List of protocol amendments:

Protocol Amendment No. 1, September 2008:

1) **2. Summary** *(page 6, line 17-19)*: Dose per fraction of EBRT should be 1.5-2.0 Gy in the elective volume whereas fractions sizes of 1.7-2.4 Gy should be used in targets encompassing macroscopic tumour not treated with BT. The total dose of EBRT must never exceed 64 Gy (EQD2) in such targets.

2) **2. Summary** *(page 6, line 32-33)*: With regard to chemotherapy, weekly Cisplatin (40 mg/m2) for 5-6 courses is standard unless chemotherapy is precluded by patient age, co-morbidity and toxicity. Other antineoplastic treatments such as other drugs, neoadjuvant chemotherapy or hyperthermia is not allowed until the event of disease progression.

3) **2. Summary (page 6, line 35-36)**: Only approved departments and investigators can contribute patients to the protocol. It is the responsibility of the study coordinators to evaluate and approve participation of a given centre.

4) **8.1 Inclusion Criteria** *(page 12, line 28)*
   - Patient informed consent if required by the ethical committee in the region/country where the patient is accrued

5) **8.2 Exclusion Criteria** *(page 12, line 38)*
   - Patients receiving neoadjuvant or adjuvant chemotherapy or any other types of non-protocol antineoplastic treatment before disease progression.

6) **9.4.1 Dose prescription for EBRT (page 16, line 15-17)**: 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 extra EBRT contribution above the dose level prescribed to the elective target should be reported. If IMRT is used it is important to keep the dose in volume of interest for BT associated morbidity and the GTV-TD as homogenous as possible, such that any dose spillage from nearby boost volumes if possible are placed elsewhere. In practice a "BT volume of interest" in the central pelvis can be used with a constraint set at the dose level used for the elective volume.
   In the event of an additional EBRT boost dose to the tumor volume but cannot be reported using PTV-E ; PTV-P and PTV-N due to uknown exact boundaries of treated volume.The dose should be reported as PTV-T (TUMOR).

7) **9.4.2 Fractionation of EBRT** *(page 16, line 19-20)*: Total number of fraction must be within 23-32 fractions. Dose per fraction is 1.5-2.0 for PTV-E and 1.7-2.4 for PTV-P and PTV-N. The total dose of EBRT for PTV-P or PTV-N must never exceed 64 Gy (EQD2).
   Fractionation for PTV-T: Dose per fraction is 1.5-2Gy. Total fractions 1-25

8) **9.5 Technique for EBRT** *(page 16, line 34-38)*:
The volume encompassed by the D95 isodose curve of the dose prescribed to the elective volume by EBRT (45-50 Gy) should not exceed 2.500 cm^3 for pelvic radiotherapy and 3.500 cm^3 if the para-aortic and/or inguinal nodes are included.

9) **10.3 Contouring of GTVB, HR-CTV, IR-CTV and organs at risk** *(page 19, line 14-23)*:
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 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)
   - Bowel: If other parts of the bowel are found close to the HR-CTV (< 1.5 cm), the outer contour of these bowel segments are contoured as a separate OAR.
   - The ICRU bladder point
   - The ICRU rectal point

   The outer contours of bladder, rectum, sigmoid and other bowel segments 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.

10) **20. The EMBRACE database and website** *(page 34, line 12-13)*
At the Embrace website (www.embracestudy.dk) the protocol, patient information folders and any other pertinent information in relation to the study will be made available.

11) **21. List of appendices** *(page 34, line 25-29)*
The appendices can be downloaded from the EMBRACE website (www
1) Cartoons for drawing of clinical findings from gynaecological examination and instructions for tumour measurements (clinical and MRI)
2) CTCAE v 3.0 with morbidity scoring sheet
3) Instructions for dummy run
4) GYN GEC-ESTRO Guidelines I+II plus appendix
5) Guidelines for applicator reconstruction
6) Patient information folder template

Protocol Amendment No. 2, July 2009:

1) The study title: An International Study on MRI-guided Brachytherapy in Locally Advanced Cervical Cancer

2) 8.2. Exclusion criteria: Patients receiving neoadjuvant chemotherapy, hyperthermia or other antineoplastic treatments not approved by the EMBRACE study committee

3) 11. Concomitant chemotherapy *(page 23, line 17-20)*: Any anti-neoplastic drug treatment different from weekly Cisplatin is only allowed if the patient is participating in a prospective trial that has been approved by an international recognized study group (such as RTOG, GOG, IGCS, EORTC, AGO etc.) and provided that the following rules are strictly respected:

- The anti-neoplastic drug treatment is given in complete accordance with the trial the patient is participating in.
- Phase I trials are not allowed.
- The inclusion and exclusion criteria for EMBRACE still have to be fulfilled.
- The EMBRACE Vienna Study Office is informed of such approved trials from the organisations and institutions involved and receives a copy.
- The identity of the trial is registered in the Embrace database for each patient as relevant. A variable in the EMBRACE database will be set up, where the trial code can be entered and also the patient number in the respective drug trial.
- The EMBRACE study office has access to the anti-neoplastic drug treatment data and other data for the individual patient if needed (drugs given, cumulative dose, toxicity data etc…)
- If appropriate, it should be possible to analyze certain trial patients separately, in particular when the major study question on the relation between DVH parameters and outcome is evaluated.

4) 12. Follow-up investigations
Assessment of Quality of Life should be performed at each 3 month follow-up visit (similar to the assessment of morbidity).
5) 16. Case record forms and procedures for data collection *(page 31, line 27-28):* Each time a CRF has been completed, a printout should be kept in the investigators own patient study file. Only Registration Form should be faxed or mailed to the study office before treatment starts.
6) 17.3. Informed consent
Patient information should be produced by a participating centre in a relevant language according to local requirements. A provisional template (in English and German languages) can be obtained from Vienna Study Office.
7) 20. The EMBRACE database and website *(page 34)*
In case a mistake is done in the submitted data, the centre should send a Query Form to the Vienna Study Office. There the query will be analysed and a permission/rejection to change the data in the database will be given. The Query Form will be available on the EMBRACE web-site under the Tools link.
The Vienna Study Office will keep a query logbook, where all the queries will be registered.