MRI-guided adaptive brachytherapy in locally advanced cervical cancer (EMBRACE-I): a multicentre prospective cohort study

*Richard Pötter, Kari Tanderup, Maximilian Paul Schmid, Ina Jürgenliemk-Schulz, Christine Haie-Meder, Lars Ulrik Fokdal, Alina Emiliana Sturdza, Peter Hoskin, Umesh Mahantshetty, Barbara Segedin, Kjersti Bruheim, Fleur Huang, Bhavana Rai, Rachel Cooper, Elzbieta van der Steen-Banasik, Erik Van Limbergen, Bradley Rumwell Pieters, Li-Tee Tan, Remi Abubakar Nout, Astrid Agatha Catharina De Leeuw, Robin Ristl, Primoz Petric, Nicole Nesvacil, Kathrin Kirchheiner, Christian Kirisits, Jacob Christian Lindegaard, EMBRACE Collaborative Group**

Lancet Oncol 2021; 22: 538–47

*Members are listed in the appendix

Department of Radiation Oncology, Comprehensive Cancer Center (Prof R Pötter MD, M P Schmid MD, A E Sturdza MD, N Nesvacil DSc, K Kirchheiner PhD, C Kirisits DSc), **and Center for Medical Statistics, Informatics and Intelligent Systems** (R Ristl PhD) **Medical University of Vienna, Vienna, Austria; Department of Oncology, Aarhus University Hospital, Aarhus, Denmark** (Prof K Tanderup PhD, L U Fokdal PhD, J C Lindegaard DMSc); **Department of Radiation Oncology, University Medical Centre Utrecht, Utrecht, Netherlands** (I Jürgenliemk-Schulz PhD, A A C De Leeuw PhD); **Department of Radiotherapy, Gustave-Roussy, Villejuif, France** (C Haie-Meder MD); **Mount Vernon Hospital, Mount Vernon Cancer Centre, Northwood, London, UK** (Prof P Hoskin MD); **Division of Cancer Sciences, University of Manchester, Manchester, UK** (Prof P Hoskin); **Tata Memorial Centre, Homi Bhabha National Institute, Mumbai, India** (U Mahantshetty MD); **Department of Radiotherapy, Institute of Oncology Ljubljana, Ljubljana, Slovenia** (B Segedin PhD, P Petric PhD); **Department of Oncology, The Norwegian Radium Hospital, Oslo University Hospital, Oslo, Norway** (K Bruheim MD); **Department of Oncology, Cross Cancer Institute and University of Alberta, Edmonton, AB, Canada** (F Huang MDCM); **Department of Radiotherapy and Oncology, Postgraduate Institute of Medical Education**

Summary

Background The concept of the use of MRI for image-guided adaptive brachytherapy (IGABT) in locally advanced cervical cancer was introduced 20 years ago. Here, we report on EMBRACE-I, which aimed to evaluate local tumour control and morbidity after chemoradiotherapy and MRI-based IGABT.

Methods EMBRACE-I was a prospective, observational, multicentre cohort study. Data from patients from 24 centres in Europe, Asia, and North America were prospectively collected. The inclusion criteria were patients older than 18 years, with biopsy-proven squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma of the uterine cervix, The International Federation of Gynecology and Obstetrics (FIGO) stage IB–IVA disease or FIGO stage IVB disease restricted to paraaortic lymph metastasis below the L1–L2 interspace, suitable for curative treatment. Treatment consisted of chemoradiotherapy (weekly intravenous cisplatin 40 mg/m², 5–6 cycles, 1 day per cycle, plus 45–50 Gy external-beam radiotherapy delivered in 1·8–2 Gy fractions) followed by MRI-based IGABT. The MRI-based IGABT target volume definition and dose reporting was according to Groupe Européen de Curiethérapie European Society for Radiation Oncology recommendations. IGABT dose prescription was open according to institutional practice. Local control and late morbidity were selected as primary endpoints in all patients available for analysis. The study was registered with ClinicalTrials.gov, NCT00920920.

Findings Patient accrual began on July 30, 2008, and closed on Dec 29, 2015. A total of 1416 patients were registered in the database. After exclusion for not meeting patient selection criteria before treatment, being registered but not entered in the database, meeting the exclusion criteria, and being falsely excluded, data from 1341 patients were available for analysis of disease and data from 1251 patients were available for assessment of morbidity outcome. MRI-based IGABT including dose optimisation was done in 1317 (98·2%) of 1341 patients. Median high-risk clinical target volume was 28 cm³ (IQR 20–40) and median minimal dose to 90% of the clinical target volume ($D_{90\%}$) was 90 Gy (IQR 85–94) equi-effective dose in 2 Gy per fraction. At a median follow-up of 51 months (IQR 20–64), actuarial overall 5-year local control was 92% (95% CI 90–93). Actuarial cumulative 5-year incidence of grade 3–5 morbidity was 6·8% (95% CI 5·4–8·6) for genitourinary events, 8·5% (6·9–10·6) for gastrointestinal events, 5·7% (4·3–7·6) for vaginal events, and 3·2% (2·2–4·5) for fistulae.

Interpretation Chemoradiotherapy and MRI-based IGABT result in effective and stable long-term local control across all stages of locally advanced cervical cancer, with a limited severe morbidity per organ. These results represent a positive breakthrough in the treatment of locally advanced cervical cancer, which might be used as a benchmark for clinical practice and all future studies.

Funding Medical University of Vienna, Aarhus University Hospital, Elekta AB, and Varian Medical Systems.

Introduction

Combined chemoradiotherapy and brachytherapy is the treatment of choice in locally advanced cervical cancer.[1] Despite increasingly sophisticated techniques for delivering external-beam radiotherapy (EBRT), brachytherapy remains a crucial element of treatment for optimal local control and long-term survival.[2,3]

About two decades ago, MRI was introduced for the planning of brachytherapy in locally advanced cervical cancer, and a new adaptive target concept was designed taking into account the topography of the primary tumour at diagnosis and the substantial regression often observed during EBRT and concomitant chemotherapy.[4,5] When image-guided adaptive brachytherapy (IGABT) was introduced, clinical evidence for the safety of this approach was scarce.[6] In small tumours and those that have responded well to chemoradiotherapy, dose adaptation to a three dimensional (3D) target can result in dose

Research in context

Evidence before this study

We searched PubMed for reports published in English between Jan 1, 2000, and June 1, 2020, using the search terms "image guided adaptive brachytherapy" (IGABT), "MRI", "cervical cancer", "local control" , "overall survival" , and "prospective clinical study". No study fulfilling these criteria was identified. The clinical evidence so far is based on several retrospective patient cohort studies pointing to improvement of local control and reduction of severe morbidity by IGABT in locally advanced cervical cancer, with only few variations in treatment and outcomes. Additionally, international recommendations have been published on the concept and reporting of IGABT (Groupe Européen de Curiethérapie European Society for Radiation Oncology [GEC ESTRO] recommendations, International Commission of Radiation Units report 89).

Added value of this study

To our knowledge, EMBRACE-I is the first prospective multi-institutional observational cohort study using MRI-based IGABT in addition to concurrent chemoradiotherapy in locally advanced cervical cancer, showing the clinical feasibility of the combined treatment. Effective dose coverage could be reached in the target while sparing organs at risk through adjustment of IGABT application technique (intracavitary and interstitial needles) and multiparametric three dimensional treatment planning. EMBRACE-I provides mature and high-quality clinical outcome data showing a high rate of local control across all stages greater than ever reported before. This improvement was associated with a high rate of pelvic control and overall survival. Severe late morbidity (eg, grade ≥3) was limited per organ site and endpoint.

Implications of all the available evidence

The results of EMBRACE-I provide the clinical evidence for MRI-guided IGABT as being the new gold-standard IGABT of locally advanced cervical cancer to be implemented across the world, replacing the traditional two dimensional point A concept. EMBRACE-I entails a comprehensive system for collecting information on patient, tumour, and treatment parameters, associating these with disease outcome and morbidity, and quality of life. The high level of local and pelvic control with limited severe morbidity and favourable overall survival will serve as a platform for future studies focusing on nodal and systemic control, which are the barriers for improved disease control and survival. IGABT, as practiced in EMBRACE-I, has become the new standard of care in Europe according to the recommendations of the European Society of Gynaecologic Oncology, the European Society for Radiotherapy and Oncology, and the European Society of Pathology. Findings from EMBRACE-I were the basis for the ongoing interventional prospective multicenter EMBRACE-II (NCT 03617133) study, in which specific planning aims and dose-volume constraints are enforced. The EMBRACE I results are also being increasingly used as a reference in many centres worldwide and in clinical studies reflecting clinical, biological, and technical parameters of importance for further optimising the therapeutic ratio for chemoradiotherapy and IGABT in locally advanced cervical cancer.

and Research, Chandigarh, India (B Rai MD)**; St James's University Hospital, Leeds Cancer Centre, Leeds, UK** (R Cooper FRCR)**; Department of Radiotherapy, Radiotherapiegroep Arnhem, Arnhem, Netherlands** (E van der Steen-Banasik MD)**; Department of Radiation Oncology, UZ Leuven, Leuven, Belgium** (E Van Limbergen PhD)**; Department of Radiation Oncology, Amsterdam University Medical Center, Academic Medical Centers, University of Amsterdam, Amsterdam, Netherlands** (B R Pieters MD)**; Department of Oncology, Addenbrooke´s Hospital, Cambridge University Hospitals, Cambridge, UK** (L-T Tan FRCR)**; Department of Radiation Oncology, Leiden University Medical Center, Leiden, Netherlands** (Prof R A Nout MD)**; Department of Radiotherapy, Erasmus MC Cancer Institute, University Medical Center Rotterdam, Rotterdam, Netherlands** (Prof R A Nout)

Correspondence to:
Dr Maximilian Paul Schmid, Department of Radiation Oncology, Comprehensive Cancer Center, Medical University of Vienna, A-1090 Vienna, Austria
maximilian.schmid@akhwien.at

de-escalation with the potential risk of local recurrence. By contrast, in large and poor-responding tumours (still large after chemoradiotherapy), IGABT allows dose escalation to the target through the use of combined intracavitary and interstitial techniques, but this strategy leads to larger volumes being treated with high radiation doses,[7,8] which could increase severe morbidity.

Therefore, IGABT was introduced with caution, initially with limited optimisation of the dose distribution for exclusively intracavitary implants, which were later supplemented with interstitial needles to treat more extensive tumours.[7] Several single-centre series,[6,9–11] a non-randomised French study using CT guidance,[12] and a large retrospective multicentre series (RetroEMBRACE) using mainly MRI guidance,[13] showed the safety and feasibility of IGABT in routine practice with clinically and statistically significant improved local and pelvic control and reduced morbidity.

Here, we report the mature overall findings of the IntErnational study on MRI-guided BRAchytherapy in CErvical cancer (EMBRACE-I), which, to our knowledge, was the first large-scale prospective study of MRI-based IGABT for locally advanced cervical cancer. The study was based on recommendations published by the Groupe Européen de Curiethérapie European Society for Radiation Oncology (GEC-ESTRO),[4,5] which provided the basis of the International Commission on Radiation Units and Measurements (ICRU) report 89.[14] The aims of EMBRACE-I were: (1) to introduce MRI-based IGABT in locally advanced cervical cancer in an international multicentre setting; (2) to present reference material of treatment parameters; (3) to investigate the effects of MRI-based IGABT on disease and late morbidity for patients with locally advanced cervical cancer treated with definitive chemoradiotherapy followed by MRI-based IGABT allowing for variations in technique and dose; and (4) to provide a benchmark for clinical outcome with MRI-based IGABT in a large patient population.

Methods

Study design and participants

EMBRACE-I was a prospective, observational, multicentre cohort study done at 24 centres in Europe, Asia, and North America. Reporting on key patient, disease, treatment, and outcome parameters and standardised target volume definition[4] and dose-volume reporting[5] for MRI-based IGABT were mandatory, whereas the

For more on the **EMBRACE-I study** see www.embracestudy.dk

brachytherapy dose prescription was according to institutional practice and was observational.

Eligibility criteria were biopsy-proven squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma of the uterine cervix, The International Federation of Gynaecology and Obstetrics (FIGO) stage IB–IVA disease or FIGO stage IVB disease restricted to paraaortic lymph metastasis below the L1–L2 interspace, suitable for curative treatment including MRI according to the study protocol, and age 18 years or older. Exclusion criteria were other primary malignancies except carcinoma in situ of the cervix and basal cell carcinoma of the skin, metastatic disease beyond the para-aortic region (L1–L2); previous pelvic or abdominal radiotherapy; previous total or partial hysterectomy; combination of preoperative radiotherapy with surgery; patients receiving brachytherapy only; patients receiving EBRT only; patients receiving neo-adjuvant chemotherapy; contraindications to MRI; contraindications to brachytherapy; active infection or severe medical condition endangering treatment delivery; and pregnant, lactating, or childbearing potential without adequate contraception.

See Online for appendix

Written, informed consent was obtained from all patients. The study protocol was approved by local ethics committees in participating centres.

For the **study protocol** see https://www.embracestudy.dk/Public/Default.aspx?main=1&sub=2&embrace=embrace

Procedures

Pelvic MRI (with T2-weighted spin-echo sequences) and gynaecological examination at diagnosis were mandatory for local tumour staging. Abdominal CT and chest x-ray were required for nodal staging and exclusion of distant metastasis. Thoracic CT, PET-CT, and pelvic or paraaortic lymphadenectomy were optional.

Patients were staged according to a modified FIGO 2009 classification—patients with hydronephrosis detected by imaging were classified as FIGO IIIB and patients with paraaortic lymph node metastases detected by imaging or lymphadenectomy as FIGO IVB. Baseline morbidity assessment was done using the Common Terminology Criteria for Adverse Events version 3.[15]

Treatment comprised EBRT to the pelvis with concomitant chemotherapy followed by IGABT based on MRI and gynaecological examination at diagnosis and at brachytherapy. Paraaortic radiotherapy was applied in case of paraaortic nodal involvement or in patients considered at high risk for paraaortic nodal recurrence at the discretion of the treating physician.[16] Inguinal radiotherapy was used for pathological inguinal nodes or lower third involvement of the vagina, or both. Permitted EBRT techniques were 3D conformal radiotherapy, intensity-modulated radiotherapy (IMRT), or volumetric arc therapy (VMAT) with CT-based treatment planning; opposed fields and midline blocks were not allowed. The EBRT dose was 45–50 Gy in 1·8–2 Gy fractions. EBRT boosts to pathological lymph nodes were encouraged, parametria or pelvic side wall boosts up to 60–65 Gy were allowed. Concomitant chemotherapy was weekly intravenous cisplatin 40 mg/m², 5–6 cycles, 1 day per cycle. Neo-adjuvant or adjuvant chemotherapy was not permitted.

MRI-based treatment planning with the applicator in place was mandatory for at least the first application and subsequent applications could be CT-planned with consideration of the previous MRI information. Any MRI-compatible applicator type was permitted; use of combined intracavitary and interstitial techniques was optional. Target volume definition and reporting were according to Gynaecological (GYN) GEC-ESTRO recommendations (eg, high-risk clinical target volume [CTV_{HR}]) and contouring of organs at risk was mandatory as well as dose volume reporting (eg, minimal dose to 90% of the clinical target volume [$D_{90\%}$], minimal dose to the most exposed 2 cm³ of the respective organ [$D_{2\ cm^3}$]).[4,5] Individual dose optimisation was encouraged to balance dose to target versus organs at risk. Dose optimisation was defined as point A (left or right) being different from the (institutional) planning aim (ICRU 89; appendix p 1).[14] The equi-effective dose in 2 Gy per fraction (EQD2) from EBRT and brachytherapy was calculated using an α/β of 10 Gy for tumour ($EQD2_{10}$) and 3 Gy for organs at risk ($EQD2_3$), and a half-time for sublethal damage repair of 1·5 h for pulsed dose rate brachytherapy.[5,14,17] The maximum overall treatment time (EBRT plus brachytherapy) was limited to 50 days. The intention was to stay below the standard threshold of 56 days to improve outcome.[18]

Patients were assessed clinically with gynaecological examination every 3 months in the first year, every 6 months in the second and third year, and annually thereafter. Pelvic MRI was mandatory at 3 months and 12 months. Additional imaging and laboratory or physical examinations were done at the discretion of the treating physician. Imaging (mainly MRI, CT, or PET-CT), but not pathological examination, was mandatory for confirmation of any recurrence and additional gynaecological examination for local recurrence (appendix p 1). Morbidity was assessed longitudinally and scored at each follow-up until a disease event (recurrence or metastasis) or last follow-up using The Common Terminology Criteria for Adverse Events (version 3).

Data were collected in a web-based database with electronic case report forms. Before beginning patient accrual, all participating centres had to pass a dummy run procedure[19] involving submission of complete 3D datasets on two patients of planning CT for EBRT with target volumes and dose distribution, MRI at diagnosis, and planning MRI at brachytherapy with applicator, target volumes, and dose distribution. Data for each patient were checked for completeness and plausibility by the study office. These checks included evaluation of all entered patient, tumour, treatment, imaging, and outcome parameters. In case of implausible data, the centre was contacted by the study office for clarification and data were subsequently re-checked. Adherence to the

follow-up schedule was monitored and completion or update of follow-up forms was requested, if necessary (appendix p 1). All disease and major morbidity (grade 3–5) events were reviewed to confirm correct classification of disease events and reason of death, and the correct documentation and grading of morbidity events. In case of uncertainties, the centre was contacted by the study office for individual case discussion (appendix p 1).

Outcomes

Due to the direct effect of brachytherapy on the primary tumour and surrounding organs, local control and late morbidity were selected as primary endpoints. Local control was defined as absence of any recurrent or progressive disease in the cervix, parametria, uterine corpus, and vagina. Late morbidity was defined as any morbidity at 3 months or longer after the end of treatment.

Pelvic control, nodal control, disease-free survival, overall survival, and quality-of-life were secondary endpoints. Overall survival was not selected as a primary endpoint because it is known to be influenced by nodal and systemic control. Primary and secondary outcomes were assessed in all patients with available data.

Pelvic control was defined as absence of any local or nodal recurrence or progression in the pelvis. Nodal control was defined as absence of any recurrent or progressive nodal disease in the pelvic, inguinal, or paraaortic region. Disease-free survival was defined as absence of any disease event or death from any cause. Overall survival was defined as absence of death from any cause.

Quality-of-life results will be presented separately due to their complexity.[20–24]

Statistical analysis

Accrual of 600 patients was planned according to the study protcol. This estimation was based on the estimated feasibility of accrual from the major contributing centers within a certain period. The initial aim was extended to more than 1300 patients due to the limited number of disease events to achieve a higher number in the order of 100 events, which allows for reliable multivariable testing of up to ten predictive or prognostic factors.[25,26] Furthermore, such extension of patient accrual allows for high precision in estimating actuarial incidence.

Medians and IQRs were calculated for metric variables (age, dose parameters, and CTV_{HR} volume) and absolute and relative frequencies were calculated for categorical variables (histology, FIGO stage, nodal status, and treatment characteristics).

Morbidity was reported as absolute number of events and patients (crude incidence) and actuarial cumulative incidence rates for grade 3–5 morbidity, for genitourinary tract, gastrointestinal tract, vagina, fistula, overall (genito-urinary, gastrointestinal, and vaginal), and by FIGO stage.

Disease events were reported by location (local, nodal [inguinal, pelvic, paraaortic], and systemic) and were registered at first recurrence and evaluated overall and by FIGO stage. A post-hoc analysis was done for comparison of outcomes by nodal status at diagnosis by FIGO stage. Time-to-event intervals were calculated from the date of diagnostic biopsy until the respective event. Patients without events were censored at the date of last follow-up. For time-to-event outcomes, the probability of a patient remaining event-free within a given time period was calculated using the Kaplan-Meier method. CIs were defined as 95% for actuarial estimates. Time-to-event curves were compared between groups using the log-rank test. The cumulative incidence curves for local control, pelvic control, and nodal control regarding death as a competing event were calculated to evaluate sensitivity.

Patients lost to follow up were censored at the timepoint when they were lost to follow-up. Monitoring of follow-up appointments was done within the quality assurance programme. Reminders to update and complete follow-up forms were sent to the participating centers, if necessary.

Analyses were done with SPSS (version 26) and R (version 3.5). The study was registered with ClinicalTrials.gov, NCT00920920.

Role of the funding source

The sponsors had no role in study design, data collection, data analysis, data interpretation, or writing of this report.

Results

Patient accrual started on July 30, 2008, and closed on Dec 29, 2015. The final analysis was based on data updated as of July 15, 2019. A total of 1416 patients were registered in the database. 21 patients were excluded for not meeting patient selection criteria before treatment, 17 patients were registered but not entered in the database, 34 patients met the exclusion criteria, and three patients were falsely excluded with no data collected. 1341 patients were available for analysis of disease and 1251 for morbidity outcome (figure 1).

Information on MRI-defined adaptive brachytherapy target volumes and dose-volume reporting was available for 1329 (99·1%) of 1341 patients (three patients died during treatment, and nine patients had no MRI at brachytherapy). Individualised dose optimisation was done for 1317 (98·2%) patients. Patient characteristics are summarised in table 1 and treatment characteristics are described in table 2. Stage-related dose and volume parameters for brachytherapy are shown in table 3.

The median follow-up was 51 months (IQR 20–64). 131 (9·8%) patients were lost to follow-up at 3 years and in total 388 (28·9%) had no 5-year follow-up form available (appendix p 2). 440 disease events were observed in 331 (24·7%) patients: 98 local, 158 pelvic, 158 nodal (pelvic, 83; paraaortic, 104; inguinal, 22; simultaneous events at different sites included), and 184 systemic

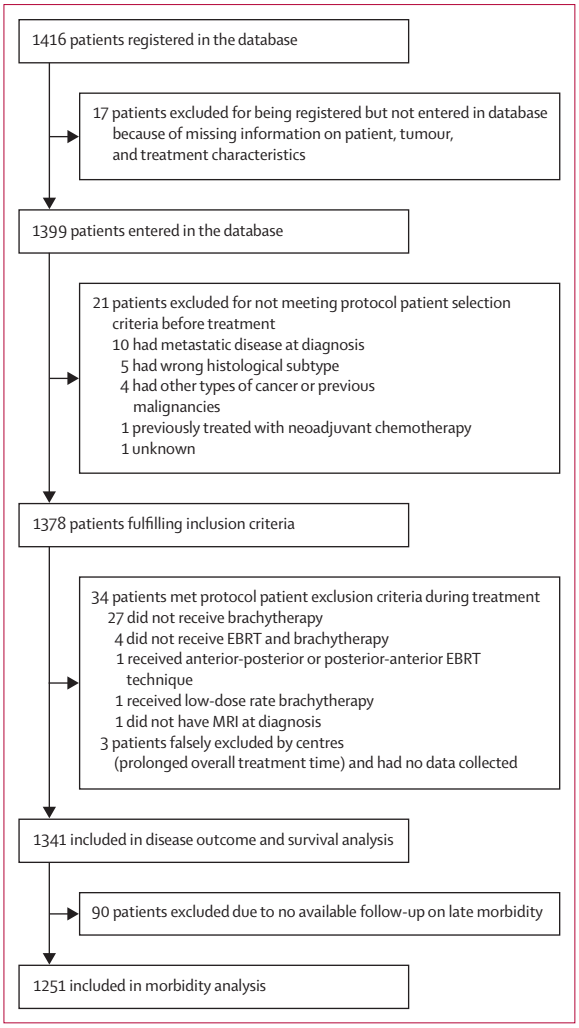


Figure 1: **EMBRACE-I trial profile**
EBRT=external-beam radiotherapy.

	Patient cohort (n=1341)
Demographics	
Age, years	49 (41–60)
Missing	0
Histology	
Squamous cell carcinoma	1097 (81·8%)
Adenocarcinoma	192 (14·3%)
Adenosquamous carcinoma	50 (3·7%)
Missing	2 (0·1%)
FIGO stage	
IB1	124 (9·2%)
IB2	119 (8·9%)
IIA1	38 (2·8%)
IIA2	31 (2·3%)
IIB	693 (51·7%)
IIIA	13 (1·0%)
IIIB	190 (14·2%)
IVA	34 (2·5%)
IVB	98 (7·3%)
Missing	1 (0·1%)
Nodal status	
N0	641 (47·8%)
N1	699 (52·1%)
Missing	1 (0·1%)

Data are median (IQR) or n (%). FIGO=The International Federation of Gynaecology and Obstetrics.

Table 1: **Baseline patient and tumour characteristics**

(table 3, appendix p 6). Overall, 363 (27·1%) patients died: 281 (21·0%) due to disease progression, 12 (0·9%) due to treatment-related toxicity with no evidence of disease, 58 (4·3%) due to other reasons, and 12 (0·9%) for unknown reasons.

The primary endpoint of actuarial overall 5-year local control was 92% (95% CI 90–93; table 3, appendix p 2). Actuarial 5-year local control per FIGO stage is shown in table 3 and figure 2.

5-year pelvic control was 87% (95% CI 85–89), 5-year nodal control was 87% (95% CI 85–89), 5-year overall survival was 74% (72–77), and 5-year disease-free survival was 68% (65–70; table 3, appendix pp 2–5).

Local control was similar across all FIGO stages (p=0·31). However, significant differences were found for disease-free survival and overall survival by FIGO stage; p<0·0001; appendix pp 3–4).

The estimates for cumulative incidence of local, pelvic and nodal control (the competing risk sensitivity analysis) had minimal variation when compared with the Kaplan-Meier estimates (appendix p 7).

In total, 330 grade 3–5 morbidity events (genitourinary, gastrointestinal, vaginal, fistulas) were observed in 183 (14·6%) of 1251 patients (table 4). The most common grade 3–5 events (5-year actuarial cumulative incidence) were fistulae (3·2%, 95% CI 2·2–4·5; 42 events), gastrointestinal stenosis (2·8%, 1·9–4·2; 26 events), gastrointestinal bleeding (2·2%, 1·4–3·4; 22 events), diarrhoea (1·9%, 1·2–3·0; 20 events), ureteric strictures (2·9%, 2·1–4·2; 36 events), urinary incontinence (2·2%, 1·4–3·3; 24 events), urinary frequency (1·8%, 1·1–2·8; 19 events), cystitis (1·3%, 0·8–2·3; 14 events), vaginal stenoses (4·0%, 2·8–5·7; 36 events), and vaginal mucositis (1·4%, 0·8–2·3; 14 events). In our post-hoc analysis, fistulae and ureteric strictures were more common in 203 patients with stage IIIA–IIIB cancer (17 fistulae, 10·2%, 95% CI 6·3–16·2; 20 ureteric strictures, 10·8%, 6·9–16·8%; n=31 patients) and in 34 patients with stage IVA cancer (six fistulae, 18·6%, 7·8–40·6; six ureteric strictures, 21·3%, 9·8–42·9; n=12 patients) than in 1005 patients with IB1–IIB cancer with 11 fistulae (1·3%, 0·7–2·5) and ten ureteric strictures (0·7%, 0·3–1·6; n=19 patients).

In our post-hoc analysis of outcomes by nodal status at diagnosis, 5-year nodal control was 93% (95% CI 90–95) in N0 and 81% (77–84) in N1 patients. Disease outcome

by FIGO stage$_{2009}$ and nodal status is provided in the appendix (p 6).

Discussion

The EMBRACE-I cohort study provides large-scale prospective clinical evidence of the feasibility and efficacy of MRI-based IGABT in the treatment of locally advanced cervical cancer and has generated benchmarks for typical individual target volumes and achievable target doses for MRI-based IGABT and for organs at risk, which can be used as references for research and clinical audit. The overall local control achieved across all stages (92%, with a small 95% CI of 90–93) was unprecedented,[10–13,27] whereas the incidence of severe morbidity was limited per organ (grade ≥3, 3·2–8·5%; grade ≥4 0·5–3·0%), but considerable overall (grade ≥3, 18·4%; grade ≥4, 5·2%), especially for patients with stage III–IVA disease.

The EMBRACE-I study has served to validate the GEC ESTRO and ICRU recommendations,[4,5,14] which were used for target selection, contouring of organs at risk, and dose and volume reporting. The protocol adherence was controlled through a dummy run[19] and a rigorous individualised quality assurance programme. 98% of the patients could be treated by IGABT on the basis of MRI with individualised target and organ at risk contouring followed by dose optimisation and multiparametric dose prescription. As previously published, this strategy resulted in 41% of the patients (with tumours that were limited in size and well-responding) receiving a significant decrease in volume and dose compared with standard two dimensional brachytherapy,[8] while maintaining excellent local control rates, thus alleviating concerns that MRI-based IGABT might inadvertently increase the risk of local recurrence. Local control rates for stage IB–IIB disease are superior to historical series using two dimensional point A-based brachytherapy.[13] Pelvic control in stage IB1 is similar to the best results from modern surgical series,[16,28] despite assumed negative selection bias for stage IB1 patients undergoing radiochemotherapy instead of surgery. In 21% of patients, the treated volume was larger than for traditional point A prescription to adequately cover large residual tumour at time of brachytherapy.[8] For these tumours in particular, many patients received interstitial needles in addition to the intracavitary component, which could also explain the little variation in delivered dose across stages despite large variations in size or extent of IGABT target volumes. Consequently, EMBRACE-I shows an absolute improvement in local control or pelvic control in FIGO stage IIIB disease of about 14–17% compared with values previously reported with IGABT[13] and with two dimensional brachytherapy.[27] This improvement in local control observed in EMBRACE-I is probably due to the aforementioned improvements in target contouring, implant technique, and 3D treatment planning. However, 25% of the patients still received less than 85 Gy EQD$_2$ to the target volume (CTV$_{HR}$ D$_{90\%}$) which could indicate potential

	Patient cohort (n=1341)
EBRT	
Target volume	..
Pelvic	1099 (82·0%)
Pelvic plus paraaortic	204 (15·2%)
Pelvic plus inguinal	23 (1·7%)
Pelvic plus paraaortic plus inguinal	12 (0·9%)
Missing	3 (0·2%)
Technique	..
Three dimensional conformal	788 (58·8%)
IMRT or VMAT	550 (41·0%)
Missing	3 (0·2%)
Dose to elective target volume, Gy	45 (45–46)
Missing	3 (0·2%)
Chemotherapy	
Concomitant chemotherapy	1265 (94·3%)
Cisplatin 40 mg/m² weekly*	1228 (91·6%)
Other	37 (2·8%)
No chemotherapy	72 (5·4%)
Missing	4 (0·3%)
Brachytherapy	
Technique	..
Intracavitary	759 (56·6%)
Combined intracavitary and interstitial	577 (43·0%)
Missing	5 (0·4%)
Dose rate	..
High	764 (57·0%)
Pulsed	562 (41·9%)
High and pulsed	10 (0·7%)
Missing	5 (0·4%)
CTV$_{HR}$ volume, cm³	28 (20–40)
Missing	6 (0·4%)
EBRT plus brachytherapy	
Cumulative CTV$_{HR}$ D$_{90\%}$ (EBRT plus brachytherapy), Gy (EQD2$_{10}$)	90 (85–94)
Missing	3 (0·2%)
Overall treatment time, days	46 (42–50)
Missing	5 (0·4%)
Cumulative bladder D$_{2cm^3}$ (EBRT plus brachytherapy), Gy (EQD2$_3$)	76 (69–83)
Missing	3 (0·2%)
Cumulative rectum D$_{2cm^3}$ (EBRT plus brachytherapy), Gy (EQD2$_3$)	62 (57–68)
Missing	3 (0·2%)
Cumulative sigmoid D$_{2cm^3}$ (EBRT plus brachytherapy), Gy (EQD2$_3$)	64 (59–69)
Missing	3 (0·2%)
Cumulative bowel D$_{2cm^3}$ (EBRT plus brachytherapy), Gy (EQD2$_3$)	58 (49–67)
Missing	3 (0·2%)
Cumulative rectovaginal point (EBRT plus brachytherapy), Gy (EQD2$_3$)	65 (60–71)
Missing	30 (2·2%)
Cumulative bladder point (EBRT plus brachytherapy), Gy (EQD2$_3$)	65 (57–76)
Missing	32 (2·4%)

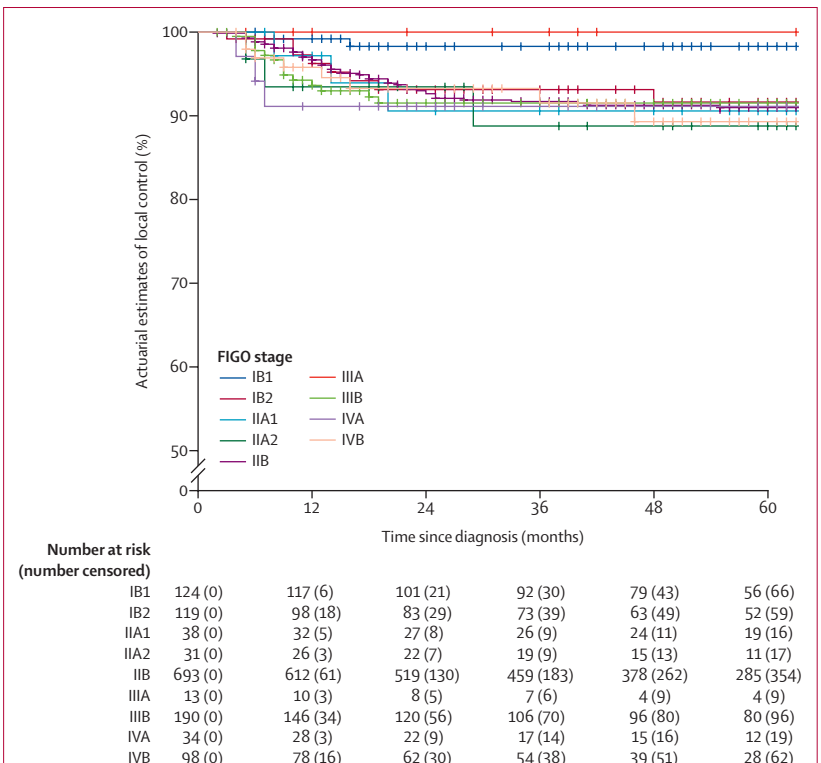
Data are n (%) or median (IQR). IMRT=intensity-modulated radiotherapy. VMAT=volumetric-modulated arc therapy. CTV$_{HR}$= high-risk clinical target volume. D$_{90\%}$=minimal dose to 90% of the clinical target volume. EBRT=external beam radiotherapy. EQD2$_{10}$=equi-effective dose in 2 Gy per fraction of 10 Gy. D$_{2cm^3}$=minimal dose to the most exposed 2 cm³ of the respective organ. EQD2$_3$=equi-effective dose in 2 Gy per fraction of 3 Gy. *634/1228 received ≥5 cycles.

Table 2: **Treatment characteristics**

	Number of patients	CTV_{HR} volume, cm^3*	CTV_{HR} $D_{90\%}$ $EQD2_{10}$, Gy	Local failure (n)	Pelvic failure (n)	Any failure (n)	Patients dead (n)	5-year local control (95% CI)	5-year pelvic control (95% CI)	5-year disease-free survival (95% CI)	5-year overall survival (95% CI)
IB1	124	22 (17–27)	91 (87–95)	2	6	20	24	98% (94–100)	95% (87–98)	76% (67–83)	83% (75–89)
IB2	119	26 (20–38)	89 (84–93)	9	18	36	35	92% (84–96)	84% (75–90)	65% (56–73)	73% (64–81)
IIA1	38	23 (14–31)	91 (85–96)	3	4	6	7	91% (73–97)	88% (71–95)	75% (58–86)	80% (63–90)
IIA2	31	34 (24–42)	87 (80–91)	3	6	10	8	89% (68–96)	77% (55–89)	65% (44–79)	74% (53–87)
IIB	693	27 (19–36)	90 (86–95)	55	78	146	152	91% (88–93)	88% (85–90)	73% (69–76)	78% (75–82)
IIIA	13	30 (24–35)	84 (82–88)	0	0	2	3	100%	100%	76% (43–92)	76% (42–91)
IIIB	190	40 (30–56)	88 (83–91)	15	24	61	78	92% (86–95)	86% (79–90)	59% (52–66)	64% (57–71)
IVA	34	57 (39–89)	86 (78–89)	3	6	10	17	91% (75–97)	81% (62–91)	47% (28–63)	52% (33–68)
IVB	98	34 (22–47)	89 (85–92)	8	16	40	38	89% (79–95)	81% (70–88)	48% (37–58)	61% (49–70)
Total	1341†	28 (20–40)	90 (85–94)	98	158	331	363†	92% (90–93)	87% (85–89)	68% (65–70)	74% (72–77)

Data are n, median (IQR), or Kaplan-Meier estimates (95% CI). *Mean dose delivered over all fractions. †One patient with unknown FIGO stage. FIGO=The International Federation of Gynaecology and Obstetrics. CTV_{HR}= high-risk clinical target volume. $D_{90\%}$=minimal dose to 90% of the clinical target volume. $EQD2_{10}$=equi-effective dose in 2 Gy per fraction of 10 Gy.

***Table 3*:CTV_{HR} volume, and dose and clinical outcomes according to $FIGO_{2009}$ stage**



Number at risk (number censored)						
IB1	124 (0)	117 (6)	101 (21)	92 (30)	79 (43)	56 (66)
IB2	119 (0)	98 (18)	83 (29)	73 (39)	63 (49)	52 (59)
IIA1	38 (0)	32 (5)	27 (8)	26 (9)	24 (11)	19 (16)
IIA2	31 (0)	26 (3)	22 (7)	19 (9)	15 (13)	11 (17)
IIB	693 (0)	612 (61)	519 (130)	459 (183)	378 (262)	285 (354)
IIIA	13 (0)	10 (3)	8 (5)	7 (6)	4 (9)	4 (9)
IIIB	190 (0)	146 (34)	120 (56)	106 (70)	96 (80)	80 (96)
IVA	34 (0)	28 (3)	22 (9)	17 (14)	15 (16)	12 (19)
IVB	98 (0)	78 (16)	62 (30)	54 (38)	39 (51)	28 (62)

***Figure 2*: Kaplan-Meier estimates of local control and $FIGO_{2009}$ stage**
FIGO=The International Federation of Gynaecology and Obstetrics.

for further improvement. According to dose-response models, 85 Gy EQD_2 is being used as hard dose constraint in the ongoing EMBRACE-II study.[29]

To our knowledge, EMBRACE-I is the first prospective multicentre study of locally advanced cervical cancer that investigates treatment-related late morbidity and patient-reported outcomes in parallel within a longitudinal design. The EMBRACE Collaborative Group has previously published morbidity crude and actuarial incidence and prevalence for physician-reported and patient-reported outcomes including quality of life.[20–24,30] The overall and major organ site-related severe morbidity data (grade ≥3) presented here are based on prospective assessment of multiple endpoints. This comprehensive spectrum of gastrointestinal, genitourinary, and vaginal morbidity findings compares favourably with retrospective studies that are well recognised as underreporting morbidity overall, particularly for the vagina.[20–24,30] The actuarial overall incidence of severe gastrointestinal, genitourinary, and vaginal morbidity in EMBRACE-I seems, however, considerable. For a comprehensive understanding of morbidity, prevalence of organ-associated morbidity should be taken into account, and these, as previously published, are low for EMBRACE I for organ-related morbidity, with 2% or less for genitourinary and 2% or less for gastrointestinal during follow-up[21,22] which was 3–4 times lower than the actuarial incidence. When comparing specific brachytherapy-associated grade 3 or worse morbidity assessed in historical cohorts such as fistula and ureteric strictures,[20–22,31] these seem to be limited in EMBRACE I (3·2%, 2·9%) and are especially low for patients with stage I–II disease (1·3%, 0·7%). Severe brachytherapy-related morbidity with IGABT is low and is similar for other organ endpoints (eg, gastrointestinal bleeding, urinary incontinence, vaginal obliteration) despite the high doses delivered to the target. This outcome is probably due to the improved dose adaptation achievable with MRI-based planning, limiting dose to adjacent organs at risk. Fistulae and ureteric strictures remain a therapeutic challenge in stage IIIA–IIIB (10·2%, 10·8%) and IVA (18·6%, 21·3%), and appear to be related to tumour extension at diagnosis.[31]

The low nodal failure rate in the pelvis alone (without paraaortic failure) in node-negative (4%) and

	Gastrointestinal	Genitourinary	Vaginal	Fistula*	Overall (gastrointestinal, genitourinary, vaginal, and fistula)
Grade 3 adverse events					
Number of events	83	93	54	18	248
Number of patients	54 (4·3%)	59 (4·7%)	50 (4·0%)	13 (1·0%)	128 (10·2%)
Actuarial 5-year cumulative incidence of grade 3 or higher morbidity (95% CI)	8·5% (6·9–10·6)	6·8% (5·4–8·6)	5·7% (4·3–7·6)	3·2% (2·2–4·5)	18·4% (16·0–21·2)
Grade 4 adverse events					
Number of events	34	19	5	24	82
Number of patients	27 (2·2%)	16 (1·3%)	5 (0·4%)	21 (1·7%)	55 (4·4%)
Actuarial 5-year cumulative incidence of grade 4 or higher morbidity (95% CI)	3·0% (2·0–4·3)	1·0% (0·6–1·9)	0·5% (0·2–1·2)	2·1% (1·5–3·2)	5·2% (4·0–6·9)

Data are n, n (%), or actuarial cumulative incidence (95% CI). Adverse events were classified according to the Common Terminology Criteria for Adverse Events, version 3.0. Data were available for 1251 patients. Grade 5 events are not listed because they were not always allocated to a single organ system. Eight gastrointestinal events, four genitourinary events, four fistulas, and five septic infections contributed to treatment-related death in 12 patients.
*15 vesico-vaginal, 10 recto-vaginal, 4 sigmoid-vagina, 13 other fistulas.

Table 4: **Grade 3–4 morbidity**

node-positive (10%) patients underlines the efficacy of nodal radiotherapy (appendix p 6). However, there appears to be room for improvement of paraaortic nodal control since two-thirds of nodal failures in node-positive patients occurred in the para-aortic region with the majority being outside the elective target volume.[32] Increased use of prophylactic para-aortic irradiation in high-risk node-positive patients is therefore under investigation in the EMBRACE-II study.[29] Additionally, intensification of nodal treatment through a simultaneously integrated boost might further decrease nodal failures.[33]

Improved local control (and high nodal control) would be expected to increase survival. However, the design of EMBRACE I makes it difficult to evaluate the magnitude of the effect. Historical comparisons of survival with cohorts treated with two dimensional point A were challenged by the introduction of concomitant chemotherapy about 20 years ago. However, compared with previous results of IGABT[13] with a similar stage distribution, the overall survival at 5 years has improved in our study from 67% to 74%. Whereas differences in local control by stage are not significant due to MRI-based IGABT, there remains a significant difference in overall survival between more limited stage (IB1–IIB) and advanced stage (IIIB–IVA) disease, which might be associated with limited nodal and systemic control.

The main limitation of EMBRACE I is the lack of an unbiased direct comparator. Regarding the single-arm study design, patient selection is considered as the main source of potential bias. Baseline demographic and tumour parameters indicate a typical distribution of these characteristics for a cohort undergoing primary radiochemotherapy in high-income countries. A representative number of advanced stages (IIIB, IVA, and IVB) is included. The high rate of concomitant chemotherapy delivered in EMBRACE-I could suggest some degree of patient selection compared with unselected consecutive cohorts.[6,9,13,34] However, the inclusion and exclusion criteria of EMBRACE-I are very similar to trials of concomitant chemotherapy. Furthermore, the observational character of EMBRACE-I (EBRT technique and dose, brachytherapy performance and dose prescription according to institutional practice) implies the potential for some variations in EBRT and brachytherapy techniques and doses by centre and over time within the frame of the study protocol. However, for EMBRACE-I, these variations have made it possible to investigate technique and dose effects for the target and for organs at risk, which is ongoing research.[30,20,35,36]

MRI-based IGABT in combination with chemoradiotherapy leads to positive local and pelvic disease control and survival throughout all stages of locally advanced cervical cancer, with limited severe organ-related morbidity. These results compare favourably with retrospective data from IGABT and data from the era of point A-based two dimensional brachytherapy and might be considered a positive development in the treatment of locally advanced cervical cancer. The benchmarks for target and organs at risk volumes and doses have been used to develop an evidence based multiparametric prescription model being prospectively investigated in EMBRACE-II together with other improvements, particularly for EBRT, such as new target concepts, image-guided IMRT and VMAT, simultaneously integrated boost for lymph node boosting, and more paraaortic radiotherapy.[29] The next step is to identify patient-related, disease-related, and treatment-related risk factors and biomarkers for outcome to define risk groups, which can be used for intensification of multimodality treatment in high-risk patients and de-escalation of treatment in low-risk patients (EMBRACE-III). MRI-based IGABT represents a paradigm shift for the treatment of locally advanced cervical cancer which affects clinical practice

and should be used as guidance for future studies of treatment for this type of cancer.

Contributors

RP was the principal investigator of the trial with CK, KT, and JCL as trial coordinators. JCL, KT, CK, and RP were involved in concept and study design. KT, MPS, IJ-S, CH-M, LUF, AES, PH, UM, BS, KB, FH, BR, RC, EvdS-B, EVL, BRP, L-TT, RAN, AACdL, PP, RR, NN, KK, CK, JCL, and RP were involved in the collection and assembly of the data. The Vienna study office (CK, MPS, AES, NN, KK, and RP) managed the study and the data collection supported by the data manager and administrative assistance in Vienna, by KT from Aarhus University, and AACdL and IJS from Utrecht University. Quality assurance was done by CK, MPS, AES, NN, and RP, supported by the study physician, study physicist, data manager, and research fellows from the Department of Radiation Oncology, Medical University of Vienna, Vienna; for EBRT quality assurance was done by KT and a research fellow in Aarhus University. Quality assurance for clinical endpoints was done by MPS and RP (disease outcome) and by KK, KT, and RP (morbidity grade 3–5) supported by research fellows in Aarhus University. KK was the lead for the patient reported outcome substudy. MPS, CK, NN, KT, JCL, RR, and RP were responsible for data analysis and interpretation. MPS, JCL, CK, and RP were responsible for the preparation and writing of the manuscript. All authors contributed to the manuscript and approved the final manuscript. MPS, KK, KT, NN, CK, and RP verified the underlying data. The principal investigator (RP) and all co-authors had full access to all the data, and the principal investigator, corresponding author, and all co-authors had the final responsibility to submit for publication.

Declaration of interests

RP, MPS, AES, KK, NN, and CK report grants from Elekta AB, during the conduct of the study. MPS, AES, and CK report personal fees from Elekta AB, outside of the submitted work. KT reports grants from Varian Medical Systems and the Danish Cancer Society, during the conduct of the study. KT reports grants from Elekta AB and Novo Nordisk Foundation, outside of the submitted work. BRP reports grants from Elekta AB outside of the submitted work. RAN reports grants from Elekta AB, Varian Medical Systems, and Accuray outside of the submitted work. JCL reports grants from Varian Medical Systems outside the submitted work. All other authors declare no competing interests.

Data sharing statement

Data collected for the study, including individual participant data and a data dictionary defining each field in the set, will be made available to others researchers. Deidentified data for all patients will be made available. The data includes registration forms, status at diagnosis, baseline morbidity, status at brachytherapy, treatment characteristics, disease and morbidity follow-up, and vital status. The study protocol, informed consent form, and case record forms will also be made available. The data has been made available since initiation of the EMBRACE-I study, shared through direct exchange of the database exported to Excel or SPSS. Research questions and proposals for analysis of the EMBRACE data can be submitted for approval to the EMBRACE coordinators and the EMBRACE strategic group. Research included analyses of treatment characteristics, descriptive analyses of clinical outcome (in entire cohort and in subgroups), and risk factor analyses of clinical outcome. Institutions having accrued patients to the EMBRACE study can provide proposals for research projects on EMBRACE data in the form of a synopsis containing: aim, hypothesis, and methods and materials. Research proposals are evaluated by the EMBRACE study coordinators (RP, KT, JCL, and CK). After approval of a given research proposal, the EMBRACE data is shared with the research group having submitted the proposal.

Acknowledgments

The EMBRACE-I study was essentially an academic study. Major in-kind contributions were provided through the Department of Radiation Oncology, Medical University Vienna, in form of academic personnel and infrastructure. Significant in-kind contributions were made by Aarhus University. Unrestricted research grants from Elekta AB and Varian Medical Systems provided financial support for personnel in the study office, IT support, and meetings. We thank the patients who participated in this trial. We thank the multidisciplinary clinical and research teams and the principal investigators and the study physicists at the 24 participating centres. We thank the Vienna study office at the Department of Radiation Oncology, Medical University Vienna, for their continuous support; at present Tamara Diendorfer (academic study secretary) and Dragan Misimovic (data manager); in the past Thomas Liederer, Ian Dilworth, and Elke Dörr. We thank Johannes Dimopoulos, Petra Georg, Elena Fidarova, and Mario Federico as study physicians and Petra Trnkova, Karen Nkiwane, and Joanna Gora as study physicists. We thank Stefan Ecker (Vienna), Stephanie Smet (Leuven), Dina Najjari Jamal (Barcelona), Katarina Majercakova (Barcelona), Laura Motisi (Zürich), Israel Fortin (Montreal), Henrike Westerveld (Amsterdam), Susovan Banerjee (New Delhi), Noha Jastaniyah (Riad), Kenji Yoshida (Tottori), Pittaya Dankulchai (Bangkok), Jusheng An (Beijing), Neamat Hegazy (Alessandria), Joyce Siu Yu Wong (Hong kong), and Margit Valgma (Tallin) as research fellows in Vienna for their academic support. We thank the Aarhus EMBRACE research group (KT, JCL, LUF) and the Aarhus research fellows Nina Boje Kibsgaard Jensen, Sofia Spampinato, Anders Schwartz-Vittrup, Monica Serban, Thomas Berger, Marianne Sanggaard Assenholt for their academic support. We thank Sören Bentzen for his support in designing the concept of EMBRACE-I. NN and CK were supported by Austrian Science Fund (FWF, project KLI-695 and project L562-B19). KT was supported by the Danish Cancer Society.

References

1 Cibula D, Pötter R, Planchamp F, et al. The European Society of Gynaecological Oncology/European Society for Radiotherapy and Oncology/European Society of Pathology guidelines for the management of patients with cervical cancer. *Int J Gynecol Cancer* 2018; **28:** 641–55.

2 Han K, Milosevic M, Fyles A, et al. Trends in the utilization of brachytherapy in cervical cancer in the United States. *Int J Radiat Oncol Biol Phys* 2013; **87:** 111–19.

3 Viswanathan AN, Creutzberg CL, Craighead P, et al. International brachytherapy practice patterns: a survey of the Gynecologic Cancer Intergroup (GCIG). *Int J Radiat Oncol Biol Phys* 2012; **82:** 250–55.

4 Haie-Meder C, Pötter R, Van Limbergen E, 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:** 235–45.

5 Pötter R, Haie-Meder C, Van Limbergen E, 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:** 67–77.

6 Pötter R, Dimopoulos J, Georg P, et al. Clinical impact of MRI assisted dose volume adaptation and dose escalation in brachytherapy of locally advanced cervix cancer. *Radiother Oncol* 2007; **83:** 148–55.

7 Kirisits C, Lang S, Dimopoulos J, et al. 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:** 624–30.

8 Serban M, Kirisits C, Pötter R, et al. Isodose surface volumes in cervix cancer brachytherapy: Change of practice from standard (Point A) to individualized image guided adaptive (EMBRACE-I) brachytherapy. *Radiother Oncol* 2018; **129:** 567–74.

9 Pötter R, Georg P, Dimopoulos JC, et al. Clinical outcome of protocol based image (MRI) guided adaptive brachytherapy combined with 3D conformal radiotherapy with or without chemotherapy in patients with locally advanced cervical cancer. *Radiother Oncol* 2011; **100:** 116–23.

10 Lindegaard JC, Fokdal LU, Nielsen SK, et al. MRI-guided adaptive radiotherapy in locally advanced cervical cancer from a Nordic perspective. *Acta Oncol* 2013; **52:** 1510–19.

11 Rijkmans EC, Nout RA, Rutten IH, et al. Improved survival of patients with cervical cancer treated with image-guided brachytherapy compared with conventional brachytherapy. *Gynecol Oncol* 2014; **135:** 231–38.

12 Charra-Brunaud C, Harter V, Delannes M, et al. Impact of 3D image-based PDR brachytherapy on outcome of patients treated for cervix carcinoma in France: results of the French STIC prospective study. *Radiother Oncol* 2012; **103:** 305–13.

13 Sturdza A, Pötter R, Fokdal LU, et al. Image guided brachytherapy in locally advanced cervical cancer: Improved pelvic control and survival in RetroEMBRACE, a multicenter cohort study. *Radiother Oncol* 2016; **120:** 428–33.

14 Prescribing, recording, and reporting brachytherapy for cancer of the cervix. *J ICRU* 2013; **13:** NP.

15 National Cancer Institute. Common Terminology Criteria for Adverse Events v 3·0. 2003. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcaev3.pdf (accessed March 3, 2021).

16 Ramirez PT, Frumovitz M, Pareja R, et al. Minimally invasive versus abdominal radical hysterectomy for cervical cancer. *N Engl J Med* 2018; **379:** 1895–904.

17 Bentzen SM, Dörr W, Gahbauer R, et al. Bioeffect modeling and equieffective dose concepts in radiation oncology—terminology, quantities and units. *Radiother Oncol* 2012; **105:** 266–68.

18 Mazeron R, Castelnau-Marchand P, Dumas I et al. Impact of treatment time and dose escalation on local control in locally advanced cervical cancer treated by chemoradiation and image-guided pulsed-dose rate adaptive brachytherapy. *Radiother Oncol* 2015; **114:** 257–63.

19 Kirisits C, Federico M, Nkiwane K, et al. Quality assurance in MR image guided adaptive brachytherapy for cervical cancer: final results of the EMBRACE study dummy run. *Radiother Oncol* 2015; **117:** 548–54.

20 Mazeron R, Fokdal LU, Kirchheiner K, et al. Dose-volume effect relationships for late rectal morbidity in patients treated with chemoradiation and MRI-guided adaptive brachytherapy for locally advanced cervical cancer: results from the prospective multicenter EMBRACE study. *Radiother Oncol* 2016; **120:** 412–19.

21 Fokdal L, Pötter R, Kirchheiner K, et al. Physician assessed and patient reported urinary morbidity after radio-chemotherapy and image guided adaptive brachytherapy for locally advanced cervical cancer. *Radiother Oncol* 2018; **127:** 423–30.

22 Jensen NBK, Pötter R, Kirchheiner K, et al. Bowel morbidity following radiochemotherapy and image-guided adaptive brachytherapy for cervical cancer: physician- and patient reported outcome from the EMBRACE study. *Radiother Oncol* 2018; **127:** 431–39.

23 Najjari Jamal D, Pötter R, Haie-Meder C, et al. Physician assessed and patient reported lower limb edema after definitive radio(chemo) therapy and image-guided adaptive brachytherapy for locally advanced cervical cancer: a report from the EMBRACE study. *Radiother Oncol* 2018; **127:** 449–55.

24 Smet S, Pötter R, Haie-Meder C, et al. Fatigue, insomnia and hot flashes after definitive radiochemotherapy and image-guided adaptive brachytherapy for locally advanced cervical cancer: an analysis from the EMBRACE study. *Radiother Oncol* 2018; **127:** 440–48.

25 Concato J, Peduzzi P, Holford TR, Feinstein AR. Importance of events per independent variable in proportional hazards analysis. I. Background, goals, and general strategy. *J Clin Epidemiol* 1995; **48:** 1495–501.

26 Peduzzi P, Concato J, Feinstein AR, Holford TR. Importance of events per independent variable in proportional hazards regression analysis. II. Accuracy and precision of regression estimates. *J Clin Epidemiol* 1995; **48:** 1503–10.

27 Shrivastava S, Mahantshetty U, Engineer R, et al. Cisplatin chemoradiotherapy vs radiotherapy in FIGO stage IIIB squamous cell carcinoma of the uterine cervix: a randomized clinical trial. *JAMA Oncol* 2018; **4:** 506–13.

28 Uppal S, Gehrig PA, Peng K, et al. Recurrence rates in patients with cervical cancer treated with abdominal versus minimally invasive radical hysterectomy: a multi-institutional retrospective review study. *J Clin Oncol* 2020; **38:** 1030–40.

29 Pötter R, Tanderup K, Kirisits C, et al. The EMBRACE-II study: the outcome and prospect of two decades of evolution within the GEC-ESTRO GYN working group and the EMBRACE studies. *Clin Transl Radiat Oncol* 2018; **9:** 48–60.

30 Kirchheiner K, Nout RA, Lindegaard JC, et al. Dose-effect relationship and risk factors for vaginal stenosis after definitive radio(chemo)therapy with image-guided brachytherapy for locally advanced cervical cancer in the EMBRACE study. *Radiother Oncol* 2016; **118:** 160–66.

31 Fokdal L, Tanderup K, Pötter R et al. Risk factors for ureteral stricture after radiochemotherapy including image guided adaptive brachytherapy in cervical cancer: results from the EMBRACE studies. *Int J Radiat Oncol Biol Phys* 2019; **103:** 887–94.

32 Nomden CN, Pötter R, de Leeuw AAC, et al. Nodal failure after chemo-radiation and MRI guided brachytherapy in cervical cancer: patterns of failure in the EMBRACE study cohort. *Radiother Oncol* 2019; **134:** 185–90.

33 Lindegaard JC, Assenholt M, Ramlov A, et al. Early clinical outcome of coverage probability based treatment planning for simultaneous integrated boost of nodes in locally advanced cervical cancer. *Acta Oncol* 2017; **56:** 1479–86.

34 Lindegaard JC, Petric P, Lindegaard AM, et al. Evaluation of a new prognostic tumor score in locally advanced cervical cancer integrating clinical examination and magnetic resonance imaging. *Int J Radiat Oncol Biol Phys* 2020; **106:** 754–63.

35 Spampinato S, Fokdal L, Pötter R et al. Importance of the ICRU bladder point dose on incidence and persistence of urinary frequency and incontinence in locally advanced cervical cancer: an EMBRACE analysis. *Radiother Oncol* 2020; published online Oct 14. https://doi.org/10.1016/j.radonc.2020.10.003.

36 Jensen NBK, Pötter R, Spampinato S et al. Dose-volume effects and risk factors for late diarrhoea in cervix cancer patients after radiochemotherapy with image-guided adaptive brachytherapy in the EMBRACE I study. *Int J Radiat Oncol Biol Phys* 2021; **109:** 688–700.