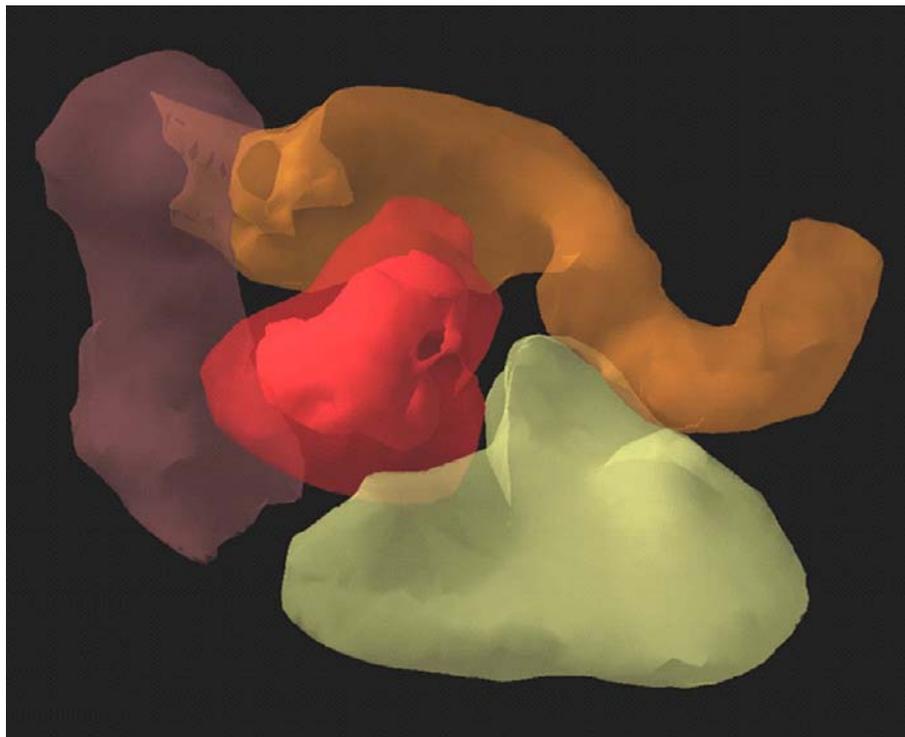


**A European study on MRI-guided brachytherapy
in locally advanced cervical cancer**

EMBRACE

(ENDORSED BY GEC ESTRO)



Contents:

1. ABBREVIATIONS.....	4
2. SUMMARY	5
3. INTRODUCTION AND PRINCIPLES OF IMAGE GUIDED GYNAECOLOGICAL BRACHYTHERAPY ..	7
4. GENERAL AND SPECIFIC AIMS OF THE STUDY.....	9
4.1 GENERAL AIMS:	9
4.2 SPECIFIC AIMS	9
5. STUDY DESIGN AND ENDPOINTS.....	10
6. OVERVIEW OF EMBRACE.....	11
7. STAGING AND PATIENT WORK-UP	12
8. PATIENT SELECTION	12
8.1 INCLUSION CRITERIA:.....	12
8.2 EXCLUSION CRITERIA.....	12
9. EXTERNAL BEAM RADIOTHERAPY	13
9.1 TREATMENT PLANNING FOR EBRT	13
9.2 CONTOURING FOR EBRT	14
9.2.1 Macroscopic extension of the primary tumour at diagnosis (GTV-T _D).....	14
9.2.2 Macroscopic Nodal-target (CTV-N)	14
9.2.3 Parametrial disease (CTV-P).....	15
9.2.4 Potential subclinical disease (CTV-E).....	15
9.3 CONTOURING OF ORGANS AT RISK.....	15
9.4 DOSE AND FRACTIONATION FOR EBRT.....	16
9.4.1 Dose prescription for EBRT.....	16
9.4.2 Fractionation of EBRT.....	16
9.5 TECHNIQUE FOR EBRT	16
9.6 REPORTING EBRT PARAMETERS	17
10. BRACHYTHERAPY	17
10.1 TREATMENT PREPARATIONS FOR BT.....	17
10.2 APPLICATOR RECONSTRUCTION	18
10.3 CONTOURING OF GTV _B , HR-CTV, IR-CTV AND ORGANS AT RISK:	18
10.4 TREATMENT PRESCRIPTION FOR BT	20
10.5 DOSE OPTIMIZATION FOR BT	21
10.6 DOSE AND VOLUME RECORDING AND REPORTING	22
11. CONCOMITANT CHEMOTHERAPY	23
12. FOLLOW-UP INVESTIGATIONS.....	23
13. PATIENT MATERIAL, EVALUATION AND STATISTICS.....	24
13.1 ESTIMATE OF PATIENT ACCRUAL AND STUDY PERIOD	24
13.2 ESTIMATE OF STAGE DISTRIBUTION, DOSE PRESCRIPTION PATTERN AND SIZE OF RISK GROUPS	25
13.3 EVALUATION AND STATISTICS ACCORDING TO THE AIMS AND ENDPOINTS OF THE STUDY.....	25
14. ACCREDITATION AND QUALITY ASSURANCE FOR EMBRACE.....	30
15. PATIENT REGISTRATION PROCEDURE	30
16. CASE RECORD FORMS AND PROCEDURES FOR DATA COLLECTION.....	31
17. ETHICAL CONSIDERATIONS.....	32
17.1 PATIENT PROTECTION	32

17.2. SUBJECT IDENTIFICATION	32
17.3. INFORMED CONSENT	32
17.4. ADVANTAGES AND DISADVANTAGE FOR THE PATIENTS	32
18. PUBLICATION OF DATA	33
19. STUDY-SECRETARIAT, STUDY-COORDINATORS AND STATISTICIAN	33
20. THE EMBRACE DATABASE AND WEBSITE	34
21. LIST OF APPENDICES	34
22. REFERENCES	36

1. Abbreviations

2D	Two-dimensional
3D	Three-dimensional
ABS	American Brachytherapy Society
BT	Brachytherapy
CRF	Case Record Form
CT	Computed Tomography
CTV	Clinical Target Volume
D90	The isodose that includes 90% of the target
D100	The isodose that includes 100% of the target = minimal target dose
D _{0.1cc}	Minimum dose in the most exposed 0.1 cm ³ of an OAR
D _{2cc}	Minimum dose in the most exposed 2 cm ³ of an OAR
EBRT	External Beam Radiotherapy
EPID	Electronic Portal Imaging Device
ESTRO	European Society for Therapeutic Radiology and Oncology
EQD2	Equivalent dose in 2 Gy fractions
GEC	Groupe Européen de Curiethérapie
GFR	Glomerula Filtration rate
GTV	Gross Tumour Volume
HDR	High Dose Rate
IMRT	Intensity Modulated Radiotherapy
IMBT	Intensity Modulated Brachytherapy
LDR	Low dose Rate
MDR	Medium Dose Rate
MLC	Multi Leaf Collimator
MRI	Magnetic Resonance Imaging
OAR	Organs at Risk
PDR	Pulsed Dose Rate
PET-CT	Positron Emission Tomography- Computed Tomography
PTV	Planning Target Volume
QoL	Quality of Life
RTOG	Radiation Therapy Oncology Group
TV	Treated Volume
V100	Percentage of the target volume receiving 100% of the prescribed dose
V _{PD}	Volume encompassed by the prescribed dose
V _{2PD}	Volume encompassed by twice the prescribed dose

2. Summary

Background:

The standard treatment of locally advanced cervical cancer is radio-chemotherapy including external beam radiotherapy (EBRT), brachytherapy (BT) and concomitant chemotherapy with weekly Cisplatin. While image based conformal EBRT is routinely used, prescription and reporting of BT is still based on specific dose points defined in 2D. Thus, for several decades the BT dose has most often been prescribed and reported to the Manchester point A defined according to different traditions.

Recently, a working group from GEC-ESTRO has published recommendations on contouring of tumour target and organs at risk (OAR) as well as on dose volume parameters to be reported for image guided BT in definitive radiotherapy for locally advanced cervical cancer. These recommendations are mainly derived from retrospective single institution experience with MRI based intracavitary BT. The major advantage of this technique is the possibility to conform the dose given by BT with regard to both volume (3D) and time (4D). Thus, by repetitive imaging performed before each BT implant it is possible adapt the dose given by BT to the anatomy of each individual patient taking into account not only the position of OAR but also the tumour regression which often is obtained by preceding EBRT and chemotherapy. Based on the experience collected so far, the image based BT approach is expected to have a major impact on the clinical outcome with a concomitant decrease in the rates of both local failure and morbidity.

Aims:

- To introduce MRI based 3D-4D BT in locally advanced cervical cancer in a multicenter setting within the frame of a prospective observational study.
- To establish a bench-mark for clinical outcome with image based BT in a large patient population with respect to local control, survival, morbidity and QoL
- To establish a reference material with regard to image based DVH parameters according to the guidelines from the GEC ESTRO working group.
- To correlate image based DVH parameters for CTV and for OAR with outcome
- To develop prognostic and predictive statistical models for clinical outcome including volumetric, dosimetric, clinical and biological risk factors
- To establish radiobiological parameter estimates that will allow a precise risk estimation in individual patients and aid in the development of new treatment protocols

Type of design:

The study is a multicenter prospective observational study. Reporting on the key clinical treatment and outcome parameters are mandatory while study of QoL and other companion studies are optional for the individual department. Patient registration and reporting will be performed by the individual investigator via the internet to a central database.

Patients to be included:

Patients with newly biopsy proven squamous carcinoma, adenocarcinoma or adeno-squamous carcinoma of the uterine cervix, FIGO stage IB, IIA, IIB, IIIA, IIIB and IVA in whom definitive radiotherapy with curative intent is planned are qualified for the study. Patients with para-aortic metastatic nodes (stage IVB) to the level of L2 are also eligible but patients with further dissemination are not.

Staging should as a minimal include gynaecological examination, MRI of the pelvis, abdominal CT or MRI and chest radiography. Further investigations are applied if necessary (e.g. cystoscopy, rectoscopy) or normally done according to institutional practice (e.g. PET-CT).

Treatment of patients in the trial:

All patients will receive both EBRT and BT. Summation of EBRT and BT doses will be performed by calculation of a biologically equivalent dose in 2 Gy per fraction (EQD2) using the linear-quadratic model with $\alpha/\beta = 10$ Gy for tumour effects and $\alpha/\beta=3$ Gy for late normal tissue damage. The repair half time is assumed to be 1.5 hrs.

EBRT should be delivered in accordance with specific defined rules for target definition, treatment planning, dose, fractionation and overall treatment time. Target definition for EBRT will be based on 3D imaging by CT or PET-CT. The elective target for nodal disease (low-risk clinical target volume LR-CTV) will be treated with 45-50 Gy by use of EBRT only. Macroscopic disease out of range from significant dose contribution from intracavitary BT (massive pelvic side wall disease or metastatic pelvic and para-aortic nodes) should be dealt with by additional measures such as combined interstitial-intracavitary BT or by a simultaneous integrated EBRT boost to a dose level of 55-65 Gy. Intensity modulated radiotherapy (IMRT) and/or Image guided radiotherapy (IGRT) may be used. Dose per fraction of EBRT should be 1.5-2.0 Gy in the elective volume whereas fraction sizes of 2.0-2.4 Gy should be used in targets encompassing macroscopic tumour not treated with BT. Maximal treatment time including both EBRT and BT is 50 days.

For BT the choice of applicator and implant procedures should follow the usual standard of the individual department. However, BT treatment planning will be based on MRI imaging with the applicator in situ according to the GEC-ESTRO guidelines and additional criteria for MRI sequencing, contouring, applicator reconstruction, and dose optimization. The intention is to treat the whole cervix and the remaining residual tumour tissue at the primary site at time of BT (high risk-clinical target volume, HR-CTV) to a dose level analogue to the dose level previously prescribed for point-A. An alternative (complementary) approach is to treat the volume according to the tumour extension at diagnosis (intermediate risk-clinical target volume, IR-CTV) to a dose level equivalent to the dose level previously prescribed for the ICRU reference volume. The dose level chosen for HR-CTV or IR CTV in this protocol and the DVH constraints is to follow the individual departmental practice, i.e. there is no general dose prescription and DVH constraints in the EMBRACE protocol.

With regard to chemotherapy, weekly concomitant Cisplatin (40 mg/m^2) for 5-6 courses is standard unless chemotherapy is precluded by patient age, co-morbidity and toxicity.

Quality assurance

Only approved departments and investigators can contribute to patients to the protocol. It is the responsibility of the study coordinators to evaluate and approve participation. Approval requires a successful dummy run and an individual assessment of the performance of each participating centre. There is no formal on site monitoring, but patient files and treatment plans must be kept at least until closure of the protocol and final analysis of the results is obtained.

Outcome measures

Local control within the specific BT targets (HR-CTV and IR-CTV) and morbidity related to OAR in the pelvis are the primary outcome measures. Secondary endpoints include regional control, disease free survival and overall survival. All endpoints will be evaluated by actuarial statistics. Morbidity will be scored by use of the Common Terminology Criteria for Adverse Events (CTCAE v3.0). QoL will also be systematically recorded in patients treated at departments participating in the QoL part of the protocol (to follow as an optional protocol amendment).

Evaluation of outcome measures

Remission status (complete, partial, stable & progressive disease) will be evaluated 3 month after treatment by pelvic MRI and gynaecological examination. Regular follow-up including gynaecological examination will then be instituted with planned appointments 6, 9, 12, 18, 24, 30, 36, 48 and 60 months after treatment. Pelvic MRI will be repeated at 12 after treatment or in case of suspected recurrence. Morbidity will be scored systematically at base line and at each time point during follow-up. Quality of life questionnaires are distributed at regular intervals both at diagnosis (base line) and during follow up.

Sample size and data maturity

The study aims at recruiting more than 600 patients in 3 years and to follow them for at least another 3 years to allow for a meaningful assessment of the endpoints by univariate and multivariate analysis.

3. Introduction and principles of image guided gynaecological brachytherapy

The standard treatment for locally advanced cervical cancer is to day radio-chemotherapy consisting of EBRT, intracavitary BT and concomitant chemotherapy with Cisplatin. While EBRT for several years has been based on 3D dose planning, BT is still based on doses to points rather than volumes. Thus, the most commonly used system is still relying on orthogonal X-rays were the BT dose is prescribed to point A and the reporting of doses to critical normal tissues is done by use of the ICRU reference points (32).

Recently, both European (GEC ESTRO) (10;31) and American (ABS) (26) recommendations for three-dimensional (3D) and adaptive (4D) intracavitary brachytherapy have been published. So far only the European GEC ESTRO recommendations are supported by published clinical data with systematic use of MRI and partly CT based planning of intracavitary BT (8;24;29;30;34;39). It has been agreed upon by representatives of both societies in 2005 (25) to base further clinical and research work in regard to image guided gynaecologic brachytherapy on the GEC ESTRO recommendations I and II as published in 2005 and 2006 (10;31).

So far systematic MRI based BT dose planning has been limited to single centre experience (e.g. Vienna, Paris, Leuven, Aarhus, Utrecht, and London). However, recently a cooperative group of additional centres with capability for doing MRI based intracavitary BT has been established (GYN GEC ESTRO network in Budapest 2005). The primary aim of the present study is to disseminate MRI based 3D BT to these departments within the frame of a well-controlled prospective clinical trial and to test dose volume effect relationships for tumour and OAR through the differences in dose and fractionation (dose rate) as applied in the various centres. Through the interplay between

the clinical, technical and radiobiological aspects of this observational study we aim to achieve the composite goals listed in section 4.

Principles of image guided gynaecological brachytherapy

The primary advantage of 3D and 4D adaptive brachytherapy is the possibility to adapt and conform the dose given by BT to the anatomy of each individual patient taking into account both tumour regression obtained by preceding EBRT and Chemotherapy and also the position of near by organs at risk (OAR). Based on the current experience, this technique has the potential for reducing both local failure rate and rate of moderate to severe morbidity (29).

This goal can only be achieved provided that both gynaecological examination and MRI (or CT) with BT applicator in situ are performed at the time of BT (31). Visualization of the tumour is very difficult with computed tomography (CT) which makes MRI necessary (18). Because changes of localization of the target and OAR in relation to the position of the applicator may occur, ideally each BT implant should be followed by a new MRI study with the applicator in situ and a new dose plan (2;13). This seems to be relevant in particular for sigmoid, bowel and bladder (15;19). As these organs at risk can be also delineated on CT (4;17;38;39), it seems to be feasible to replace MRI by CT, if more than one fraction is applied for brachytherapy.

For each fraction of BT contouring of the clinical target volume, based on MRI (10) and organs at risk based on MRI or CT (38) are done in a 3D treatment planning system. Subsequently, the applicator is carefully reconstructed and the conventional standard loading pattern matching the prescribed dose to point A is applied. From this starting point dose optimization is performed with the goal of adapting the dose to the target volume (GTV at the time of BT plus whole cervix plus suspected residual extra cervical disease) analogue to the dose level previously prescribed for point A or the reference volume without exceeding the dose volume constraints for the surrounding normal tissues (16). Dose optimization should be conservative, i.e. the standard loading pattern should be retained as far as possible (16;31).

Evaluation of the DVH parameters obtained by BT is performed by use of the Gyn GEC ESTRO recommendations (31). For each BT fraction the D90 and D100 for GTV, HR-CTV and IR-CTV is recorded. For the OAR the $D_{0.1cc}$ and D_{2cc} of rectum, sigmoid, bladder are determined. Both the physical dose as well as the EQD2 is recorded.

Assessment of dose from EBRT is done based on the assumptions given in the Gyn GEC ESTRO Recommendation (II) (31): For the regions of interest (CTV and OAR) it is assumed that they receive the full dose of EBRT as represented by the ICRU point. Thus, for dose reporting these doses are taken and calculated in EQD2 and then added to the dose for defined BT volumes like D90 for the CTV and $D_{0.1cc}$ and D_{2cc} for OAR, which also have been expressed in EQD2.

4. General and Specific Aims of the study

4.1 General aims:

- To introduce MRI based 3D-4D BT in locally advanced cervical cancer in a multicenter setting within the frame of a prospective observational study.
- To establish a bench-mark for clinical outcome with image based BT in a large patient population with respect to local control, survival, morbidity and QoL.
- To establish a reference material with regard to image based DVH parameters according to the guidelines from the GEC ESTRO working group.
- To correlate image based DVH parameters for CTV and for OAR with outcome.
- To develop prognostic and predictive statistical models for clinical outcome including volumetric, dosimetric, clinical and biological risk factors.
- To establish radiobiological parameter estimates that will allow precise risk estimation in individual patients and aid in the development of new treatment protocols.

4.2 Specific Aims

- To assess prospectively outcome for disease (local control, survival), for morbidity and for QoL life applying appropriate clinical, imaging and QoL protocols.
- To test that there are three groups representing different risks of recurrence: small tumours; large tumours with favourable response; large tumours with unfavourable response to initial radio-(chemo)therapy.
- To correlate local control (survival) and dose volume parameters for GTV and CTV for the overall cohort and for the 3 different risk groups and to establish hazard ratios and dose effect curves for the primary tumour.
- To correlate outcome data and dose volume parameters for the different OAR (rectum, sigmoid, bladder) and to establish hazard ratios and dose effect curves for OAR.
- To correlate QoL outcome to morbidity outcome.
- To quantify the change in DVH parameters obtained by image guided dose optimization of BT in the individual patient.
- To compare volumetric data on GTV and CTV at diagnosis and during treatment and relate them to dose volume parameters within the 3 different risk groups of the overall patient cohort.

- To evaluate the indicators for quality assessment throughout the whole study period in order to define systematic and random variations for the different indicators (e.g. contouring, applicator reconstruction, dose volume assessment).
- To validate from clinical outcome data the radiobiological equivalence calculations used for assessing dose and volume parameters in gynaecological radiotherapy.
- To test if the GYN GEC ESTRO recommendations for BT in cervical cancer are feasible in a multi-centre setting.

5. Study design and endpoints

A prospective observational multicenter study will be performed in patients with locally advanced cervical cancer considered to be potentially curable by definitive radio-(chemo) therapy. The patients will be divided and analyzed in three strata according to risk of recurrence:

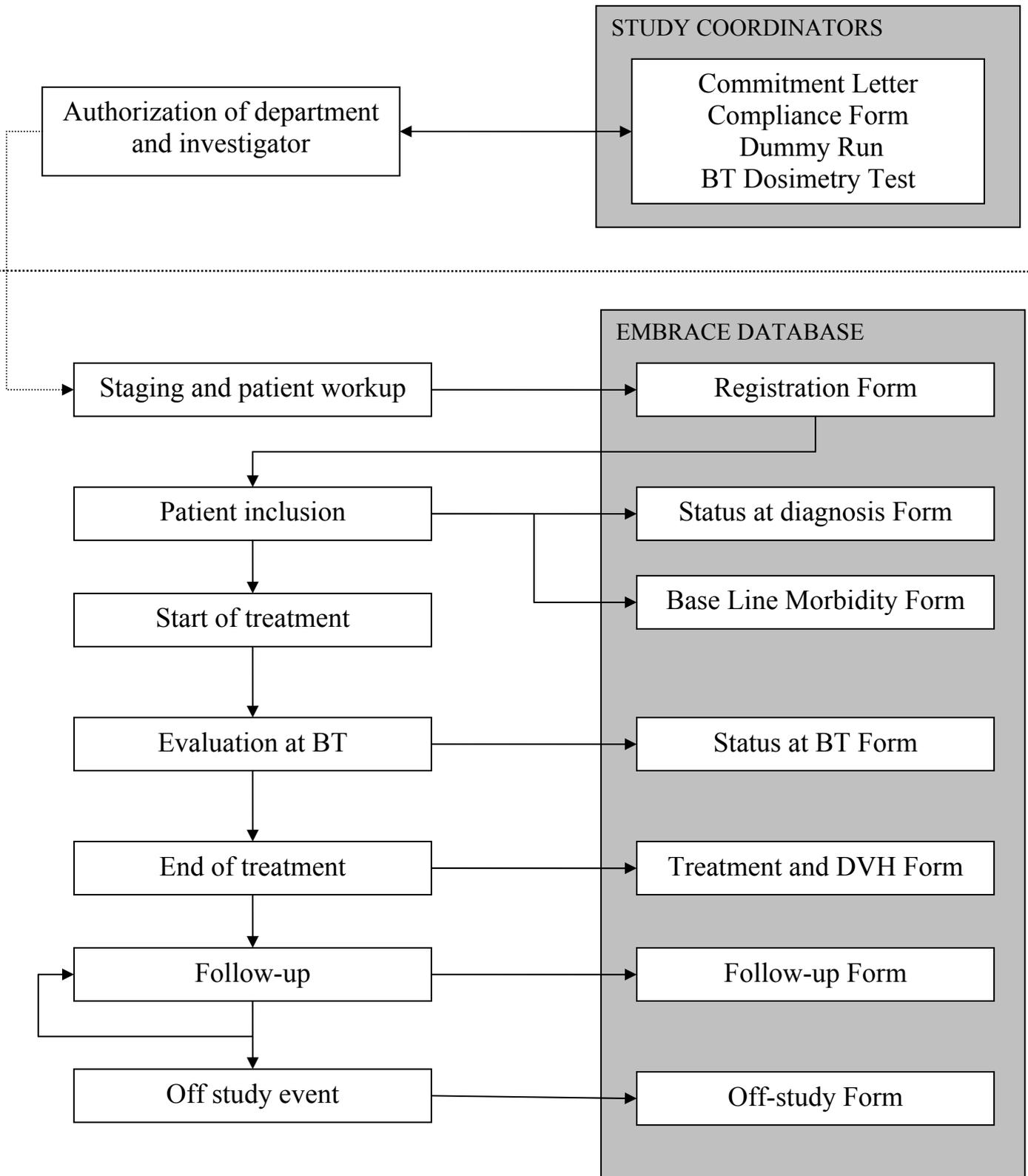
- 1) Small tumours
- 2) Large tumours favourable response
- 3) Large tumours with unfavourable response to the initial radio-(chemo) therapy.

Primary endpoints are response during and after treatment, local control and morbidity. Secondary endpoints comprise regional control, disease free survival and overall survival and QoL.

A clinical local failure has to be validated by MRI and topographically correlated to the MRI based BT targets (HR CTV and IR-CTV) and the dose volume parameters of the treatment plan. It has to be classified as “inside”, “at the edge”, “outside”.

Major events with regard to morbidity have to be reported using 3D imaging information integrating e.g. clinical examination, endoscopy and MRI. The location of organ damage (i.e. fistula) has to be identified in 3D and a correlation to the dose volume parameters for the affected region should be investigated.

6. Overview of EMBRACE



7. Staging and patient work-up

All examinations must be completed before treatment and no investigation should be more than 4 weeks old at the time of treatment initiation. For the purpose of this study the following examinations have to be performed

- General physical examination, assessing also performance status (WHO)
- Blood tests including haemoglobin
- Gynaecological examination (supplemented by cystoscopy and rectoscopy if organ involvement is suspected) with topographic documentation on a specific cartoon (see appendix 1)
- Biopsy of primary tumour
- Imaging of pelvis by MRI
- Imaging of the retroperitoneal space and abdomen (CT, PET-CT or MRI),
- Imaging of thorax (X-Ray, CT or PET-CT)
- Staging according to FIGO and TNM
- Morbidity scoring (CTC v3.0)
- QoL questionnaire (optional)

8. Patient selection

8.1 Inclusion criteria:

- Cancer of the uterine cervix considered suitable for curative treatment with definitive radio-(chemo)therapy including MRI guided BT
- Positive biopsy showing squamous-cell carcinoma, adenocarcinoma or adeno-squamous cell carcinoma of the uterine cervix.
- Staging according to FIGO and TNM guidelines
- MRI of pelvis at diagnosis is performed
- MRI, CT or PET-CT of the retroperitoneal space and abdomen at diagnosis is performed
- MRI with the applicator in place at the time of (first) BT will be performed
- Para-aortic metastatic nodes below L1-L2 are allowed
- Patient informed consent

8.2 Exclusion criteria

- Other primary malignancies except carcinoma in situ of the cervix and basal cell carcinoma of the skin
- Metastatic disease beyond para-aortic region (L1-L2)
- Previous pelvic or abdominal radiotherapy
- Previous total or partial hysterectomy
- Combination of preoperative radiotherapy with surgery
- Patients receiving BT only
- Patients receiving EBRT only
- Patients receiving neoadjuvant chemotherapy
- Contra indications to MRI
- Contra indications to BT

- Active infection or severe medical condition endangering treatment delivery
- Pregnant, lactating or childbearing potential without adequate contraception

9. External Beam Radiotherapy

The focus of the protocol is impact of image guided BT on clinical outcome. The following paragraphs on EBRT are therefore intended to provide a basis for harmonization of this important part of the overall treatment.

Harmonization is mandatory for the component of the EBRT dose which is relevant with regard to the tumour related CTV: HR-CTV and IR-CTV. Harmonization is also mandatory for the EBRT dose in small volumes of OAR adjacent to the volume later treated to a high dose by BT. This applies in particular for the dose in the anterior-lateral rectal wall, anterior-lateral sigmoid wall, posterior-inferior bladder wall, and the adjacent vaginal wall. This probably also applies for nearby structures like ureter, urethra, vessels and nerves, but this is not in the focus of this study.

EBRT has to be performed for these volumes in a homogenous way in order to arrive at a homogenous comparable EBRT dose contribution for the tumour related CTV and for the small volumes of adjacent OAR.

The way in which the elective lymph node areas are planned and treated is in principle up to the decision of each individual department. The same applies for any EBRT boost to macroscopic disease not significantly affected by the BT or affecting the dose in the HR-CTV and IR-CTV, respectively. However, for the overall outcome of the study with regard to secondary endpoints like regional control and survival as well as to morbidity associated with EBRT, the contribution from EBRT may have a certain impact. Therefore some harmonization is also aimed at for the treatment of regional disease. Furthermore, there may be even some (minor) impact on radiation induced morbidity from EBRT in small volumes which is mainly associated with BT.

The following paragraphs may serve as recommendations for planning and performance of modern 3D image based conformal radiotherapy or even IMRT. Within the course of the study, interest may further grow to harmonise also EBRT on a broader basis due to reasons mentioned above.

9.1 Treatment planning for EBRT

Treatment planning is performed on a 3D dose planning system based on a 3D CT data set, preferably with not more than 3-5 mm slice thickness. The use of contrast media is recommended to ease identification of structures of interest: vessels, involved lymph nodes, vessels, uterus (tumour), bowel, bladder, and vagina.

Immobilization in supine position ensures reproducible positioning both for treatment planning and treatment execution with the same method for immobilization throughout the whole procedure.

Prone position using the belly board may be used for certain situations (1;22;28;40). However, supine positioning should be used if para-aortic irradiation is planned (5).

To minimize internal motion it is important to obtain reproducible bladder fillings at the time of dose planning CT and during treatment. Also the problems related to standardizing recto-sigmoid filling should be addressed by each participating department. The method applied has to be reported in the study compliance form and accepted by the study coordinators.

Planning, recording and reporting follow the general principles as given in the ICRU reports 50, 62 and in the forthcoming ICRU report for IMRT (if applied). Irrespective of technique (conformal or IMRT) the D95 should be reported for all targets including the GTV_D (see below). For conformal 4-field box technique also the dose the ICRU reference point should be reported. Dose is given as physical dose, as total dose and dose per fraction and as EQD2. The dose inhomogeneity is specified for the different targets and the encompassing isodose is specified for the PTV.

9.2 Contouring for EBRT

The volumes of interest are in principle defined according to ICRU 50/62:

GTV: Gross Tumor Volume (at diagnosis).
 CTV: Clinical Target Volume = GTV + suspected microscopic tumor extension.
 ITV: Internal Target Volume = CTV + internal margins to compensate for internal motions.
 PTV: Planning Target Volume = CTV + set-up margin.
 OAR: Organs at Risk

EBRT Target contouring requires an integration of the spatial information obtained by CT, MRI (and PET-CT) and gynaecological examination. GTV and CTV are drawn individually. The following targets needs to be considered:

- GTV-T_D
- CTV-N
- CTV-P
- CTV-E

For delineation of ITV and PTV a certain (additional) margin is added. With regard to margins, each department must determine its own strategy as there is little consensus on margins and some of them are dependent on institutional practice. For example set-up margin (PTV) varies with both field localization and patient fixation. Normally this would result in a total safety margin (including ITV) from CTV to PTV of approximately 10 mm (11).

9.2.1 Macroscopic extension of the primary tumour at diagnosis (GTV-T_D)

GTV-T_D is delineated in order to have a clear understanding of the primary tumour and its topography at diagnosis. This mainly serves as a basis for the definition of the HR-CTV and IR-CTV for BT, which will follow later during or after EBRT.

A CTV-T_D is not constructed, as this is not according to the intention of this study. Furthermore, there is growing evidence that major uncertainties due to organ and tumour movement and tumour shrinkage would have to be taken into account for the design of such a CTV for fractionated EBRT reflecting GTV at diagnosis.

- GTV-T_D: Whole tumour extension at diagnosis within the cervix plus macroscopic extension into the uterine corpus, into the parametria, into the vagina and into adjacent organs or lymph nodes

9.2.2 Macroscopic Nodal-target (CTV-N)

Pathological lymph node(s) separated from GTV-T_D by a distance necessitating a separate EBRT boost.

- GTV-N: Pathological lymph node itself with no margin
- CTV-nodes: GTV-N with 10 mm margin unless safe anatomical barriers such as bone or uninvolved muscle/fascia allow for a smaller margin

9.2.3 Parametrial disease (CTV-P)

Tumour in the parametria and/or at the pelvic side wall not appropriately treated by brachytherapy

- GTV-P: The gross tumour volume in question with no margin
- CTV-P: GTV-P plus safety margin of 5-10 mm; matching with the HR-CTV and IR-CTV has to be performed

9.2.4 Potential subclinical disease (CTV-E)

The elective volume (CTV-E) should include the following lymph node regions depending on the potential risk of involvement:

- GTV-T_D and CTV-N (when present) should be fully embedded in CTV-E with a margin of at least 10 mm, unless safe anatomical barriers such as bone or uninvolved muscle/fascia allow for a smaller margin
- Both parametria and the whole uterus and (part of) the vagina (at least 20 mm below GTV-T_D)
- The pelvic lymph node region including parametrial, para-rectal, internal iliac, external iliac, presacral and iliaca communis (23).
- The para-aortic lymph node region is included in case of pathological nodes at the level of the iliaca communis or proximal
- Inguinal nodal regions are included in case of stage IIIA

The nodal volumes should follow the relevant vessels with a margin of 7-18 mm in the loose connective tissue (37).

9.3 Contouring of Organs at risk

For reporting dose in defined absolute tissue volumes it is necessary to report the dose for EBRT in the different OAR. It is assumed that the dose in the small volumes of interest for BT (anterior-lateral walls of rectum and sigmoid; posterior-inferior wall of the bladder; and wall of the vagina adjacent to macroscopic disease) will receive the EBRT dose prescribed dose for CTV-E. Therefore, no specific dose volume assessment is required for the different organs at risk apart from the confirmation that the EBRT dose received in the volumes of interest does not exceed the 45-50 Gy dose limit ($\pm 5\%$) for CTV-E (see section 9.4.1).

If a boost given by EBRT is contributing to a specific OAR volume adjacent to the target of interest for BT (HR-CTV and IR-CTV) the total dose including the EBRT boost dose received by this particular organ volume has to be reported and used for the EQD2 calculations in summation of EBRT and BT.

A different issue is the question of assessing EBRT related morbidity for instance by assessing DVH parameters based on hollow organs and organ wall contouring. This question is not included in the protocol. It is therefore the responsibility of the particular institution to evaluate their own EBRT with regard to this question, especially if for instance IMRT and/or simultaneous integrated boost techniques are used to obtain higher dose level than the standard EBRT dose of 45-50 Gy.

9.4 Dose and fractionation for 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 HR-CTV and the IR-CTV and the small volumes in the adjacent OAR. If this homogeneity is not achieved it will be difficult/impossible to evaluate the dose volume effects of BT on local control and on morbidity.

Biological equivalence calculations by use of the linear-quadratic formulation should be used whenever dose per fraction deviates from 2.0 Gy. For equivalence calculations (EQD2), it is assumed that the α/β is 10 Gy for tumour effects and 3 Gy for late normal tissue damage.

9.4.1 Dose prescription for EBRT

The following physical dose ranges should be applied for EBRT:

- PTV-E: 45-50 Gy
- PTV-P: 60-65 Gy
- PTV-N: 60-65 Gy

In case of additional EBRT boost dose adjacent to the HR-CTV and IR-CTV and to the volume of interest for BT associated morbidity, the EBRT contribution to these volumes should be stated, in practice by reporting a higher dose for GTV-T_D than for PTV-E

9.4.2 Fractionation of EBRT

The total number of fractions must be within the range 25-32. Dose per fraction is 1.5-2.0 Gy for PTV-E, 2.0-2.4 Gy for PTV-P and 2.0 to 2.2 for PTV-N.

Standard fractionation involves 1 fraction per day, 5 fractions per week, except on days with BT, where EBRT should be omitted. All beams and segments involved in a given part of the treatment must be treated at each fraction.

Hyperfractionation is not allowed. In order to compensate for unplanned treatment breaks, however, two daily EBRT fractions at least 6 hours apart can be used. To minimize the risk of consequential late damage the dose accumulation of EBRT must, however, not exceed 12 Gy per week.

Maximal overall treatment time including external beam radiotherapy, brachytherapy and concomitant chemotherapy is 50 days!

9.5 Technique for EBRT

- Iso-centric technique with more than two opposed fields
- No midline block is allowed
- 3D image-based conformal radiotherapy or IMRT.
- Individualized beam shaping according to target definitions by use of MLC or blocks.
- The volume encompassed by the D95 isodose curve of the dose prescribed to the elective target by EBRT (45-50 Gy) should not exceed 2.500 cm³ for pelvic radiotherapy and 3.500 cm³ if the para-aortic nodes are included.
- For boost volumes treated by EBRT (60-65 Gy) the volume encompassed by the D95 isodose curve of the boost dose should not be larger than 300 cm³
- 2D or 3D verification of patient position at least for the first fraction of EBRT

9.6 Reporting EBRT parameters

- For each PTV: D95 (conformal and IMRT).
- For each PTV treated with conformal RT: ICRU point dose
- Dose per fraction for each target and overall treatment time for each target
- Overall treatment time of whole EBRT
- Dose in small volumes of OAR adjacent to HR/IR CTV of BT, if different from dose to PTV-E. If the dose contribution from EBRT to the most exposed 2 cm³ of an organ is significantly different than the prescribed dose of the PTV-E ($\pm 5\%$), report the representative dose using detailed dose analysis using point dose evaluation or similar.

10. Brachytherapy

Treatment planning for BT is based on gynaecological examination performed at the time of BT applicator implantation and MRI taken with the BT applicator in place. Treatment planning for the first BT implant and the first BT fraction must always be based on MRI. Each subsequent BT applicator implant must also be subject to 3D imaging (CT as a minimum, preferably MRI) and 3D treatment planning. However, it is allowed to administer more than one BT fraction by use of the same implant (15).

10.1 Treatment preparations for BT

Bowel preparation should always 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.

Before placement of the BT applicator a clinical assessment of the tumour extension is performed describing tumour dimensions (width, height and thickness) as well as the possible involvement of parametria, vagina, bladder and rectum. The clinical examination is documented by drawings by use of standard cartoons (see appendix 1).

A Foley catheter is placed in the bladder and 7 ml of diluted contrast medium is injected into the balloon suitable for MRI and for X-rays (e.g. contrast medium for conventional radiography mixed with Gadolinium). Each participating department should define standard rules for bladder filling which should be followed both during MRI footage and the subsequent BT treatment.

Dilatation of the uterine canal can be guided by ultrasound and the depth of the uterine cavity is measured. An MRI compatible applicator is then chosen depending on the anatomical topography of tumour, uterus, cervix and vagina and placed in close contact with the tumour and cervix. The choice of the applicator type is up to the decision of each centre. Additional implantation of MR compatible needles in the parametrium can be used (14). Vaginal packing can then be performed with gauze filled with diluted gadolinium to push away the rectum and bladder and to fix the applicator against the cervix. Alternatively, an individual mould or other customized procedures may be used for fixation of the applicator according the practice of the participating institution. Rectal diodes can also be used according to institutional practice (35).

Orthogonal X-rays in the anterior-posterior and lateral projection with radio-opaque guide wires in the applicator can be used (optional) to ensure that the spatial 2D relation between applicator and

target and OAR is satisfying. Unless the ICRU points are inserted directly on the MRI study these radiographs can be used to determine the ICRU bladder and rectum points for reporting.

The patient is transferred to the MRI scanner to obtain appropriate images with the patient in the supine treatment position. With sufficient vaginal packing and/or fixation of the application by other means, there is according to available evidence so far no indication of movement of the applicator relative to the CTV or to adjacent OAR.

To ensure a reliable reconstruction of the applicator the slice thickness of MRI should be ≤ 5 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. Sequences taken parallel to the applicator, i.e. paratransversal, paracoronal and parasagittal (16) are superior to straight transversal, coronal and sagittal images with regard to both target contouring and applicator reconstruction.

10.2 Applicator reconstruction

Uncertainties of at least half the slice thickness can be present in applicator reconstruction. Deviations of dose $>10\%$ are common for applicator displacement of 3 mm (along intrauterine axis) for HR-CTV (D100, D90) and rectum, bladder and sigmoid (D_{2cc}). Great care should therefore be exercised when the applicator is reconstructed in the dose planning system. Each department must ensure that the applicator reconstruction can be performed with an uncertainty of ≤ 3 mm.

For CT reconstructions library plans or direct reconstruction based on CT markers may be the optimal solution. For MRI reconstructions special techniques have to be applied. Reconstruction based on radiographs or CT can be registered to the MRI dataset by using defined marker points or other registration techniques. Direct reconstruction can be applied in MRI when markers are inserted into the applicator channels. Currently, MR markers are not commercially available and have to be produced in the departments. Another practical solution is the use of predefined applicator geometries, which are matched to certain visible structures on or inside the applicator.

Actual source positioning and source movement in the BT applicator should be rigorously checked for instance by auto radiographs.

10.3 Contouring of GTV_B, HR-CTV, IR-CTV and organs at risk:

Contouring for both tumour and OAR is performed for each insertion/implant of BT applicators by contouring on T2 weighted (para)-transversal MRI sequences in a dedicated 3D brachytherapy dose-planning system according to the GEC ESTRO Recommendations (10;31). The MRI based target delineation can be reused by superimposition in the process of contouring on CT, if for subsequent fractions of brachytherapy only CT can be used with the applicator in place.

According to available evidence no safety margins are needed for internal movement (“tracking brachytherapy”) since the applicator moves with the CTV (15;19). Although there are some uncertainties for setup (applicator reconstruction), these seem to be rather negligible, if the systematic error can be kept below 2 mm and the slice thickness below 5 mm (random error) (36). In the present study it is therefore assumed that for BT no margins should be added to CTV, i.e. CTV = PTV.

The following tumor targets and dose points should be defined:

- GTV_B: Macroscopic tumour (if present) at time of brachytherapy
- High risk target (HR-CTV): Macroscopic tumour extension at time of brachytherapy (GTV_B) + whole cervix + presumed extra cervical tumour extension
- Intermediate risk target (IR CTV): HR CTV + macroscopic tumour extension at diagnosis (GTV_D) providing a minimal margin of 10 mm to residual disease at time of brachytherapy (GTV_B) in direction of potential spread. A reduced margin should be used towards an intact anatomical barrier
- Point-A left and right

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 (paragraph 10.6). The clinical evaluation of these concepts is one of the main 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 in the future.

For OAR's the following organs and dose points should be defined:

- Bladder: The outer bladder wall is contoured
- 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)
- The ICRU bladder point
- The ICRU rectal point

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 IR-CTV to 2 cm above the uterus. The reference points are defined according to ICRU 38 on the orthogonal X-rays or directly in the MRI study. In addition, the point of expected dose in a specific organ may be determined and used for in vivo dosimetry for instance if rectal diodes are used (optional).

To study uncertainties in fractionated BT a companion study (optional) is planned in which the organ contour of interest is compared on 3D images from insertion to insertion and classified according to geometric changes in topography by use of a scoring system:

No change	0
Minimal change	1-3
Moderate change	4-6
Major change	7-9
Complete change	10

In the same companion protocol it is suggested further to specify the position of the hot spots in the bladder (D_{0.1cc} and D_{2cc}) as these small volumes may have an impact on clinical outcome:

Upper posterior wall
 Medium posterior wall
 Low posterior wall
 Upper bladder neck
 Lower bladder neck

A part of this protocol will be designed for PDR brachytherapy where repetitive imaging on subsequent days during the BT treatment will be used.

10.4 Treatment prescription for BT

BT is prescribed according to the tradition of each individual participating institution. The recording and reporting process, however, has to be uniform (see paragraph 10.6). To avoid ambiguities, it seems to be practical, to prescribe - according to the institutional practice taking into account the clinical experience collected so far with traditional approaches (point A/reference volume) or with preliminary image guidance approaches - to the minimum dose in the target volume, which may be the HR-CTV or the IR-CTV.

There is no dose level recommended for this study, as there is little evidence which dose level is to be used in which clinical situation using 3D image based gynaecological brachytherapy. In contrast, every centre is encouraged to follow the specific institutional practice which reflects the clinical experience accumulated during a long time period and to translate this experience into image guided brachytherapy.

Centres in the tradition of point-A prescription (Vienna, Leuven, and Aarhus) have found some correlation between the dose to point A and the D90 obtained in the HR-CTV. However, there is a significant variation from patient to patient according to the pathoanatomical situation. By applying 3D image based treatment planning it is possible that this variation can be taken into account by individual volume and dose adaptation (6;21). So for centres previously using point-A, it is recommended to use the point-A dose as the dose (D90) used for prescription to the HR-CTV and to report dose both for HR-CTV and IR-CTV.

For centres in the tradition of 60 Gy reference volume (Paris), the experience is that the mean dose to this volume correlates well with the dose to the IR-CTV with a coverage > 95% (6). Again variations can most likely be more appropriately taken into account applying 3D image based treatment planning. It is recommended to these centres to prescribe to the IR-CTV and report dose both for IR-CTV and HR-CTV.

For the OAR's there is also no general prescription or recommendation for dose volume constraints within this study. Some correlation has been found between the mean dose of the ICRU rectum point and D_{2cc} of the rectum (6;9;17;21;27). This also implies that dose effect relationships found for dose point calculations for the rectum will likely translate into dose volume constraints for the rectum. For the sigmoid there has been no sigmoid point so far. Thus, there is no correlation between points and volume. However, preliminary data indicate that DVH values obtained by 3D brachytherapy planning are predictive of mucosal changes in both rectum and sigmoid (17). Thus, a DVH constraint for the sigmoid should also be obtainable. So far, no clear correlation between the ICRU bladder point and any small volume representing the minimum dose in the most exposed bladder tissue has been shown (6;9;21;27). However, it seems that the ICRU bladder point underestimates the minimum dose in the most exposed tissue of the bladder (3;27). It also has to be taken into account that in the literature, no clear dose effect relations have been reported so far for the ICRU bladder point.

Based on this situation each centre is encouraged to follow its traditional experience in dose constraints for points and to transpose this to DVH constraints as described in the GEC ESTRO

Recommendation II and establish an institutional practice of 3 D based gynaecologic brachytherapy (31). DVH constraints are therefore to be defined according to institutional practice. The reporting of dose volume parameters is to follow the GEC ESTRO Recommendations in a uniform way (see paragraph 10.6). As there has been little evidence so far on 3D based DVH constraints for organs at risk one of the primary aims of this study is to establish such constraints based on a heterogeneous data set and correlation to clinical outcome.

10.5 Dose optimization for BT

The balancing of target dose coverage and dose in defined volumes of OAR is pursued by optimization. The optimization procedure is performed using one of the following:

- Dose point optimisation
- Manual dwell time or dwell weight optimization
- Graphical optimization (“dose shaping”) combined with manual verification and adjustments for unnecessarily large deviations from standard loading patterns

The starting point is usually a standard plan, which has been in use for a long time for x-ray based BT in the institutional tradition (14;16). It is recommended to follow this tradition and to adapt dose and volume according to the specific individual needs of the clinical situation. It is not recommended to create a plan which is completely new, as this may imply uncertainties which may result in outcome, little predictable, the worst in significant adverse events (31).

Inverse planning tools are not recommended at present. It should only be used if individual centres perform reproducible and safe additional adaptations during or after the inverse optimization process. DVH constraints as having been suggested and used by now are not taking into account high dose volumes within the target and not dose distribution to all structures of adjacent normal tissue. This applies for all adjacent normal tissue where no recommendations for delineation have been developed so far (e.g. vagina, ureter, vessels, nerves or connective tissue in the pelvis). Therefore in order to avoid any significant adverse clinical events specific attention is needed to ensure that dose distributions (especially for high dose volumes) are within the range and place of clinical experience collected so far and which seems to be achievable by not allowing for too large differences from traditional approaches.

Integrated into this individual 3D image based treatment planning is a biological modelling process that accounts for the different doses per fraction (dose rates) applied in the target and the nearby OAR's which have to be taken into account. The aim is to express dose in a uniform way, which is to “normalize” it to conventional fractionation (2 Gy per fraction, EQD2) and to use this information for individual treatment planning. This process is facilitated by introducing a spreadsheet. Details of this treatment planning are given in the literature (16;20). It is well understood that this biological modelling approach has to be critically applied, as many uncertainties are introduced at the same time. Some basic radiobiological assumptions which are agreed upon are the following using the linear-quadratic model (10;31).

- $\alpha/\beta=10$ for tumor
- $\alpha/\beta=3$ for normal tissue
- Repair half time, $T_{1/2}=1.5$ hours
- The linear-quadratic model with correction for incomplete repair of PDR is used to derive at a biologically weighted dose

When balancing target coverage and dose volume constraints, it has to be underlined that according to current practice within the GYN GEC ESTRO network so far, the D90 is suggested as the major indicator of total dose for the target. There is some rationale for this mainly based upon a reduction of uncertainties (16;31). Clinical evidence is also emerging suggesting that D90 represents a major factor for predicting outcome (7;8). This implies that the prescribed dose (“minimum dose”) shows a high correlation to the D90 and less correlation to D100.

In order to provide some orientation within this new field of image guided brachytherapy, some information on dose volume parameters for target volumes are listed here: Within the clinical experience collected in the GYN GEC ESTRO network, the following doses were reported for the target volume:

- For the HR-CTV D90 doses of 75-96 Gy are reported depending on tradition, technique, tumour volume and response (Leuven, Aarhus, Vienna, Paris IGR).
- For the IR CTV D90 doses of 60-75 Gy are reported dependent on tradition, technique, tumour volume and response (Paris, IGR; Nancy, Aarhus, Vienna).

As pointed out above, there is little evidence so far from outcome data that a certain dose has to be prescribed to a certain target for a tumour with a certain response after radio-chemotherapy. There is no clear understanding on the amount of dose needed for a certain types of tumour and response: small; large-favourable response; large-unfavourable response. In addition, the impact of various tumour parameters (in terms of volume, spread and response) and differences in doses, dose rates, and doses per fraction that are applied are not clear. It is therefore emphasized again to follow the institutional practice for dose prescription and to translate this into an institutional practice of 3D image based brachytherapy and then to collect data comprehensively within the EMBRACE study in a uniform way of reporting.

The following dose volume constraints for OAR are applied at present within the GYN GEC ESTRO network based on institutional experience and clinical tradition derived from point assessment. However, there is very limited clinical data to support these values. Also the dose volume assessment is associated with many uncertainties from geometry, dosimetry and biology, which are not comprehensively understood. The following dose-volume constraints therefore have to be taken with much caution. If applied, they have to be checked and controlled continuously. The total dose values are based on the expected cumulative dose of EBRT and BT and are expressed in EQD2 using an α/β value of 3 and $T_{1/2}=1.5$ hours:

- Rectum $D_{2cc} < 70-75$ Gy
- Sigmoid colon $D_{2cc} < 75$ Gy
- Bladder $D_{2cc} < 90$ Gy

In order to assess geometric and dosimetric uncertainties more appropriately, it is recommended to check dose volume parameters as derived from DVH on 3D images showing the topography for rectum, bladder and sigmoid using the scoring system described in section 10.3.

10.6 Dose and volume recording and reporting

Uniform dose volume reporting according to the GEC ESTRO guidelines (10;31) is crucial for the aims of this study. For dose recording and reporting the GEC ESTRO recommendations therefore

have strictly to be followed. For each BT fraction the following basic parameters should be calculated and recorded in the dose planning system:

- TRAK
- Point-A dose, left, right and average
- D100 for GTV, HR-CTV and IR-CTV
- D90 for GTV, HR-CTV and IR-CTV
- D50 for HR-CTV
- V100 for the target used for dose prescribing (HR-CTV or IR-CTV)
- D_{0.1cc} and D_{2cc} of the bladder, rectum and sigmoid contour.
- ICRU bladder and ICRU rectal point

Additional DVH parameters may be included at a later stage (protocol amendment) according to the development in the field.

Departments using standard plan as basis for optimisation are encouraged also to report the central DVH parameters of the standard plan (D90 of HR-CTV and D_{2cc} for bladder, rectum and sigmoid) for each BT fraction (optional sub-study).

11. Concomitant chemotherapy

Chemotherapy is given according to the studies reported Key et al (12) and Rose et al (33). Cisplatin is to be given intravenously at a dose 40 mg/m² once a week for a total of 5-6 cycles according to institutional practice. No other schedules are allowed. Neoadjuvant or adjuvant chemotherapy is also not allowed.

Treatment with Cisplatin should be withheld if the total white-cell count falls below 2.5x10⁹ per litre or the platelet count drops below 50x10⁹ per litre. Cisplatin dose is recorded as zero. Cisplatin can be resumed in the next cycle once the blood counts exceed these limits. The dose of Cisplatin should be reduced to 30 mg/m² if two consecutive cycles of chemotherapy have been given at dose zero. Cisplatin dose should also be reduced to 30 mg/m² in case of febrile leucopenia. Cisplatin should be totally discontinued if blood tests remain unacceptable or febrile leucopenia recurs despite dose reduction. Cisplatin should also be abandoned in case significant auditory problems (tinnitus, deafness) or neuropathies \geq grade 2 develops.

Measurement or calculation (Cockroft-Gault) of GFR is performed before treatment and repeated after 3 cycles. 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.

12. Follow-up investigations

Follow-up will as a minimum be performed according to this table:

Follow-up, month:	0*	3	6	9	12	18	24	30	36	48	60
Clinical examination	●	●	●	●	●	●	●	●	●	●	●
Gynaecological exam.	●	●	●	●	●	●	●	●	●	●	●
MRI pelvis	●	●			●						
CT abdomen & retroperitoneum [‡]	●										
Chest X-ray [§]	●										
Assessment of morbidity (CTC) [#]	●	●	●	●	●	●	●	●	●	●	●
Assessment of QoL (optional)	●	●	●		●		●		●	●	●

*Pre-treatment work-up,

[‡]May be replaced by PET-CT or MRI

[§]CT or PET-CT is allowed as alternative

[#]Appendix 2

The results of follow-up (both on-schedule and off-schedule) must be reported to the database within 4 weeks. In case of suspected recurrence a complete patient work-up must always be performed at least including gynaecological examination (in GA, with biopsy if possible/relevant), MRI of pelvis, CT thorax, abdomen and US guided fine needle aspiration of suspected nodes Full morbidity assessment should always be performed if major morbidity is encountered and the patient is seen off-schedule.

13. Patient material, evaluation and statistics

In November 2007 information about the EMBRACE protocol and a study invitation was sent out to potential candidate centres. Based on the response from the invitation 20 centres have indicated at this stage to participate in the EMBRACE already in 2008 and additional 12 intend to join in 2009.

13.1 Estimate of patient accrual and study period

For each participating centre a statement was obtained on the average number of patients treated per year. In addition the centres have indicated the number of patients they expect to be able to include in the EMBRACE study.

The average number of patients treated in the committed centres is 20 per year and the expected number to be accrued for EMBRACE is 10 per year. Based on these data it is assumed that an overall accrual rate of 200-300 patients per year is realistic. For a study period of 3 years this would come to a conservative overall estimated number of at least 600 patients.

The vast majority of local recurrences is observed within 2-3 years after treatment (>90%). The majority of late effects for rectum and sigmoid is also observed within 3 years, whereas for bladder it is estimated that about one third of the expected long term late effects (10 years) occur within 3 years.

Based on these premises, it seems to be reasonable to plan for an accrual period of three years and a follow-up period of three years for assessing the different endpoints of this study.

13.2 Estimate of stage distribution, dose prescription pattern and size of risk groups

The expected stage distribution and dose prescription pattern are derived from data collected in the November 2007 questionnaire.

The estimated distribution of stages is as follows: 1B1 (4%), 1B2 (12%), IIA (7%), IIB (37%), IIIA (4%), IIIB (32%), and IVA (4%). For an overall number assumed to be 600, this would result in the following distribution:

- stage IB1 and IIB (<4cm) n=90 (15%),
- stage IB2 and IIB (>4 cm) n=252 (42%),
- stage IIIB, IIIA and IVA n=258.(43%)

As stated in section 5, the patients will be analyzed in 3 risk groups according to the response to initial treatment with EBRT ± concomitant chemotherapy. Based on the current clinical experience it can be assumed that the following distribution into the 3 risk groups will be observed.

- Group 1: Small tumours: ~ 15% (n=90)
- Group 2: Large tumours with favourable response ~ 50% (n=300)
- Group 3: Large tumours with unfavourable response ~ 35% (n=210)

In this distribution it is assumed that a limited number of stage IIB patients (> 4cm) will have to be categorized into group 3 according to pattern of spread (distal) and pattern of response, unfavourable residual disease. On the other hand a certain number of patients with stage III and IVA disease may switch into the favourable response group.

According to the answers obtained by the questionnaire we expect to have about half of the centres to prescribe a dose of EBRT and BT less than 80 Gy (EQD2) to the HR-CTV and about half of the centres to prescribe 80 Gy (EQD2) or more to the HR-CTV.

13.3 Evaluation and statistics according to the aims and endpoints of the study

Aim 1: Defining risk groups in relation to local recurrence

Based on the current clinical experience it is expected that it will be possible to define 3 groups representing different risks of local recurrence: small tumours, large tumours with favourable response and large tumours with unfavourable response to initial radio-(chemo) therapy.

A systematic clinical evaluation and evaluation by MRI both at diagnosis and at time of BT will be performed. Both the traditional FIGO staging system as well as new parameters describing growth pattern and pattern of response will be employed with regard to the following parameters:

- Tumour dimensions
- Tumour volume
- Growth pattern
- Spread of disease
- Pattern of response

Based on the findings at diagnosis an initial stratification will be defined either by MRI or by clinical examination (FIGO)

Stratification at diagnosis based on MRI findings:

- Small tumours < 4 cm
- Large tumours with at most proximal parametrial infiltration/at most proximal vaginal infiltration/at most proximal uterine corpus infiltration
- Large tumours with at least mid-parametrial infiltration, at least mid-vaginal infiltration, at least beyond proximal uterine infiltration

Stratification at diagnosis based on clinical findings (FIGO):

- Stage \leq IB1, IIA and \leq IIB (<4 cm)
- IB2, IIB (\geq 4cm)
- IIIA, IIIB, IVA

After radio (chemo) therapy large tumours can be further divided into tumours with favourable and unfavourable response primarily by quantification of tumour volume regression.

Additional parameters recorded both at diagnosis and again at BT such as patterns of spread (intact cervix, infiltration of proximal parametrium, distal parametrium, pelvic wall [all uni- vs. bilateral], hydronephrosis, proximal vagina, distal vagina [lower third], partial and total uterine corpus, bladder and rectum) growth pattern (exophytic and infiltrative growth) will be used in an explorative analysis to optimize the stratification.

The ability of different combinations of parameters to stratify the whole patient population as well as conformity between different combinations of parameters will be evaluated by descriptive statistics. The clinical relevance of the constructed risk groups will then be tested by correlation with the risk of local recurrence. In addition other prognostic factors such as lymph node status, haemoglobin, and histology will be evaluated. For all evaluations both uni- and multivariate analysis will be applied.

The assumption is that it will be possible to identify independent prognostic factors that will enable the construction of a simple yet comprehensive stratification system that will divide the patient population in 3 groups characterized by definite steps of increasing risk of local recurrence (assumed risk of local recurrence in percent):

- Small tumours with low risk of local recurrence (10%)
- Large tumours with favourable response (20%)
- Large tumours with unfavourable response to initial radio-(chemo) therapy (30%)

Aim 2: To define volumes of GTV and CTV and dose volume parameters for GTV, CTV and OAR according to GEC ESTRO recommendations:

To collect and compare volumetric data on GTV and CTV at diagnosis and during treatment and 3 months after treatment (including also cervix/uterus) and dose volume parameters within the three different strata of the overall patient cohort and for the different OAR (Rectum, Sigmoid, bladder).

Aim 3: Improvement in target coverage and in fulfilling dose volume constraints for OAR

A quantification of the changes in DVH parameters obtained by image guided dose optimization of BT per patient in the different strata will be performed by comparing the DVH parameters of standard versus 3D optimized BT dose plans.

According to published evidence standard treatment plans with available applicators may provide a sufficient target coverage in a certain number of these cases (D90 corresponds to the prescribed dose). The precise number is unknown. On the other hand it is assumed that in a certain number of patients at the same time the dose volume constraints for organs at risk can not be fulfilled based on standard plans.

The aim is to provide precise data on the amount of patients where one of these criteria (D90 of HR CTV, dose volume constraints for 2cc of OAR) cannot be fulfilled based on standard plans. This will then be compared to the amount of patients where all criteria are fulfilled based on 3D image based brachytherapy.

Aim 4: Quality assessment

To evaluate the indicators for quality assessment throughout the whole study period and to define systematic and random variations for the different indicators (e.g. contouring, applicator reconstruction, dose volume assessment)

Aim 5: Prospective assessment of outcome of disease, morbidity and QoL

Outcome will be assessed with regard to disease (local control, survival), morbidity (CTCAE v3.0) and QoL (EORTC C30 and QLQ-CX24) by applying appropriate clinical, imaging and QoL protocols and standard actuarial statistics. In addition a possible correlation between QoL and morbidity will be evaluated (optional)

Aim 6: Dose volume effects for OAR

To correlate outcome data and dose volume parameters for the different OAR (0.1 and 2 cc) and to establish hazard ratios and dose effect curves for certain volumes for the different OAR. For the OAR the dose volume effect relationship between tissue damage and dose is defined (small) volumes in organs at risk adjacent to the HR CTV (rectum, sigmoid, bladder) will be analyzed (0.1, 2 cc).

At present there is only few fixed dose volume constraints agreed upon based on clinical evidence (for the rectum there seems to be some evidence). However, it can be expected that the variation found in the study will be rather limited, as there is some understanding, that e.g. for sigmoid the same dose volume constraint should be applied as for the rectum. For bladder it is assumed that the total dose in 2 cc should be kept below 90 Gy (EQD2).

For early reactions the main statistical analysis will be ordinal logistic regression (ref. Bentzen 2001). Dosimetric descriptors as well as patient and treatment-related covariates will be tested. In case of late side-effects, the main statistical analysis will be a time-to-event analysis, correcting for censored observations, using the Cox Proportional Hazards Model.

Further refinement of the dose-response curves will be explored by correlating the specific topographical location of the most exposed part of the OAR at different fractions of BT.

For rectal morbidity the whole cohort of 600 patients will be available for analysis. If we expect differences in the range of 15% versus 8% G3+ morbidity between dosimetrically favourable versus unfavourable patients (dividing the patients according to the median of 75 Gy), we will be able to detect this difference at the 5% significance level with a power of 90%.

For all other organs at risk we also have the whole cohort of 600 patients for analysis. However, there are no valid data for sigmoid and bladder yet to be able to give any estimate and no clear dose effect relations at present.

Aim 7: Dose volume effects for tumours according to risk group stratification (Variation of D90 for CTV and local control)

To correlate local control (survival) and dose volume parameters for GTV and CTVs for the overall cohort and for the 3 different risk groups and to establish hazard ratios and dose effect curves for certain tumour volumes.

The improvement in target coverage and the fulfilment of dose volume constraints for OAR is expected to result in a therapeutic benefit: on the one hand local control is likely to be improved, on the other hand radiotherapy associated morbidity is likely to be stable or may be even reduced.

As there is no homogeneous dose prescription for brachytherapy foreseen in this study according to lacking clinical evidence for a volume based dose response at present, it is expected that the dose range applied and evaluated as D90 for the different strata will vary between 70 and 95 Gy (EQD2).

At present there is limited evidence from published prospective multi-centre clinical trials on the importance of dose with regard to local control even in the different subsets of patients (strata). The aim is therefore to collect prospectively precise data on dose volume parameters achieved in the individual patients according to institutional practice as well as on local control and on radiation associated morbidity and to correlate these findings.

This will enable us to find or not to find dose effects for the HR CTV and/or for the IR CTV in the overall group comparing the different doses (D90) applied by the different centres.

Given that we are able to identify risk groups as pointed out above (2 or 3 strata) we will in a second step test if each risk group has its specific dose volume effect relationship between local failure and dose to defined volumes of GTV and HR and IR CTV.

We compare the numbers per group with the local recurrence rate to be expected in each subgroup according to dose prescription and to D90, respectively, given to the HR/IR CTV.

This is based on published reports from radiotherapy series (overview in Gerbaulet et al. 2002), from radiochemotherapy series (Morris, Keys, Green) and first results from 3D image-based gyn brachytherapy (Pötter et al. 2007).

If we take the number of patients treated per year and being accrued in the study, we assume the following numbers:

	Overall numbers	D 90 < 80 Gy		D 90 > 80 Gy	
Small	90	45	10%	45	5%

Large favourable resp	300	150	20%	150	10%
Large unfavourable resp	210	105	30%	105	15%
Total	600	300		300	

This analysis will be performed by a classical logit analysis as well as comprehensive statistical models as the Cox proportional hazards model that also take differences in observation time and adjustment for various covariates into account.

1: small tumours: 2-4 cm in width (about 5-25 ccm): stage IB1, IIA, IIB (< 4 cm)

As the overall patient number expected is only 90 and as there are at most 45 patients expected in each dose group and as the expected local control rate will be from 90% to 95+% no statistically meaningful statement will likely be possible.

However, this data collection can serve as a confirmation of the overall local control rate which is expected to be at least 90-95% according to preliminary experience with 3D image-based brachytherapy applying a significant dose and may then serve as a bench mark. At the same time the corresponding dosimetric and clinical data on organs at risk will define the therapeutic ratio and will also serve as a benchmark. This benchmark will be compared to historical series.

From institutional clinical series the local failure rate seems to be around 10% when applying doses around 80 Gy (overview Gerbault et al. 2002). In a randomized trial this was 20% when applying mean doses of 76 Gy at point A (Landoni et al. 1997)

Based on these findings a hypothesis may be generated during this study on dose volume effect relationships in small tumours. A prospective clinical trial may be subsequently initiated to investigate for 3D image based brachytherapy, if a dose escalation for limited volume tumours (e.g. with a D 90 of 75 versus 85 versus 95 Gy) will result in improved local control. Prospective assessment of dose volume parameters with validated dose volume constraints would be in parallel correlated to radiation associated morbidity.

2: large (>25 ccm) - favourable response

We expect a patient number of 300 patients with 150 patients in each dose group

For an expected difference in local failure from 20% to 10% this group is expected to become large enough for a statistical meaningful comparison. To illustrate the statistical power of the study, a two-group comparison of high-versus-low dose patients would have 80% power to detect the above difference at the 5% significance level. The plan is to use a multivariate model adjusting for clinical co-variables in testing the dose-response relationship (see above).

3. large (>25 ccm) -unfavourable response

We expect a patient number of 210 patients with 105 patients in each dose group

For an expected gain in local failure from 30% to 15% this group is large enough for a statistical meaningful comparison. In this case, a two-group comparison of high-versus-low dose patients would have 90% power to detect the above difference at the 5% significance level. Again, the plan is to use a multivariate model adjusting for clinical co-variables in testing the dose-response relationship (see above).

Aim 8: To validate from clinical outcome data the radiobiological equivalence calculations used for assessing dose and volume parameters in gynaecological radiotherapy: for tumour and for OARs.

A specific issue is to test the assumptions included in the applied biological model (alpha-beta values, half time of repair) from the background of homogeneous groups of patients showing a certain degree of tissue damage and tumour effects.

Aim 9: Relevance of Gyn GEC ESTRO Recommendations

The criteria for testing the relevance of the Gyn GEC ESTRO recommendations for assessing dose and volume for gynaecological BT in a multi-centre setting will be that we are successful in establishing dose effect curves for both tumour and OAR applying the proposed parameters: D 90 for the HR and IR CTV and 0.1 and 2 ccm for OAR. If this is not possible other more appropriate parameters will be looked for and tested.

14. Accreditation and Quality assurance for EMBRACE

Each institution/investigator has to submit a Commitment Letter to the study coordinators. The centres are also required to complete a Compliance Form that documents procedures for imaging, treatment planning, delivery and verification demonstrating that the centre in question will be able to meet the requirements of the protocol. This will ensure that the radiotherapy procedures of different centres are consistent, and that the reported DVH parameters are reliable. Principles of contouring and treatment planning will be reviewed in a Dummy Run.

All centres are required to provide a positive independent evaluation of brachytherapy dosimetry (e.g. EQUAL ESTRO dosimetry test, IAEA or similar) within the first year of participation. Instructions for dummy run are provided in (appendix 3).

It is the responsibility of the study coordinators to evaluate and approve participation. Approval requires a successful dummy run with an individual assessment of the performance of each participating centre. There is no formal on site monitoring, but patient files and treatment plans must be kept at least until closure of the protocol and final analysis of the results is obtained. Continuous quality assurance during the study is needed and projected. The procedure will include a check of the treatment planning process focussing on the parameters of interest for this study and a check of the CRFs. However, due to the complexity of this issue in particular in regard to image guided brachytherapy, there is no clear plan provided for continuous quality assurance at this moment.

Approval of the institution/investigator must be accomplished prior to any patient enrolment in the protocol.

15. Patient registration procedure

Patient's registration will only be accepted from authorized investigators. A patient can be registered after verification of eligibility by the EMBRACE database.

Patients must be registered and accepted before any treatment procedures are initiated.

A list of questions to be answered during the registration procedure is included in the registration checklist, which is part of the case report forms (appendix 4).

- Patient's initials
- Patient's birthday
- Date of scheduled treatment start

Eligibility criteria will be checked by the EMBRACE database and if the patient is accepted a number will be allocated to the patient (patient sequential identification number). This number has to be recorded by the investigator and identifies the patient in all future communication between the investigator and the EMBRACE database or the study coordinators. After successful registration the investigator should make a print out of the registered data to keep in the department (investigators patient study file, see section 16). A copy of this printout should be faxed or mailed to the study secretariat (see section 19).

16. Case record forms and procedures for data collection

Patient data will be collected by web based CRF system (see section 20). The CRFs must be completed and reported according to the time table below.

It is the responsibility of the investigator to check that all CRFs are completely, correctly and timely filled out.

The following CRFs will be used:

- Registration form: **To be reported before treatment.**
- Status at diagnosis Form: To be reported at start of treatment
- Base Line Morbidity Form: To be reported at start of treatment
- Status at BT Form: To be reported within 4 weeks after treatment completion
- Treatment and DVH Form: To be reported within 4 weeks after treatment completion.
- Follow-up form: To be completed within 4 weeks after each regular follow-up. Visits not scheduled should also be reported within 4 weeks if they concern an event of interest such as recurrence or morbidity
- Off study Form: Should be reported within 4 weeks after the off-study event. Patients who go off-study for other reasons than death (i.e. recurrence) should be followed for survival as best as possible and additional information on vital status reported.

The database will automatically send out an e-mail if a CRF report is missing according to the treatment and follow-up schedule. Each time a CRF has been completed, a printout should be kept in the investigators own patient study file and copy should be faxed or mailed to the study secretariat (see section 19). The patient study file is simply a patient specific port folio including a paper copy of the registered CRF data for each patient.

17. Ethical considerations

17.1 Patient protection

The investigators will ensure that this study is conducted in agreement with either the Declaration of Helsinki (Tokyo, Venice, Hong Kong, Somerset West and Edinburgh amendments) or the laws and regulations of the country, whichever provides the greatest protection of the patient. The protocol has been written, and the study will be conducted according to the ICH Harmonized Tripartite Guideline for Good Clinical Practice. The protocol will be approved by the local Research Ethics Committee in accordance with national guidelines and legislation in the participating centres.

17.2. Subject identification

The name of the patient will not be asked for nor recorded at the Study Office. A sequential identification number will be automatically attributed to each patient registered in the trial. This number will identify the patient and must be included on all case report forms. In order to avoid identification errors, patient's initials (maximum of 4 letters), date of birth and local chart number (if available) will also be reported on the case report forms.

17.3. Informed consent

Patient information sheets will be produced in all the relevant languages. All patients will be informed of the aims of the study, the possible adverse events, the procedures and possible hazards to which he/she will be exposed.

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

It will be emphasized that the participation is voluntary and that the patient is allowed to refuse further participation in the protocol whenever he/she wants. This will not prejudice the patient's subsequent care. Documented informed consent must be obtained for all patients included in the study before they are registered at the Study Office. This must be done in accordance with the national and local regulatory requirements.

For European Union member states, the informed consent procedure must conform to the ICH guidelines on Good Clinical Practice. This implies that "the written informed consent form should be signed and personally dated by the patient or by the patient's legally acceptable representative".

17.4. Advantages and disadvantage for the patients

At present the standard treatment for patients with locally advanced cervical cancer is EBRT, concurrent chemotherapy with Cisplatin and intracavitary BT. These treatments will also be used in the present protocol. Participation in the protocol will ensure the patient external review and quality assurance of the treatment planning and execution, which is expected to enhance the therapeutic ratio for the individual patient with a reduction of the risk for both local failure and development of severe morbidity.

The patients will be fully informed about the background for the study and that the standard treatment in most departments not participating in the protocol today is relying on two-dimensional treatment planning of BT. The new aspect of prescribing dose of BT to volumes rather than points

will be explained and the patients will be told that recent international guidelines recommend this practice. The patients will also be informed that these new recommendations have been based on single institutional experience and that they have not been applied in a broader context so far. The patients will be informed about the possible risks and side effects connected to the involved treatments. If they do not wish to participate, this will not prevent them from obtaining the standard treatment. On this background it seems reasonable to conduct the investigations. The potential benefits will likely be greater than the potential drawbacks.

Should patients decide not to participate in the protocol they will as a rule be offered standard treatment according to institutional guidelines.

18. Publication of data

All papers and abstracts will be co-authored by the investigators of the protocol according to the Vancouver rules. Centres contributing at least 15 patients to the EMBRACE study will qualify for one co-author ship. A second co-author ship may be given to the centres with the largest number of accrued patients.

The study coordinators and the study statistician will prepare the primary articles concerning the overall clinical subject of the project. Any investigator in the protocol group responsible for a specific aim can prepare companion papers based on the specific aim; these papers should be in accordance with the papers on the overall clinical subject of the project, as feasible. Presentations at national or international meetings may be given by any of the protocol investigators, but will require the approval from the group of investigators prior to submission in all cases. In case of disagreement simple majority by vote will decide the matter.

19. Study-secretariat, study-coordinators and statistician

Study-secretariat (at present: 12/2007):

Johannes Dimopoulos, MD

Department of Radiotherapy, Medical University of Vienna, Vienna, Austria

Telephone: +43 1 40 400 2720

E-mail: Johannes.Dimopoulos@akhwien.at

Anna Stepien, MA

Department of Radiotherapy, Medical University of Vienna, Vienna, Austria

Telephone: +43 1 40 400 2692

FAX: +43 1 40 400 2693

E-mail: Anna.Stepien@akhwien.at

Study Coordinators:

Principal Coordinator:

Richard Pötter, Vienna, Austria: Richard.Poetter@akhwien.at

Coordinators:

Jacob Lindegaard, Aarhus, Denmark: jlind@as.aaa.dk (overall)

Christian Kirisits, Vienna, Austria: Christian.Kirisits@akhwien.at (Physics)

Kari Tanderup, Aarhus, Denmark: ktanderup@as.aaa.dk (Physics)

Senior advisors:

Christine Haie-Meder (haie@igr.fr), Erik Van Limbergen (erik.vanlimbergen@uz.kuleuven.ac.be)

The coordinators, the senior advisors and the study secretariat communicate regularly (at least twice per year) on relevant questions of the EMBRACE study and take joint decisions.

Study committee: one member of each participating centre, all coordinators, senior advisors, statistician, study secretariat

Statistician:

Søren Møller Bentzen, Madison, USA: bentzen@humonc.wisc.edu

20. The EMBRACE database and website

At the Embrace website the protocol, appendices, patient information folders and any other pertinent information in relation to the study will be made available.

The Embrace database is currently being established, and will be placed at Aarhus University Hospital, Denmark. The Danish Board of Registry has approved the database (pending). Access to the database can be gained through the Embrace website, by providing a valid username and password. Entering of all data will be carried out over the Internet using a standard web-browser.

All data will be encrypted before transmission. A number of validation procedures will be installed in order to ensure a high data quality. There will be sent out reminders of all follow-up visits and examinations, and data from these will also be entered via the Internet.

Each centre will be able to log on to the database via the Embrace website at any time in order to see descriptive data and number of included patients for own centre as well as for the entire study population. The database will ensure that data is available for statistical analysis immediately after termination of the study.

21. List of appendices

- 1) Cartoons for drawing of clinical findings from gynaecological examination.
- 2) CTCAE v 3.0.
- 3) Instructions for dummy-run
- 4) GYN GEC-ESTRO Guidelines I+II plus appendix

22. References

- (1) Adli M, Mayr NA, Kaiser HS, Skwarchuk MW, Meeks SL, Mardirossian G et al. Does prone positioning reduce small bowel dose in pelvic radiation with intensity-modulated radiotherapy for gynecologic cancer? *Int J Radiat Oncol Biol Phys* 2003; 57(1):230-238.
- (2) Al Booz H, Boiangiu I, Appleby H, French C, Coomber H, Humphery P et al. Sigmoid colon is an unexpected organ at risk in brachytherapy for cervix cancer. *J Egypt Natl Canc Inst* 2006; 18(2):156-160.
- (3) Barillot I, Horiot JC, Maingon P, Bone-Lepinoy MC, Vaillant D, Feutray S. Maximum and mean bladder dose defined from ultrasonography. Comparison with the ICRU reference in gynaecological brachytherapy. *Radiother Oncol* 1994; 30(3):231-238.
- (4) Brooks S, Bownes P, Lowe G, Bryant L, Hoskin PJ. Cervical brachytherapy utilizing ring applicator: comparison of standard and conformal loading. *Int J Radiat Oncol Biol Phys* 2005; 63(3):934-939.
- (5) Chun M, Kang H, Kim J, Ryu H, Shin H. Comparison of the kidney dose between supine and prone position for pelvic and periaortic irradiation. *Radiother Oncol* 1996; 41(3):273-275.
- (6) De Brabandere M, Mousa AG, Nulens A, Swinnen A, van Limbergen E. Potential of dose optimisation in MRI-based PDR brachytherapy of cervix carcinoma. *Radiother Oncol* 2007.
- (7) Dimopoulos J, Georg P, Kirisits C, Lang S, Berger D, Pötter R. The predictive value of dose volume parameters on local tumor control in MRI assisted brachytherapy of cervix cancer. *Radiother.Oncol* 81[S1], S39. 2006.
- (8) Dimopoulos JC, Kirisits C, Petric P, Georg P, Lang S, Berger D et al. The Vienna applicator for combined intracavitary and interstitial brachytherapy of cervical cancer: clinical feasibility and preliminary results. *Int J Radiat Oncol Biol Phys* 2006; 66(1):83-90.
- (9) Georg P, Dimopoulos J, Kirisits C, Lang S, Berger D, Pötter R. Dose volume parameters in cervical cancer patients treated with MRI based brachytherapy and their predictive value for late adverse side effects in rectum, sigmoid and bladder. *Radiotherapy and Oncology* 81[S1], S38-S39. 2006.
- (10) Haie-Meder C, Potter R, van Limbergen E, Briot E, De Brabandere M, Dimopoulos J et al. Recommendations from Gynaecological (GYN) GEC-ESTRO Working Group() (I): concepts and terms in 3D image based 3D treatment planning in cervix cancer brachytherapy with emphasis on MRI assessment of GTV and CTV. *Radiother Oncol* 2005; 74(3):235-245.
- (11) Kaatee RS, Oloffsen MJ, Verstraate MB, Quint S, Heijmen BS. Detection of organ movement in cervix cancer patients using a fluoroscopic electronic portal imaging device and radiopaque markers. *Int J Radiat Oncol Biol Phys* 2007; 54(2):576-583.

- (12) Keys HM, Bundy BN, Stehman FR, Muderspach LI, Chafe WE, Suggs CL et al. Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage Ib cervical carcinoma. *New Engl J Med* 1999; 340:1154-1161.
- (13) Kirisits C, Dimopoulos J, Lang S, Oechs K, Georg D, Pötter R. Do we need individual MRI based treatment planning for each insertion of cervix cancer brachytherapy? Findings based on 11 patients with 44 individual fractions. *Radiother Oncol* 2005; 75(Supplement 1):S9.
- (14) Kirisits C, Lang S, Dimopoulos J, Berger D, Georg D, Potter R. The Vienna applicator for combined intracavitary and interstitial brachytherapy of cervical cancer: design, application, treatment planning, and dosimetric results. *Int J Radiat Oncol Biol Phys* 2006; 65(2):624-630.
- (15) Kirisits C, Lang S, Dimopoulos J, Oechs K, Georg D, Pötter R. Uncertainties when using only one MRI-based treatment plan for subsequent high-dose-rate tandem and ring applications in brachytherapy of cervix cancer. *Radiother Oncol* 2006; 81(3):269-275.
- (16) Kirisits C, Potter R, Lang S, Dimopoulos J, Wachter-Gerstner N, Georg D. Dose and volume parameters for MRI-based treatment planning in intracavitary brachytherapy for cervical cancer. *Int J Radiat Oncol Biol Phys* 2005; 62(3):901-911.
- (17) Koom WS, Sohn DK, Kim JY, Kim JW, Shin KH, Yoon SM et al. Computed tomography-based high-dose-rate intracavitary brachytherapy for uterine cervical cancer: preliminary demonstration of correlation between dose-volume parameters and rectal mucosal changes observed by flexible sigmoidoscopy. *Int J Radiat Oncol Biol Phys* 2007; 68(5):1446-1454.
- (18) Krempien RC, Daeuber S, Hensley FW, Wannemacher M, Harms W. Image fusion of CT and MRI data enables improved target volume definition in 3D-brachytherapy treatment planning. *Brachytherapy* 2003; 2(3):164-171.
- (19) Lang S, Georg P, Kirisits C, Kuzucan A, Georg D, Pötter R. Uncertainty analysis for 3D image based cervix cancer brachytherapy by repeated MRI examinations: DVH-variations between two HDR fractions within one applicator insertion. *Radiotherapy and Oncology* 81[S1], 79. 2006.
- (20) Lang S, Kirisits C, Dimopoulos J, Georg D, Potter R. Treatment planning for MRI assisted brachytherapy of gynecologic malignancies based on total dose constraints. *Int J Radiat Oncol Biol Phys* 2007; 69(2):619-627.
- (21) Lindegaard JC, Tanderup K, Nielsen SK, Haack S, Gelineck J. MRI-guided 3D optimization significantly improves DVH parameters of pulsed dose rate brachytherapy in locally advanced cervical cancer. *Int J Radiat Oncol Biol Phys* 2007; in press.
- (22) Martin J, Fitzpatrick K, Horan G, McCloy R, Buckney S, O'Neill L et al. Treatment with a belly-board device significantly reduces the volume of small bowel irradiated and results in low acute toxicity in adjuvant radiotherapy for gynecologic cancer: results of a prospective study. *Radiother Oncol* 2005; 74(3):267-274.

- (23) Martinez-Monge R, Fernandes PS, Gupta N, Gahbauer R. Cross-sectional nodal atlas: a tool for the definition of clinical target volumes in three-dimensional radiation therapy planning. *Radiol* 1999; 211:815-828.
- (24) Muschitz S, Petrow P, Briot E, Petit C, De Crevoisier R, Duvillard P et al. Correlation between the treated volume, the GTV and the CTV at the time of brachytherapy and the histopathologic findings in 33 patients with operable cervix carcinoma. *Radiother Oncol* 2004; 73(2):187-194.
- (25) Nag S. Controversies and new developments in gynecologic brachytherapy: image-based intracavitary brachytherapy for cervical carcinoma. *Semin Radiat Oncol* 2006; 16(3):164-167.
- (26) Nag S, Cardenes H, Chang S, Das IJ, Erickson B, Ibbott GS et al. Proposed guidelines for image-based intracavitary brachytherapy for cervical carcinoma: report from Image-Guided Brachytherapy Working Group. *Int J Radiat Oncol Biol Phys* 2004; 60(4):1160-1172.
- (27) Pelloski CE, Palmer M, Chronowski GM, Jhingran A, Horton J, Eifel PJ. Comparison between CT-based volumetric calculations and ICRU reference-point estimates of radiation doses delivered to bladder and rectum during intracavitary radiotherapy for cervical cancer. *Int J Radiat Oncol Biol Phys* 2005; 62(1):131-137.
- (28) Pinkawa M, Gagel B, Demirel C, Schmachtenberg A, Asadpour B, Eble MJ. Dose-volume histogram evaluation of prone and supine patient position in external beam radiotherapy for cervical and endometrial cancer. *Radiother Oncol* 2003; 69(1):99-105.
- (29) Pötter R, Dimopoulos J, Georg P, Lang S, Waldhausl C, Wachter-Gerstner N et al. Clinical impact of MRI assisted dose volume adaptation and dose escalation in brachytherapy of locally advanced cervix cancer. *Radiother Oncol* 2007; 83(2):148-155.
- (30) Pötter R, Dimopoulos J, Georg P, Waldhäusl C, Lang S, Wachter-Gerstner N et al. MRI assisted 3D treatment planning in intracavitary and interstitial cervix cancer HDR brachytherapy and its impact on local tumour control: Vienna experience in 145 patients treated 1998-2003. *Radiotherapy and Oncology* 75[Supplement 1], S11. 2005.
- (31) Pötter R, Haie-Meder C, Limbergen EV, Barillot I, Brabandere MD, Dimopoulos J et al. Recommendations from gynaecological (GYN) GEC ESTRO working group (II): Concepts and terms in 3D image-based treatment planning in cervix cancer brachytherapy-3D dose volume parameters and aspects of 3D image-based anatomy, radiation physics, radiobiology. *Radiother Oncol* 2006; 78(1):67-77.
- (32) Pötter R, van Limbergen E, Gerstner N, Wambersie A. Survey of the use of the ICRU 38 in recording and reporting cervical cancer brachytherapy. *Radiother Oncol* 2001; 58(1):11-18.
- (33) Rose PG, Bundy BN, Watkins EB, Thigpen JT, Deppe G, Maiman MA et al. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. *New Engl J Med* 1999; 340:1144-1153.

- (34) Steggerda MJ, Moonen LM, Damen EM, Lebesque JV. An analysis of the effect of ovoid shields in a selectron-LDR cervical applicator on dose distributions in rectum and bladder. *Int J Radiat Oncol Biol Phys* 1997; 39(1):237-245.
- (35) Tanderup K, Christensen JJ, Granfeldt J, Lindegaard JC. Geometric stability of intracavitary pulsed dose rate brachytherapy monitored by in vivo rectal dosimetry. *Radiother Oncol* 2006; 79(1):87-93.
- (36) Tanderup K, Kirisits C, Lang S, Hellebust TP, Pötter R, Lindegaard JC. Uncertainties of DVH parameters associated with systematic and random errors of applicator reconstruction in 3D image base gynaecological brachytherapy. *Radiother.Oncol* 83 S1, 10-11. 2007.
- (37) Taylor A, Rockall AG, Reznik RH, Powell ME. Mapping pelvic lymph nodes: guidelines for delineation in intensity-modulated radiotherapy. *Int J Radiat Oncol Biol Phys* 2005; 63(5):1604-1612.
- (38) Viswanathan AN, Dimopoulos J, Kirisits C, Berger D, Potter R. Computed Tomography Versus Magnetic Resonance Imaging-Based Contouring in Cervical Cancer Brachytherapy: Results of a Prospective Trial and Preliminary Guidelines for Standardized Contours. *Int J Radiat Oncol Biol Phys* 2007; 68(2):491-498.
- (39) Wachter-Gerstner N, Wachter S, Reinstadler E, Fellner C, Knocke TH, Potter R. The impact of sectional imaging on dose escalation in endocavitary HDR-brachytherapy of cervical cancer: results of a prospective comparative trial. *Radiother Oncol* 2003; 68:51-59.
- (40) Weiss E, Eberlein K, Pradier O, Schmidberger H, Hess CF. The impact of patient positioning on the adequate coverage of the uterus in the primary irradiation of cervical carcinoma: a prospective analysis using magnetic resonance imaging. *Radiother Oncol* 2002; 63(1):83-87.