that the CTV-T_{HR} should always include the whole cervix in addition to the GTV-T_{res} and areas at high risk for significant residual disease in the parametrial and paracolpic space.

In case of macroscopic residual tumour at time of brachytherapy inside the urinary bladder, rectum, urethra or anal canal should be contoured as GTV-T_{res} and included into the CTV-T_{HR}. In case of infiltration of these organs before EBRT and no residual infiltration at brachytherapy, only the initially involved organ wall without the lumen should be included in the CTV-T_{IR}. Initially expansive tumour parts inside the lumen which resolved at the time of brachytherapy should not be included.

Figure 8.3 Schematic representation of the IGABT target concept[32]



Schematic representation of IGABT target concept.

The following OAR should be contoured:

- *Vagina*: outside CTV-T_{HR} contouring of organ wall
- *Bladder*: The outer bladder wall is contoured
- *Urethra*: The outer urethral wall is contoured
- *Anal canal*: The outer wall of the anal canal is contoured from the anal verge to the level of the anal sphincter
- *Rectum*: The outer rectal wall is contoured from above the anal sphincter to the level of transition into the sigmoid
- *Sigmoid*: The outer sigmoid wall is to be contoured from the recto-sigmoid flexure to well above the parametria and the uterus (at least 2 cm)

For all these organs the outer wall/boundary should be contoured. The outer contours of bladder, rectum and sigmoid are contoured systematically on each slice where the organ is represented from at least 2 cm below the CTV-T_{IR} to 2 cm above the uterus.

The following dose points should be defined:

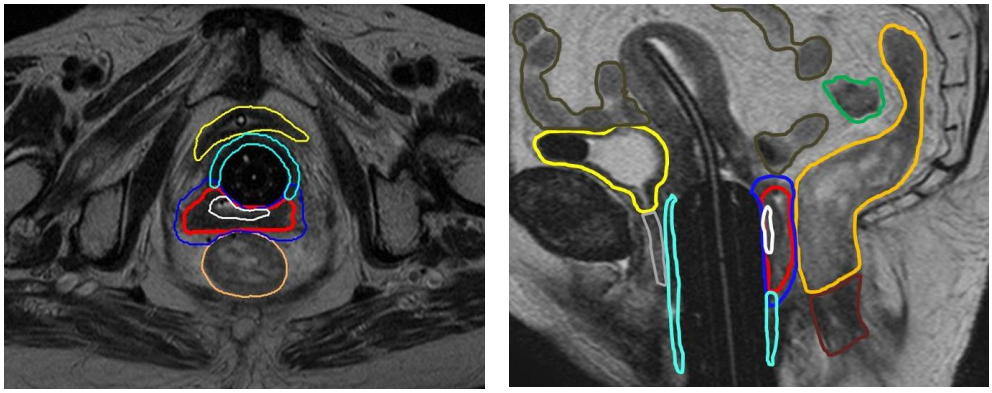
- *ICRU bladder point*

The reference points are defined according to ICRU 38.[9]

An example of target and OAR delineation according to the GEC-ESTRO target concept[51] is provided in **Figure 8.4**.

It should be kept in mind that these target concepts are not based on broad clinical evidence but represents an international agreement for an unambiguous method of recording and reporting. The clinical evaluation of these concepts is one of the aims of the present study. The results obtained may then be used to further develop these concepts for evidence based target definition and dose prescription for future IGABT in vaginal cancer.

Figure 8.4 Example of target and OAR delineation



Target delineation and OAR based on the recommended structures: GTV-T_{res} (white), CTV-T_{HR} (red), CTV-T_{IR} (blue), vagina outside CTV-T_{HR} (light blue), urinary bladder (yellow), rectum (light brown), sigmoid(green), bowel (olive), urethra (lilac), anal canal (dark brown).

8.6 Treatment planning for brachytherapy

It is mandatory that BT treatment planning of the first fraction is based on MR imaging according to the target concepts for vaginal cancer.[51] Treatment planning for each BT fraction must always be based on information from MRI. It is allowed to administer more than one BT fraction by use of the same implant. In this case, it is allowed to do the actual dose-planning of subsequent fractions on CT as long as the target has been defined by incorporating information from MRI conducted at time of BT.

The intention is to treat the remaining residual tumour and pathologic tissue at the primary site, at time of BT (high risk-clinical target volume, CTV-T_{HR}) and a safety margin that includes the original tumour extent at time of diagnosis (intermediate risk-clinical target volume, CTV-T_{IR}) with a dose according to the general practice in the institution.

The dose level chosen for the CTV-T_{HR} or CTV-T_{IR} and the DVH constraints for the OAR is to follow the individual departmental practice. Hence, there is no general dose prescription and DVH constraints demanded by this study; in accordance with the observational design of this study.

8.7 Planning aims & constraints for target and OAR

Due to the rareness of vaginal cancer, there are currently no evidence-based recommendations for planning aims and constrains for the targets and the organs at risk.

For primary vaginal cancer, the study of Hiniker et al.[73], found a cumulative total dose >70Gy as independent prognostic factor for improved locoregional control and overall survival. In the retrospective study of this research group on the treatment of primary vaginal cancer using image-based brachytherapy, there seemed to be an advantage in oncological outcome for patients

treated with a dose to the target of >80Gy, keeping in mind that no uniform target concept was used.[6] The American Brachytherapy Society recommends to treat patients with vaginal cancer in the upper vagina with a total dose of 70-85Gy.[74] For disease involving the distal vagina in close proximity to the vulva or rectovaginal septum however, caution should be exercised and consideration should be given to a lower total dose of 70-75 Gy and/or a lower dose per fraction to reduce the probability complications.[74] Patients who have had poor response to EBRT or have large residual disease may benefit from higher total dose of 80-85 Gy.[67] However, it should be stated that the ABS dose recommendations are not accompanied by a uniform, defined target volume definition. This illustrates the lack of data to support well defined dose planning aims and constraints, which this study aims to provide.

With regard to organs at risk, the EMBRACE study has demonstrated dose-effect relationships for late morbidity to several organs at risk: amongst others bowel[75], vagina[76], rectum[77] and bladder.[78] Based on these dose-effect relationships planning aims and limits for the doses to several OAR were defined for the treatment of cervical cancer in the EMBRACE II study[67] using D2cc EQD2: Bladder aim <80Gy, limit <90Gy; Rectum aim <65Gy, limit <75Gy; Sigmoid aim <70Gy, limit <75Gy; Bowel <70Gy, limit <75Gy; ICRU rectovaginal point aim <65Gy, limit <75Gy.

Based on the EMBRACE studies it would be possible to formulate dose aims and limits for vaginal cancer. However, because there hasn't been any prospective registration study yet, it is not known whether application of the aims and limits for cervical cancer is feasible and if they apply in the treatment of vaginal cancer. Since vaginal cancers may be localized lower in the vagina than cervical cancers, and may have a different pattern of growing into the surrounding organs (such as urethra, bladder, rectum and anal canal), the dose distributions needed to treat the cancer effectively may induce a different dose distribution in the organs at risk, compared to cervical cancer. It is one of the objectives of this study to get an overview of the dose distributions in the targets and OAR. Once this overview has been obtained dose aims and limits can be developed more specifically for vaginal cancer. Importantly, these will also include the urethra and anal canal due their anatomic proximity.

Concluding, in the current study it is expected that the participating centres follow the individual departmental practice during brachytherapy dose planning and optimisation. Only centres experienced in performing MRI-based IGABT will be included, and it is expected that the doses to the OAR are kept as low as reasonably achievable while optimally covering the targets.

8.8 Dose and volume reporting

For clinical purposes, the following dose and volume parameters are recorded. Recording and reporting follows the recommendations of ICRU Report 89 for cervical cancer, where all parameters included in level 1 and level 2 of the reporting standards are included: The physical absorbed doses will be registered, EQD2 doses may be calculated at a later stage by the research group for statistical analysis.

Volume (nomenclature)	**Dose and volume parameters**
GTV-T_{res}	Volume, D98
CTV-T_{HR}	Volume, D98, D90, D50
CTV-T_{IR}	Volume, D98, D50
Bladder	D0.1 cm^3, D2 cm^3
Urethra	D0.1 cm^3, D1 cm^3
Rectum	D0.1 cm^3, D2 cm^3
Anal canal	D0.1 cm^3, D2 cm^3
Sigmoid	D0.1 cm^3, D2 cm^3
Bowel	D2 cm^3

ICRU bladder point	Point dose
Vagina outside CTV-T_{HR}	D0.1 cm^3, D98, D50
TRAK	total, intracavitary component, interstitial component

For research purposes, full DICOM-RT (imaging and treatment data) will be stored.
Data on the planning and execution of the brachytherapy procedure that cannot (easily) be deducted from the DICOM data will be registered in the database by the local investigators.

9. SYSTEMIC THERAPY

9.1 Introduction and aims

There are no randomized data that address the use of chemotherapy concomitant to RT of vaginal cancer. Weekly Cisplatin is recommended based on data from cervical cancer[79] and a large population study in vaginal cancer[72], suggesting an additional survival benefit of concomitant radiochemotherapy compared to radiotherapy alone.

9.2 Concurrent chemotherapy

Chemotherapy is given according to the meta-analysis on the added value of concurrent cisplatin to radiation therapy in cervical cancer. Cisplatin is to be given intravenously at a dose 40 mg/m2 once a week for a total of preferably 5-6 cycles according to institutional practice. While cisplatin is the preferred radiation sensitizer, other combination systemic therapies are also allowed during radiotherapy. Treatment with Cisplatin should be withheld at the discretion of the centre. Several guidelines on chemo-radiation protocols exist for cisplatin withhold.[80-82] Leucocytes and granulocyte numbers are used as constraints for withhold of cisplatin. Guidelines for withhold vary for leucocytes counts around 2.500 or for granulocytes counts between <1,5 to 1.0 X 10^9 cell/L. For platelets institutional guidelines for cisplatin dose reduction should be followed and cisplatin can be resumed in the next cycle once the blood counts exceed these limits.
The dose of Cisplatin should be reduced if two consecutive cycles of chemotherapy have been given at dose zero. Cisplatin dose should also be reduced in case of neutropenic fever. Cisplatin should be totally discontinued if blood tests remain unacceptable or neutropenic fever recurs despite dose reduction. Cisplatin should also be abandoned in case significant auditory problems (tinnitus, deafness) or neuropathies > grade 2 develop.
Measurement or calculation (Cockroft-Gault) of GFR is performed before/during treatment. Treatment with Cisplatin is abandoned if GFR < 50 ml/min. Haemoglobin should be monitored during treatment. Corrections by transfusion according to institutional guidelines are allowed.

Recommended agent	dose/day	Route	Frequency
Cisplatinum	40mg/m2	i.v. in 3 hours	Weekly for 5-6 cycles

9.3 Use of (neo)adjuvant systemic treatments

Currently, use of (neo)adjuvant systemic treatment for downsizing of the tumour in vaginal and cervical cancer is used. Research is ongoing regarding the use of neoadjuvant chemotherapy in patients with high risk feature, or the use of other systemic treatments (e.g. immunotherapy) in cervical or endometrium cancer based on specific molecular profile classification.
Given the current evolution of application of other systemic treatments in the context of vaginal cancer and vaginal recurrences of cervical and endometrial cancer, the use of these treatments, despite not being the current standard of care, will be register in the EMBRAVE database. These patients will be evaluated for response after the neo-adjuvant systemic treatment, and at this moment will be eligible for inclusion in the study if planned to receive primary radiotherapy according to the EMBRAVE protocol including EBRT followed by an IGABT boost.

10. METHODS

This is an international registration study of patients with vaginal cancer that aims to improve clinical outcomes after curative treatment. Several aims and endpoints were defined to ascertain proper effectuation of the study. Below the procedures and statistical methods are described per research aim.

10.1 Establishing a reference for clinical outcomes of vaginal cancer

If there is, at any time after inclusion, suspicion of disease recurrence or metastasis a complete patient work-up should be performed according to local standard practice. This preferably includes a gynaecological examination, pelvic MRI, CT thorax-abdomen or a full-body (PET-)CT. Procedures to obtain material for pathological examination, such as biopsies of local recurrences or US-guided fine needle aspiration in case of suspected lymph nodes, are recommended. Imaging at time of recurrence if available will be collected as part of this study protocol.

Definitions

- *'Local failure'* is defined as: a new, recurrent or progressive residual tumour within the external beam low-risk clinical target volume (CTV-T_{LR}). This also applies to local failures in the area that retrospectively should have been included in the CTV-T-LR at diagnosis. E.g. distal vaginal recurrences outside the CTV-T-IR in patients with a proximal tumour at diagnosis.
- *'Regional failure'* is defined as: a new, recurrent or progressive residual tumour within the clinical target volume of the external beam radiotherapy (CTV-E) and/or the area that should have been treated with EBRT; which is not a local failure.
- *'Locoregional failure'* is defined as: a recurrence that is either a local recurrence, or a regional recurrence, or both.
- *'Distant metastasis'* is defined as: one or more new tumour localization(s) outside the clinical target volume of the external beam radiotherapy (CTV-T_{LR} and CTV-E) and/or the area that should have been treated with EBRT.
- *'Disease control'* is defined as absence of: a local, regional, locoregional failure or distant metastasis, or a combination of these events.
- *'Disease-specific death'* is defined as: death directly or indirectly due to vaginal cancer, including fatal treatment-related morbidities.
- *'Death'* is defined as: death due to any cause, including disease-specific death.

Definitions of the survival times for the oncological outcomes:

- *Local-, regional-, locoregional-control and distant control* times are all defined to start at the first day of radiotherapy. These survival times are defined to end, for patients with the event of interest, at the date of diagnosis of the failure event. For patients who died without the failure event of interest, the endpoint of survival time is defined as the date of death. For patients who are alive without diagnosis of the failure event of interest, the endpoint of survival is the date of the last follow-up examination. For patients who got lost to follow-up, without a known status of the failure event of interest, the endpoint of survival is also the date of the last follow-up examination, or the date of the last treatment day in patients who are lost to follow-up before their first follow-up examination.
- *Disease-free survival* is defined to start at the first day of radiotherapy and to end at the date of diagnosis of the first failure event, which may be local, regional, locoregional failure or distant metastasis. For patients who died without any of these events, the endpoint of survival time is defined as the date of death. For patients who are alive without diagnosis of any of these events, the endpoint of survival is the date of the last follow-up examination. For

patients who are lost to follow-up, without a known diagnosis of any of the events, the endpoint of survival is the date of the last follow-up examination, or the date of the last treatment day in patients who got lost to follow-up before their first follow-up examination.

- *Disease-specific* and *overall survival* time are defined to start at the first day of radiotherapy and to end at the date death. For patients lost-to-follow-up, survival time ends at the date of lost to follow-up. For patients who are alive, survival time ends at the last date that is was known that they were alive; this may be the date of the last follow-up examination, but this may also be the last date they had contact with any health care provider, or the last date they are known to be alive according to (national) registries.

Definitions for morbidity outcomes:

- Relevant morbidity (definition in chapter 13) will be assessed by the physician and the severity will be graded (from 0 'absent' to 5 'lethal') according to the CTCAE v5.0 system, which is a validated and internationally established system developed by the National Cancer Institute.[56]
- Patient-reported morbidity and quality of life will be assessed using the EORTEC QLQ-C30 and additional items from 3 EORTC QLQ modules (defined in chapter 13).[57]
- Acute treatment-related morbidity is defined as any morbidity event occurring after start of treatment (first fraction of EBRT) and ≤3 months since completion of treatment. In patients with morbidity before start of treatment (at baseline), morbidity will be considered treatment-related if the grading increases compared to baseline.
- Late treatment-related morbidity is defined as any morbidity event persisting over or occurring > 3 months after completion of treatment.
- For actuarial analysis, the most severe (highest graded) morbidity event per organ at risk will be considered for analysis. In case of multiple equally high graded morbidity events in one OAR, the earliest event will be considered for analyses.
- Morbidity will be censored in patients with disease recurrence 3 months before the date of diagnosis of the recurrence.

Statistical methods

Tumour response to therapy will be described as crude percentages of the different response categories. For any subgroup analysis, the significance of the difference between groups will be assessed using the Chi^2 or Fisher's exact test, depending on the numbers available for analysis. Statistical significance will be defined as a p-value <0.05.

For all oncological outcomes, mean and median survival times and the percentage of patients that is still event-free at 2 and 5 years of follow-up will be calculated using Kaplan-Meier's methodology. For any subgroup analysis, the significance of the difference between groups will be assessed using the log-rank test and/or univariable regression analysis using Cox proportional hazard models. Statistical significance will be defined as a p-value <0.05.

For all morbidity outcomes, the prevalence at listed time points will be calculated and the cumulative incidence of the various morbidity events will be estimated at 2 and 5 years of follow-up using Kaplan-Meier's methodology. For any subgroup analysis, the significance of the difference between groups will be assessed using the log-rank test. Statistical significance will be defined as a difference with a p-value <0.05.
In addition, morbidity will be also evaluated by a specific methodology developed within the EMBRACE I study for evaluating late, persistent, substantial, treatment-related symptoms (LAPERS).[83]

10.2 Identification of prognostic parameters for clinical outcomes

Identification of prognostic parameters is essential to understand disease behaviour and to guide future treatment decisions. The final selection of the relevant outcomes and candidate predictors

will be made when sufficient data has accrued based on the incidence and severity of the oncological and morbidity events.
Concerning the clinical outcomes, these are expected to include:

- Local. regional and distant control at 2 and 5 years
- Disease recurrence at 2 and 5 years
- Overall survival at 2 and 5 years
- Overall grade 3-5 morbidity at 2 and 5 years
- Substantial and persistent morbidity as defined by the LAPERS method[69]
- Summary score of the QLQ-C30 over time
- Functional and/or symptom scales or items from the EORTC questionnaires over time

Concerning candidate predictors, they are expected to include:

- Radiotherapy dose
- Completion of (a substantial part of) concurrent systemic therapy
- Tumour histological type, size and stage
- Response to external beam radio(chemo)therapy as assessed at time of brachytherapy
- Tissue and/or imaging based biomarkers

Cumulative radiotherapy dose of external beam radiotherapy and brachytherapy will be calculated as biologically equivalent dose in 2 Gy per fraction (EQD2) of these two treatments using the linear-quadratic model with a α/β = 10 Gy for targets and α/β = 3 Gy for late normal tissue damage. The repair half time is assumed to be 1.5 hrs.

Statistical methods
Cox proportional hazards models will be used to identify prognostic parameters for time-dependent events with a single occurrence (such as the oncological outcomes and occurrence of severe morbidity). Initially, the uncorrected prognostic value of a-priori defined candidate predictors (such as tumour stage and radiotherapy dose) will be estimated by univariable regression analyses. Thereafter, the candidate predictors that had a p-value <0.10 in univariable analysis, will be entered together in a multivariable regression analysis. Multivariable models consisting of only independent prognostic predictors will be built using a step-wise backward elimination procedure of variables with p-values ≥0.05. If necessary, corrections will be made for multiple testing by lowering the latter cut-off for the p-value to ≥0.01.

Linear mixed models (LMM; for continuous outcomes) or generalized estimated equations (GEE; for categorical outcomes) will be used to identify prognostic parameters for outcomes that regularly measured during follow-up; such as morbidity and QoL. The exact set-up of these analyses will depend on the eventually selected outcomes and candidate predictors. Patients will be included as random effects in the analysis and time as fixed effect. Independent predictors of will be identified by subsequent univariable and multivariable analyses with corrections for multiple testing if necessary.

10.3 Development of evidence-based recommendations for radiotherapy treatment

The recommendations for the radiotherapy dose planning will be determined by consensus of the research group. Optimized dose aims & constraints for targets and organs at risk will be defined. The doses will be chosen based on the balance between the chance to reach tumour control and the risk of radiation-induced morbidity.

Statistical methods
To determine the relation between radiation dose in the targets and oncological outcomes, univariable Cox regression analysis (described in chapter 10.2) will be conducted with the array of

DVH parameters. To determine the relation between radiation dose in the OAR and late morbidity, univariable Cox regression analysis (described in chapter 10.2) will be conducted with the array of DVH parameters and the a-priori defined morbidity outcomes of the appurtenant OAR.
Based on radiobiological principles, it is expected that these analyses will show a consistent pattern between dose and tumour response on the one hand and a relation between dose in the OAR and late morbidity. Hence, dose-effect curves will be deducted from the estimates of the analyses.
Once the dose-response relationships of both tumour control and late morbidity are known and can be presented graphically to leading clinical experts, consensus meetings to determine optimized dose aims and constraints can be organized.

10.4 Evaluation of the use of systemic therapy

The use of systemic concurrent treatment will be evaluated based on the following evidence from this study:

- Feasibility of completing current systemic therapy
- Prevalence of systemic-therapy-related morbidities limiting completion of concurrent chemotherapy
- Use of (neo)adjuvant systemic therapies
- Estimated benefit of systemic therapy, compared to radiotherapy alone

Definitions

- Concurrent systematic therapy is defined to be completed if the patient has received (an equivalent of) the prescribed dose at start of therapy. The most commonly prescribed systemic therapy is expected to be Cisplatin. Patients who have received at least 5 cycles of Cisplatin dosed at 40mg/m^2 during radiotherapy are defined to have completed their treatment. Other types of radio-sensitizing concurrent (systemic) therapies will be registered.
- (Neo)adjuvant systemic therapy refers to any systemic therapy that is regarded as part of the complete curative intent therapy either preceding or following (chemo)radiotherapy and brachytherapy.
- Morbidity events (defined in chapter 13) will be scored by the physician (from 0 'absent' to 5 'lethal') according to the CTCAE v5.0 system developed by the National Cancer Institute.[56] In addition, physicians will register the reason for not completing systemic treatment; e.g. haematological morbidity, reduced kidney function, hearing deficits, nausea/vomiting etc.

Statistical methods

The feasibility of completing concurrent systemic therapy will be described by the mean and/or median received dose and cycles. In addition, the percentage of patients that completed a full concurrent systemic therapy course will be described as a crude percentage.

Prevalence of reasons for not completing systemic therapy will be reported as crude percentages. For any subgroup analysis, the significance of the difference between groups will be assessed using the Chi^2 or Fisher's exact test, depending on the numbers of events. Statistical significance will be defined as differences with a p-value <0.05.

Estimation of the added value of concurrent systemic therapy compared to radiotherapy alone in this observational study is expected to be biased due to confounding by indication. Nonetheless, an attempt will be made to produce a reliable estimate (corrected for confounding) because there will probably never be a randomized controlled trial on the added value of chemotherapy as vaginal cancer is such a rare malignancy. The difference in the hazard of having a disease recurrence between treatment with or without systemic therapy will be estimated using a Cox proportional hazard model. A multivariable model will be built with this variable and the significant prognostic parameters identified in chapter 10.2. The model's estimate of the hazard ratio will give an indication whether there is an association between treatment with or without systemic therapy

and disease recurrence, but it should be interpreted with caution. If the numbers of events suffice, analysis will also be performed stratified by disease stage at diagnosis. To assess whether patients at high risk of disease recurrence, benefit more from systemic therapy than those with a low risk of recurrence.

11. QUALITY ASSURANCE

This study will have two study phases: in the first phase only 6 institutions (Aarhus, Amsterdam, Leiden, Rotterdam, Vienna and Villejuif) will open for inclusion. In the second study phase, other institutions are expected to obtain accreditation and open for inclusion as well.

11.1 Entry requirements for study phase I

The first 6 institutions (Aarhus University Hospital, Amsterdam UMC, Leiden UMC, Erasmus MC, Medical University of Vienna and Gustave Roussy) have their usual care for vaginal cancer patients protocolled in accordance with the entry criteria:

- *Diagnostic work-up* as described in chapter 6.2.
- *External beam radiotherapy* as described in chapter 7.
- *Brachytherapy* as described in chapter 8.
- *Concurrent systemic treatment* as described in chapter 9.
- *Follow-up* as described in chapter 5.1.

In addition, the centres will provide the central data manager with (proof of) the following:

- Signed research contract (details in chapter 13.3).
- Permission from the local authorities to conduct the study, such as an institutional medical ethics committee, the Board of Directors, departmental science committee or department head
- Names and contact details (including direct phone numbers and email addresses) of the local principal investigator, other investigators and research nurses or assistants.
- Choice for either the paper or the digital procedure for the data collection of patient-reported outcomes (described in chapter 13.1) and proof of having put in place the means to follow the appurtenant procedure in.
- The local responsible for data entry should have read the instructions and will receive a training on data-entry in the e-CRF system.

Confirmation of accreditation for study phase I will be given by a letter of principal investigator to the local investigator.

11.2 Eligibility questionnaire and dummy run

An eligibility questionnaire will be administered to new centres that express interest in being included in the study. The questionnaire is intended to verify that the centre meets the minimum requirements of the protocol. If not, the centre will receive detailed feedback and the accreditation will not continue further. If the screening is positive, the centre will be invited to continue the accreditation to the study with a dummy run focused on brachytherapy contouring according to the new target definitions. The dummy run procedure is based on the experience of the 6 main study centres. In general, new centres should be experienced with the treatment of cervical cancer IGABT to get accreditation for participation in study phase II. The aim of the dummy run is to ensure that all participating institutes adhere to the brachytherapy target concept contouring as described by the protocol. The coordinating group will provide the candidate centres with an (anonymous) patient case and imaging data. The candidate centres have to simulate contouring for brachytherapy targets and organs at risk. Centres will be given the opportunity to improve their contouring and perform another dummy run in the case the first attempt is not successful. Confirmation of a successful dummy run will be given by a letter from principal investigator to the local investigator.

11.3 Accreditation for study phase II

Other institutions that aim to get accreditation for participation will need to successfully complete a dummy run for brachytherapy contouring (described at 11.2). Further, they will need to provide the central data manager (based in Erasmus MC) with (proof of) the following to obtain accreditation for participation in study phase II:

- Confirmation that local usual care for vaginal cancer patients is protocolled in accordance with the entry criteria:
  - *Diagnostic work-up* as described in chapter 6.2.
  - *External beam radiotherapy* as described in chapter 7.
  - *Brachytherapy* as described in chapter 8.
  - *Systemic treatment* as described in chapter 9.
  - *Follow-up* as described in chapter 5.1.
- Signed research contact (details in chapter 13.3).
- Permission from the local authorities to conduct the study, such as an institutional medical ethics committee, departmental science committee or department head
- Names and contact details (including direct phone numbers and email addresses) of the local principal investigator, other investigators and research nurses or assistants.
- Choice for either the paper or the digital procedure for the data collection of patient-reported outcomes (described in chapter 13.1) and put in place the means to follow the appurtenant procedure.
- The local responsible for data entry and will receive a training on data-entry in the e-CRF.

Confirmation of accreditation for study phase II will be given in writing by the principal investigator to the local investigator.

11.4 Quality Assessments procedures

During the first phase of the study, the Quality Assessment (QA) procedure will be developed based on the experience of the 6 main study centres. In general, a QA procedure will be performed of every participating centre after the first year of opening the study. The first patient included by the centre will be evaluated to verify that to the brachytherapy contouring as described by the protocol. Contouring will be compared to the concept recommendations[32,addrecurrences] Dose planning will be compared to the accepted dose ranges. Centres will be given feedback on their performance, and additional cases will be reviewed if necessary. Confirmation of a successful QA will be given by a letter from principal investigator to the local principal investigator.

11.5 Safety evaluations

As this is an observational study, no independent DSMB will be installed.

12. ETHICAL CONSIDERATIONS

12.1 Regulation statement

This study will be conducted according to the principles of the Declaration of Helsinki (last amended by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013).[84] and in accordance with the Medical Research Involving Human Subjects Act (WMO)[85]and the General Data Protection Regulation of the EU (GDPR)[86] This study protocol will be approved by the local Research Ethics Committees in each of the participating centres, in accordance with national legislation and guidelines, before start of the study. This trial is already registered at the registry www.clinicaltrials.gov with identification number NCT06514235..

12.2 Patient identification

As this study will be conducted in accordance with the General Data Protection Regulation[86], directly identifiable patient data will not be processed in this study. Instead, patient data will be handled in a coded fashion. Each patient consenting to participate in the study will get a unique study number. All data that will be entered in the central study database is stored in a record identifiable by this study number. The data that will be entered in the central study database will not be directly identifiable. Hence, directly identifiable data such as names, date of birth or identification number of the local hospital will not be stored centrally. Moreover, only the local data managers and local investigators will be able to link the study number to the identity of the patient. The key file containing the link between the study number and the identity of the patient is stored at a safe location at the recruiting centre and will only be accessible for the local study team. Data protection procedures will be put in place according to local legislations and guidelines. Once the link between the study number and the identity of the patient is no longer necessary according to applicable laws and regulations the key file will be deleted.

12.3 Informed consent and patient enrolment procedure

If a patient with vaginal cancer is diagnosed in or referred to one of the participation hospitals, the local investigator will check whether she is eligible to participate in this study (in- and exclusion criteria described in chapter 6.2).
If the patient is eligible, the patient will be informed by her treating radiation oncologist or (research) nurse about the possibility to participate in this study. All patients will be informed about the aims of the study and its observational design. It will be emphasized that participation in this study is voluntary and that their treatment will not be influenced by the decision to participate or not participate in the study. Patients will be asked to participate in all aspects of the study; however, patients may decline participation in the quality of life questionnaire study and/or decline permission for the storage and use of tumour tissue at any time point in the future. Relevant aspects of the handling of their data will be communicated. The patient information folder of this study will be used to guide the communication of the information and will be provided to the patient to reflect on the information afterwards. The informed consent document will be also be explained and provided to the patients.
Thereafter, patients will be given a reasonable period of time to reflect on the information and to take an informed decision on participation. Written informed consent must be obtained before patients can be included in the study and registered in the central study database. Informed consent must be dated and signed by the patient, or its legal representative, before inclusion in the study. In addition, patients who consent to participate in the morbidity & quality of life study should fill out the baseline morbidity and QoL questionnaires before start of treatment. After inclusion in the study, patients always have the right to withdraw from the study. At any moment,

patients have the right to ask questions and to be informed about the study by local investigator or an independent person.

12.4 Benefits and risks for patient

The current study is an observational study wherein clinical outcomes of usual care for vaginal cancer patients, provided in accordance with local treatment guidelines, are registered. As such, there are no experimental interventions performed in this study. Hence, there is no potential benefit or risk for the patients participating in this study. However, the aim of this study is to collect data in order to optimize treatment of vaginal cancer and improve clinical outcomes of future vaginal cancer patients.
Communication of the potential benefits and risk of the treatment (which is thus not experimental, but usual care) is the responsibility of the local treating physician(s).

12.5 Insurance of study participants

Since this is an observational study, participation does not expose the patients to additional risks. Therefore, insurance of study participants is deemed not necessary.

13. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

13.1 Handling and storage of data and documents

Data will be handled and stored in accordance with the regulations stated in chapter 12.1.

Handling and storage of essential study documents
The sponsor will store essential documents in the Trial Master File. For each site the essential study documents, like the documentation of the local permission procedures and the signed informed consents of the locally included patients, will be stored locally. Storage as long as the study is active will be at a secured location that is accessible for only authorized personnel. It is each centre's responsibility to arrange this according to the local regulations. At the end of study documentation will be moved to the study archive until the legal storage period of 15 years has passed. The department heads are responsible for the management of the archive and destruction of the files.

Collection and handling of physician-reported data
Data will be collected by the local investigators on the following fixed moments during the study (which is conform the follow-up schedule in standard care):

- *Baseline* (which is before start of radiotherapy)
- *End of Treatment (EoT)*
- *3 months of follow-up*
- *6 months of follow-up12 months of follow-up*
- *18 months of follow-up*
- *24 months of follow-up*
- *36 months of follow-up*
- *48 months of follow-up*
- *60 months of follow-up*

And data will be collected by the local investigators on the following events at the moment these occur:

- *Any disease recurrence (defined in chapter 10.1)*
- *Death*
- *Lost to follow-up*
- *Withdrawal (of consent)*

A dedicated web-based CRF is designed for each of these moments and events. The local investigator will be responsible for the timely and accurate completion of the CRF on the specific time points within a reasonable time (i.e. within 3 months after patient visited the hospital).

Collection and handling of patient-reported data
Morbidity and quality of life questionnaires will be filled out by the patients at all aforementioned fixed moments. Each participating centre will be responsible for the distribution and collection of patient reported outcome measures (PROMs) for their own patients in the native language of the patient conform study protocol. The Dutch participating sites will be offered the opportunity to delegate the scheduled digital distribution and collection of questionnaires during follow-up to the study team in Erasmus MC. The patients included in these sites should give explicit written consent for the transfer of identifying personal data to the Datacentre at Erasmus MC for this purpose. For logistic reasons it is recommended to always collect the baseline set of questionnaires on paper during a pre-treatment visit at the clinic, to ensure this pre-treatment assessment will not be missed for logistical or administrative reasons of any kind in the relative small time window between date of written informed consent and start of treatment. The paper baseline questionnaire can be entered manually in the e-CRF afterwards by the local investigator or his/her

delegate. For the non-Dutch participating centres, the PROMs should be entered manually in the e-CRF by the local investigator or his/her delegate.

Procedure for digital data collection: The local site staff will provide the Datacentre at Erasmus MC with the following patient details for the purpose of central distribution and collection of on-line questionnaires: patient's full name, email address, date of birth, telephone number, and (expected) date of treatment completion. These identifying patient data will only be transferred to the Datacentre after explicit written informed consent has been obtained for this purpose by the local site staff ("NAW form"). The identifying data will be stored at Erasmus MC at a secured server location. During follow-up, the local investigator is responsible for providing the Datacentre with relevant updates in these patient data such as study withdrawal, disease progression, death, change of email address or telephone number, change in (expected) date of treatment completion. At the Datacentre all questionnaires will be scheduled and distributed according to the study protocol using a validated tool for the management of online questionnaires for patients. On protocol time points the patients will receive an e-mail containing a secure link to the online questionnaires, together with instructions on completion. The Datacentre will monitor the patient compliance on a weekly base and remind/contact the patient and/or site staff in case of any non-response to the scheduled questionnaires.

Procedure for paper data collection: The local investigators will provide the patient with the bundle of printed questionnaires (which are all marked at each page with the patients' study number and not with any identifiable data) around each follow-up visit (allowed range: a maximum of 3 weeks before or 3 weeks after). Each participating site will put decent procedures in place to ease and assure collection of the filled out questionnaires. Examples are: letting patients fill out the questionnaires directly at the outpatient clinic at the day of their visit; or handing out (or sending by mail) the bundle of questionnaires with addressed and stamped return envelopes combined with a protocolled sequence of reminders to non-responders. After the completed questionnaires have been retrieved from the patients, the local investigator, or his/her delegate, is responsible for entering the data into the database. In addition, they are responsible for monitoring and quality assurance of this paper-to-digital data transfer. Finally, the local investigators are responsible for safe storage of the questionnaires during the storage period conform applicable laws, regulations and institutional policies.

Data storage

The online database system Castor will be used to collect and store the data. Castor e-CRF is GCP (Good Clinical Practice) compliant and has a build-in audit trail. Data storage is compliant with all relevant regulations, such as FDA, EMA, GDPR, ICH-GCP, and applicable data practices and security standards. The local investigators will only have access to the data of the study participants of their centre. The central team of investigators and data managers, based in Erasmus Medical Centre, will have access to the data of all study participants. Access to the data may be secured by two-factor-authentication where needed to comply with (local) information security requirements. A detailed description of protection of the participant's privacy and handling of the key to the code is described in chapter 12.2.

Imaging data

Central storage of pseudonymized DICOM images and dose distributions will be done at a secured server at Erasmus MC, using the unique patient study number (12.2) as identifier. DICOM images from diagnosis and treatment including dose distributions will be sent or uploaded directly after completion of treatment. Follow-up DICOM images will be sent or uploaded within a reasonable time period after they have become available. Further logistical details are provided in the most recent version of the study manual.

Data will be stored during the applicable legal storage period for study data of 15 years after the end of the study.

13.2 Monitoring and Quality Assurance

Data will be monitored on a continuous base by the principal investigator and his delegates on missings, data inconsistencies and protocol deviations. As part of the site activation procedures the Sponsor will train the Local Investigator (and his/her team) on study procedures such as informed consent, patient enrolment, CRF completion and administration of essential trial documents. The Local Investigator should ensure that study related tasks will only be delegated to qualified persons who are familiar with the study protocol and applicable procedures. If indicated, the Sponsor may decide to perform a monitoring site visit in a participating site. The scope and purpose of such a monitoring visit will be communicated with the Local Investigator in the announcement letter sent by the independent Monitoring Team that will perform the monitoring visit on behalf of the Sponsor.

13.3 Public disclosure and publication policy

Research contracts need to be signed by each participating centre as part of the accreditation procedure (described in chapter 11). Policy concerning public disclosure and publication policy are defined in the research contract.
Briefly, results of this study will be unreservedly (regardless of a favourable or unfavourable outcomes) disclosed by publication in peer-reviewed scientific journals. Study participants are entitled to public disclosure of the results of the trial, after publication in peer-reviewed scientific journals, on the basis of their participation.
Further, the agreements on publication between the investigators are according to the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals[87] (previously known as the rules of the Vancouver convention) of the International Committee of Medical Journal Editors (ICMJE) and the editors' statements of a number of authoritative biomedical scientific journals.[88]

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15. APPENDICES

15.1 APPENDIX 1: WHO classification of tumors of the vagina, ICD-O coding

Tumor	ICD-0	subtypes
Epithelial tumors		
Squamous cell papilloma NOS	8052/0	Vestibular micropapillomatosis; solitary vaginal papilloma
Atrophy	-	-
Tubulosquamous polyp	8560/0	-
Squamous intraepithelial lesions of the vagina	8077/0 Low-grade squamous intraepithelial lesion	Vaginal intraepithelial neoplasia, grade 1
	8077/2 High-grade squamous intraepithelial lesion	Vaginal intraepithelial neoplasia grade 2 vaginal intraepithelial neoplasia, grade 3
Squamous cell carcinoma, HPV-associated	8085/3	-
Squamous cell carcinoma, HPV-independent	8086/3	-
Squamous cell carcinoma NOS	8070/3	-
Villous adenoma NOS	8261/0	-
Müllerian papilloma	-	-
Vaginal adenosis	-	-
Endocervicosis	-	-
Cysts	-	-
Adenocarcinoma	8140/3 Adenocarcinoma NOS 8483/3Adenocarcinoma, HPV-associated	-
Endometrioid adenocarcinoma NOS	8380/3	-
Clear cell adenocarcinoma NOS	8310/3	-

Mucinous carcinoma, gastric type	8310/3	
Mucinous carcinoma, intestinal type	8480/3	
Mesonephric adenocarcinoma	9110/3	
Carcinosarcoma NOS	8980/3	
Mixed tumour NOS	8940/0	
Carcinoma of Skene, Cowper, and Littré glands	8140/3	
Adenosquamous carcinoma	8560/3	
Adenoid basal carcinoma	8560/3	
Mixed epithelial and mesenchymal tumors		
Adenosarcoma	8933/3	
Miscellaneous tumors		
Germ cell tumour NOS	9064/3	Yolk sac tumour, pre-pubertal type Mature teratoma NOS Dermoid cyst NOS

15.2 APPENDIX 2: Overview of vaginal cancer stage classifications

FIGO 2018	AJCC, 8th Edition		IUCC, 8th Edition	Description
Stage	**Stage**	**Grouping**	**Stage**	
0			Tis N0 M0	Carcinoma in situ
I	IA	T1a N0 M0	T1 N0 M0	The cancer is only in the vagina and is no larger than 2 cm (4/5 inch) (T1a). It has not spread to nearby lymph nodes (N0) or to distant sites (M0).
	IB	T1b N0 M0		The cancer is only in the vagina and is larger than 2.0 cm (4/5 inch) (T1b). It has not spread to nearby lymph nodes (N0) or to distant sites (M0).
II	IIA	T2a N0 M0	T2 N0 M0	The cancer has grown through the vaginal wall, but not as far as the pelvic wall and is no larger than 2.0 cm (4/5 inch) (T2a). It has not spread to nearby lymph nodes (N0) or to distant sites (M0).
	IIB	T2b N0 M0		The cancer has grown through the vaginal wall, but not as far as the pelvic wall and is larger than 2.0 cm (4/5 inch) (T2b). It has not spread to nearby lymph nodes (N0) or to distant sites (M0).
III	III	T3 N0 M0 **OR** T1 to T3 N1 M0	T3 N0 M0 **OR** T1 to T3 N1 M0	The cancer is growing into the pelvic wall and/or has blocked the flow of urine (hydronephrosis) which is causing the kidneys to not work. (T3). **OR** The cancer can be any size and might be growing into the pelvic wall and/or has blocked the flow of urine (hydronephrosis) which is causing the kidneys to not work. (T1 to T3). **AND** It has also spread to nearby lymph nodes in the pelvis or groin (inguinal) area (N1) but not distant sites (M0).
IVA	IVA	T4 Any N M0	IVA	The cancer is growing into the bladder or rectum or is growing out of the pelvis (T4). It might or might not have spread to lymph nodes in the pelvis or groin (inguinal area) (Any N). It has not spread to distant sites (M0).
IVB	IVB	Any T Any N M1	IVB	The cancer has spread to distant organs such as the lungs, liver, or bones. (M1). It can be any size and might or might not have grown into nearby structures or organs (Any T). It might or might not have spread to nearby lymph nodes (Any N).

Vaginal cancer staging. Includes tumors with primary site of growth in vagina only; tumors with secondary spread to the vagina from other genital (vulva, cervix, endometrium) or extra-genital sites should not be included. Staging is mostly clinical; however, information available from pathologic evaluation of resection specimens needs to be used

Based on:

- American Joint Committee on Cancer. Vagina. In: *AJCC Cancer Staging Manual*. 8th ed. New York, NY: Springer; 2017:641-647.
- Mary K. Gospodarowicz (Editor)and Christian Wittekind (Editor). TNM Classification of Malignant Tumours, 8th Edition (UICC)
- Tracey Adams and Mauricio Cuello. Cancer of the Vagina. FIGO cancer report 2018

15.3 APPENDIX 3: EORTC QLQ Questionnaire

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year): 31

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

EORTC ILXX

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	Not at all	A little	Quite a bit	Very much
31. When you felt the urge to move your bowels, did you have to hurry to get to the toilet?	1	2	3	4
32. Have you had any leakage of stools?	1	2	3	4
33. Have you been troubled by passing wind?	1	2	3	4
34. Have you had cramps in your abdomen?	1	2	3	4
35. Have you had a bloated feeling in your abdomen?	1	2	3	4
36. Have you had blood in your stools (motions)?	1	2	3	4
37. Did you pass water/urine frequently?	1	2	3	4
38. Have you had pain or a burning feeling when passing urine?	1	2	3	4
39. Have you had leaking of urine?	1	2	3	4
40. Have you had difficulty emptying your bladder?	1	2	3	4
41. Have you had swelling in one or both legs?	1	2	3	4
42. Have you had tingling or numbness in your hands or feet?	1	2	3	4
43. Have you had hot flushes and/or sweats?	1	2	3	4
44. Have you had pain in your genital area?	1	2	3	4
45. Have you had itchy or irritated skin in your genital area?	1	2	3	4
46. Have you had unpleasant discharge from your vagina or genital area?	1	2	3	4
47. Have you had swelling in the genital area?	1	2	3	4

Please go on to the next page

During the past 4 weeks:	Not at All	A Little	Quite a Bit	Very Much
48. Have you worried that sex would be painful?	1	2	3	4
49. Have you been sexually active?	1	2	3	4

Answer these questions only if you have been sexually active during the past 4 weeks:	Not at All	A Little	Quite a Bit	Very Much
50. Has your vagina felt dry during sexual activity?	1	2	3	4
51. Has your vagina felt short?	1	2	3	4
52. Has your vagina felt tight?	1	2	3	4
53. Have you had pain during sexual intercourse or other sexual activity?	1	2	3	4
54. Was sexual activity enjoyable for you?	1	2	3	4

15.4 APPENDIX 4: Clinical drawings of the vagina with and without uterus

15.4.1a Clinical drawing of vagina without uterus

15.4.1b Clinical drawing of vagina with intact uterus

Left:

Speculum view: from centre to periphery: cervical os, portio, fornixes (grey area surrounded by thick dashed line), upper third, middle third, lower third (all separated by thin dotted lines), hymnal remnants marking the lower vaginal boundary (grey thick dashed line); u = urethra; for clockwise "3D" tumour delineation

Right:

Sagittal view (top) with reference structures including uterus, cervical os, portio, fornixes, upper third, middle third, lower third (all separated by thin dotted lines) of the vagina, ostium urthrae, anus; for longitudinal tumour delineation

Coronal view (below) with reference structures including uterus, cervical os, portio, fornices, upper third, middle third, lower third (all separated by thin dotted lines) of the vagina, parametria, paravaginal space; for longitudinal tumour delineation

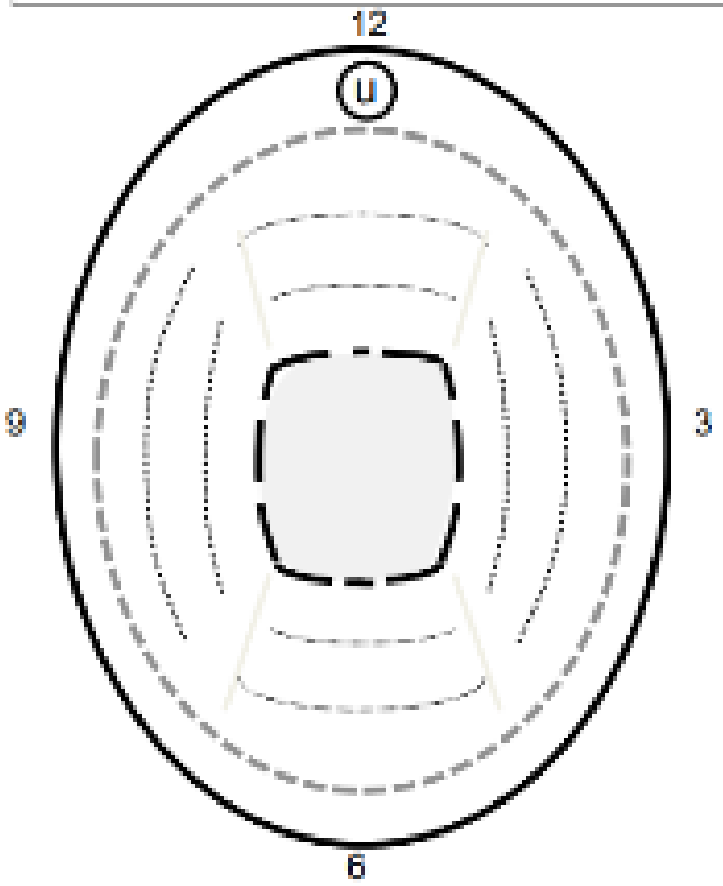
15.4.2 Clinical drawing of vagina with intact uterus, axial view

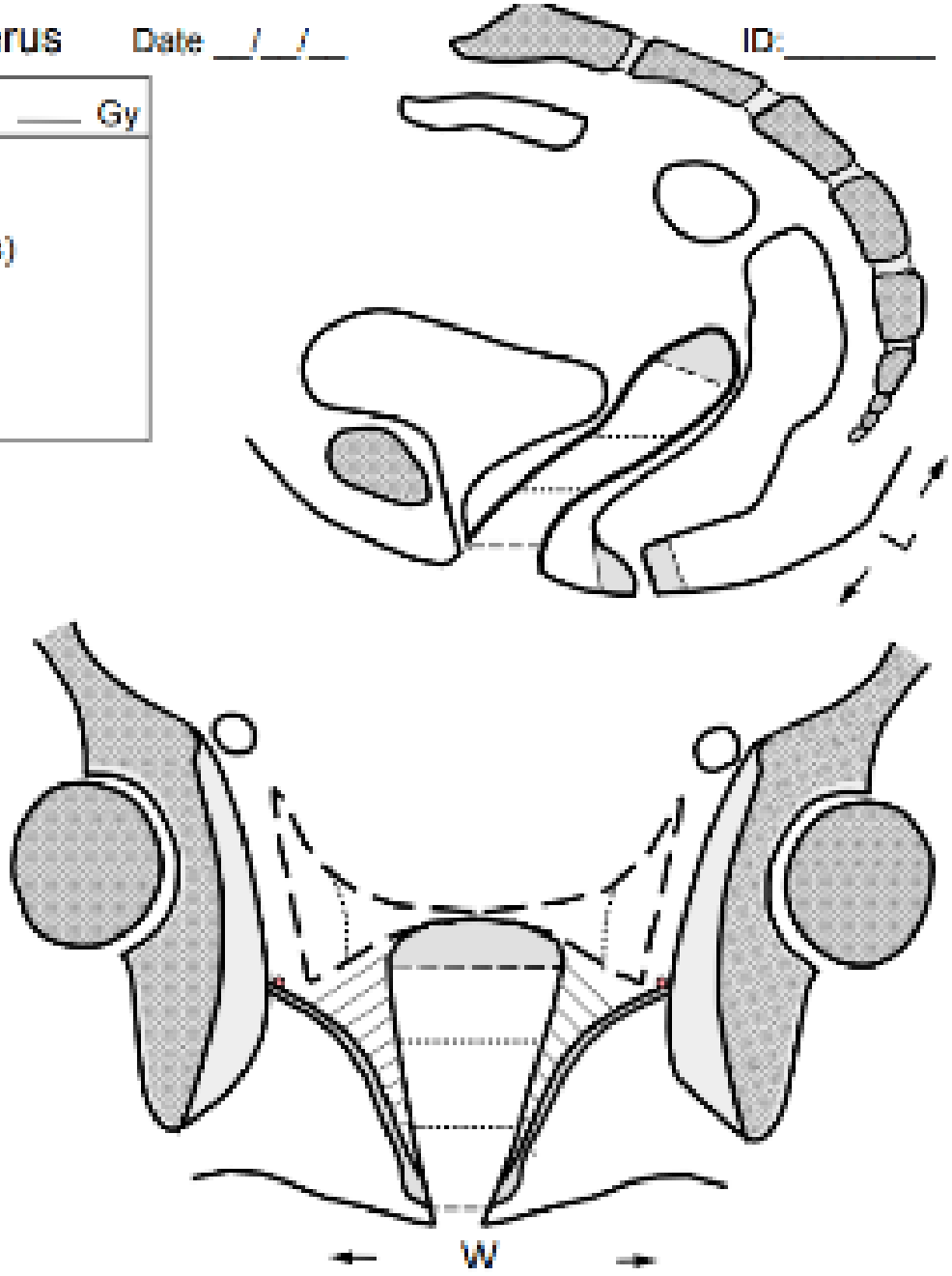
Clinical Drawing: Vagina + without uterus

Date __/__/__ ID:_____

At Diagnosis ☐ At Brachytherapy ☐ EBRT ____ Gy

Maximal tumour dimensions
Clockwise involvement ___ to ___ o'clock
Thickness =___ cm (perpendicular to vaginal axis)
Width = ___ cm (incl. paravaginal extension)
Length =___ cm (along vaginal axis)
Proximal tumour free distance (length) =___cm
Distal tumour free distance (length) =___ cm



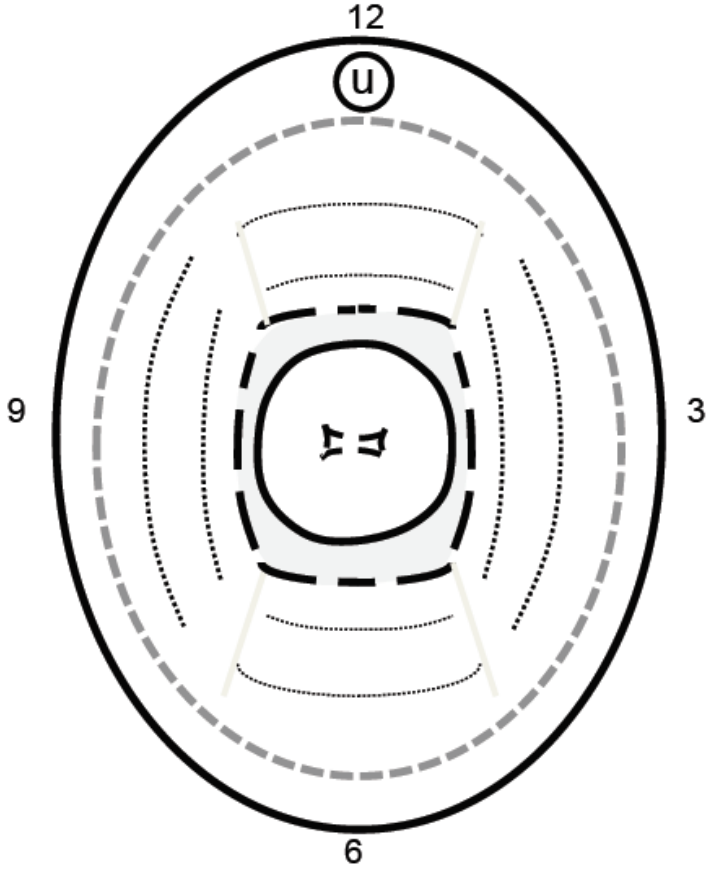


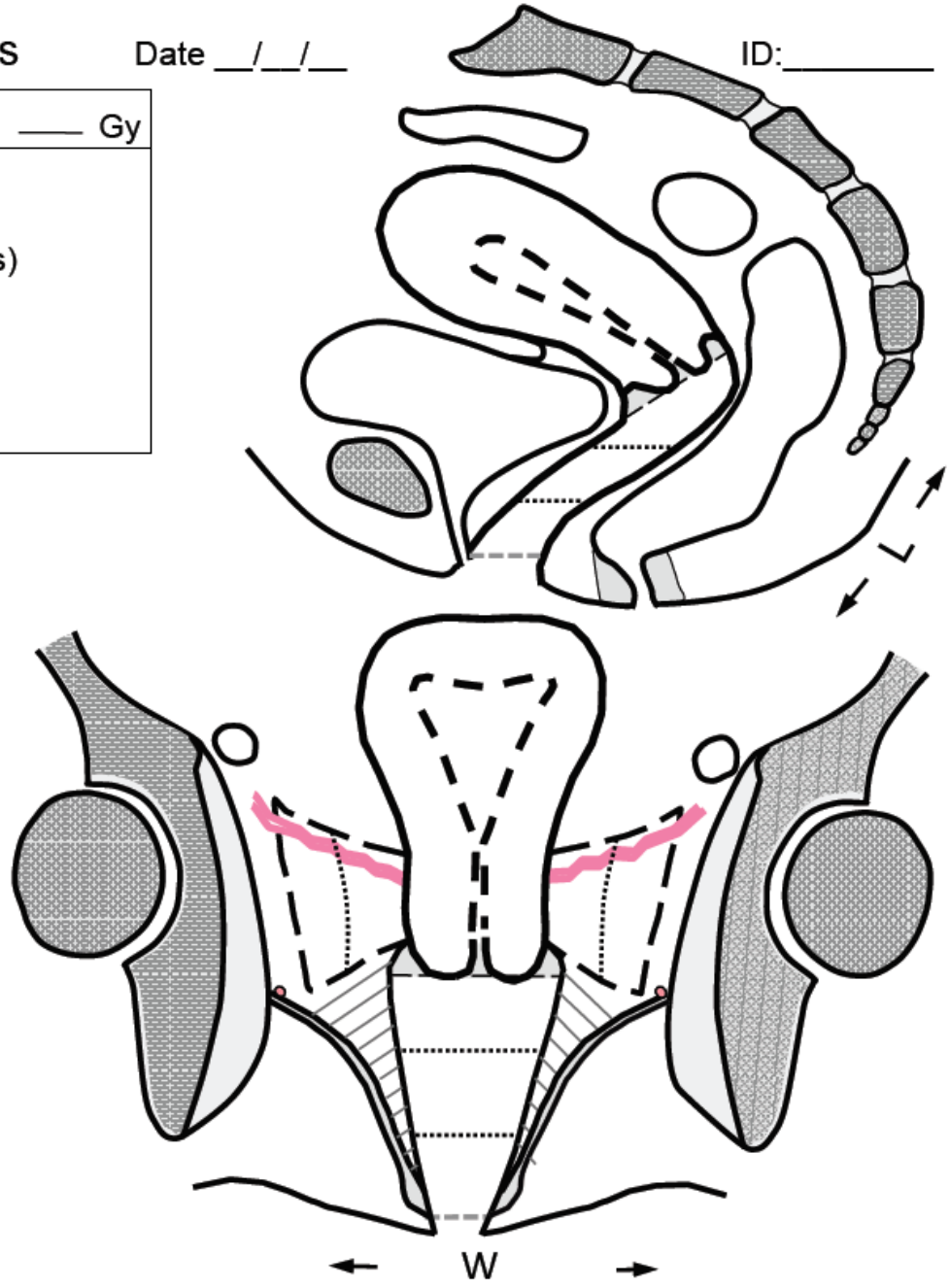
Clinical Drawing: Vagina + intact uterus

Date __/__/__ ID:_____

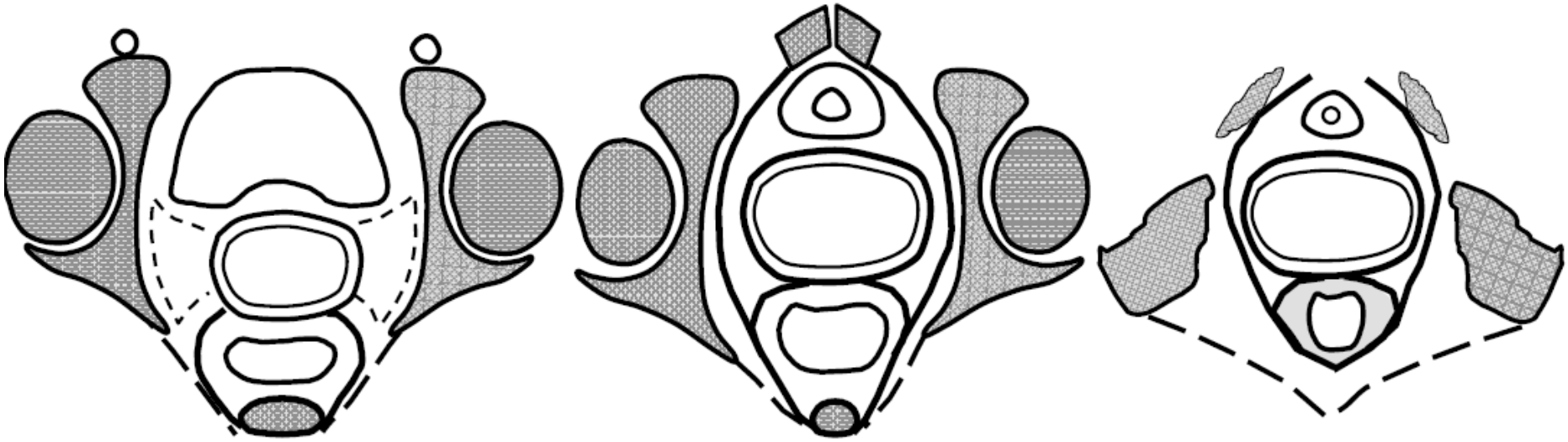
At Diagnosis ☐	At Brachytherapy ☐	EBRT ____ Gy

Maximal tumour dimensions
Clockwise involvement ___ to ___ o'clock
Thickness =___ cm (perpendicular to vaginal axis)
Width = ___ cm (incl. paravaginal extension)
Length =___ cm (along vaginal axis)
Proximal tumour free distance (length) =___cm
Distal tumour free distance (length) =___ cm





Clinical Drawing: Vagina + intact uterus



Upper 1/3 vagina | **Middle 1/3 vagina** | **Lower 1/3 vagina**