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Original article

# Image guided brachytherapy in locally advanced cervical cancer: Improved pelvic control and survival in RetroEMBRACE, a multicenter cohort study

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ABSTRACT

*Purpose:* Image guided brachytherapy (IGBT) for locally advanced cervical cancer allows dose escalation to the high-risk clinical target volume (HRCTV) while sparing organs at risk (OAR). This is the first comprehensive report on clinical outcome in a large multi-institutional cohort.

*Patients and methods:* From twelve centres 731 patients, treated with definitive EBRT ± concurrent chemotherapy followed by IGBT, were analysed. Kaplan–Meier estimates at 3/5 years were calculated for local control (LC, primary endpoint), pelvic control (PC), overall survival (OS), cancer specific survival (CSS). In 610 patients, G3–4 late toxicity (CTCAEv3.0) was reported.

*Results:* Median follow up was 43 months, percent of patients per FIGO stage IA/IB/IIA 22.8%, IIB 50.4%, IIIA–IVB 26.8%. 84.8% had squamous cell carcinomas; 40.5% lymph node involvement. Mean EBRT dose was 46 ± 2.5 Gy; 77.4% received concurrent chemotherapy. Mean D90 HRCTV was 87 ± 15 Gy ($EQD2_{10}$), mean D2cc was: bladder 81 ± 22 Gy, rectum 64 ± 9 Gy, sigmoid 66 ± 10 Gy and bowel 64 ± 9 Gy (all $EQD2_3$). The 3/5-year actuarial LC, PC, CSS, OS were 91%/89%, 87%/84%, 79%/73%, 74%/65%. Actuarial LC at 3/5 years for IB, IIB, IIIB was 98%/98%, 93%/91%, 79%/75%. Actuarial PC at 3/5 years for IB, IIB, IIIB was 96%/96%, 89%/87%, 73%/67%. Actuarial 5-year G3–G5 morbidity was 5%, 7%, 5% for bladder, gastrointestinal tract, vagina.

*Conclusion:* IGBT combined with radio-chemotherapy leads to excellent LC (91%), PC (87%), OS (74%), CSS (79%) with limited severe morbidity.



The standard of care for locally advanced cervical cancer is external beam radiotherapy (EBRT) with concurrent chemotherapy followed by brachytherapy (BT) [1]. BT is a crucial component and has been shown to be an essential independent treatment factor associated with improved pelvic control [2] and overall survival [2,3]. In most institutions worldwide, BT is based on orthogonal X-rays for treatment planning with standard treatment plans irrespective of tumour stage, size, response to EBRT, or the topographic position of organs at risk (OAR).

Over the past 15 years, image guided brachytherapy (IGBT) with magnetic resonance imaging (MRI) or computed tomography (CT) guidance has been an emerging subject. IGBT allows for individualisation of treatment with dose adaptation, and dose escalation when appropriate, to take into account tumour size at diagnosis, and at the time of BT, while simultaneously sparing OAR [4,5]. Mono-institutional reports from some pioneering institutions have shown 3-year local control rates ranging from 85%- to 97%, with

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limited or reduced toxicity [6–15]. These figures compare favourably with historical series using conventional BT [16–21], but the patient numbers were relatively small (40–225 patients).

In 2008, a prospective observational study, EMBRACE (IntErnational MRI-guided BRAchytherapy in CErvical cancer, www.embracestudy.dk), was launched to investigate the clinical outcome of MRI-based IGBT when implemented in a multi-institutional setting with systematic application of the Gynaecological (Gyn) GEC-ESTRO (Groupe Européen de Curiethérapie (GEC) and the European Society for Radiotherapy & Oncology) recommendations on contouring [4] and reporting [5]. This paper reports the outcome of a large patient cohort, the RetroEMBRACE cohort, treated with IGBT in mono-institutional settings prior to participation in EMBRACE.

## Material and methods

### *Study design*

RetroEMBRACE is a retrospective observational study involving 12 institutions worldwide. Institutions were invited to participate based on their known use of IGBT and active participation in the Gyn GEC ESTRO network (www.estro.org). The patient inclusion criteria were: histologically confirmed cervical cancer, treatment with curative intent by definitive EBRT (±concomitant chemotherapy) followed by IGBT with MRI/CT guidance, and treatment outside the EMBRACE study. Patients with para-aortic nodal disease as the exclusive site of extra-pelvic disease at the time of diagnosis were also eligible.

Patient, tumour, treatment and outcome data were collected by direct entry from participating institutions into a web-based database (www.retroembrace.com). Data collection began in October 2010 and closed in September 2013. Due to the variable launch time of IGBT in the participating institutions, patients treated between January 1998 and August 2012 were included. Seven centres included 525 consecutive patients (71.8%) and five centres 206 (28.2%) selected patients depending on the availability of MRI for treatment planning.

All patients were clinically staged according to the International Federation of Gynaecology and Obstetrics (FIGO) criteria [22]. The clinical tumour size was defined as the maximum width of the palpable mass on pelvic examination. Tumour size on MRI was defined as the maximum width on axial T2-weighted sequences. Pathological lymph nodes were defined as lymph nodes >1 cm in size, loss of oval shape on imaging, or positive on PET CT imaging. In 3 centres histological lymph node staging was performed through laparoscopy/laparotomy (188 patients). Imaging for distant metastases followed institutional guidelines and included chest X-ray as a minimum.

In the centres using MRI-based IGBT, the high-risk clinical target volume (HRCTV) and/or the intermediate-risk CTV (IRCTV) was contoured according to Gyn GEC-ESTRO recommendations I [4]. In those using CT guidance, only the HRCTV was contoured [23]. Dose volume histogram (DVH) parameters for the HRCTV, IRCTV and OAR were calculated and reported according to Gyn GEC-ESTRO Recommendations II [5]. Dose prescription for target and dose constraints for OAR was applied according to institutional guidelines. The equieffective dose in 2 Gy per fraction (EQD2) from EBRT and BT was calculated using an a/β of 10 Gy for tumour ($EQD2_{10}$) and 3 Gy for OAR ($EQD2_3$), and a half-time for sublethal damage repair of 1.5 h for pulsed dose rate (PDR) BT [5,24].

Patients were assessed for disease status and adverse effects according to institutional guidelines at regular intervals. In general, this was every 3 months in the first 2 years, every 6 months for the next 3 years, then annually thereafter.

### *Endpoints and statistical analysis*

The primary endpoint was local control (LC), defined as absence of disease in the cervix (uterus), upper vagina and parametria on clinical examination, imaging, and biopsy.

Secondary endpoints were pelvic control (PC), overall survival (OS), cancer-specific survival (CSS) and severe late toxicity. Pelvic control was defined as absence of local and nodal disease within the pelvis. OS was defined as death from any cause and CSS as death from cervical cancer. Distant failure was any extra-pelvic nodal and/or organ recurrence. Severe late toxicity was defined as G3–G5 complications (Common Toxicity Criteria v 3.0) [25] present at or after 91 days from completion of RT.

Time to event analyses at 3 and 5 years were computed using the Kaplan Meier method and log rank test and IBM SPSS v.21 statistical software (Chicago, IL). Time intervals for survival analyses were calculated from the date of biopsy to the date of event or last follow-up. Patients lost to follow up were censored at the time of last follow up.

## Results

A total of 852 patients were registered, 49 patients were excluded as there was no information on disease status. A further 72 patients were excluded for receiving supplementary treatments (neo-adjuvant/adjuvant chemotherapy or surgery as standard treatment) leaving 731 patients for analysis (Electronic appendix Fig. 1). Plausibility checks were performed for major patient, tumour, treatment, and outcome characteristics to identify and correct major reporting errors.

### *Patients*

Median age at diagnosis was 53 years (range 23–91). FIGO stage distribution was IA = 2 (0.3%), IB = 123 (16.8%), IIA = 42 (5.7%), IIB = 368 (50.3%), IIIA = 23 (3.1%), IIIB = 145 (19.8%), IVA = 23 (3.1%) and IVB = 5 (0.7%). 620/731 patients (84.8%) had squamous cell carcinomas, 71 (9.7%) adenocarcinomas, 29 (4%) adenosquamous carcinomas and 11 (1.5%) other histology (Table 1). There was some variation in stage distribution between the different centres as only selected patients were treated with IGBT in some centres due to resource limitations and variations in treatment policies (Electronic appendix Table 1).

Nodal status was assessed by imaging in all patients. 188/731 patients (25.7%) had additional laparoscopic lymph node staging. 435/731 patients (59.5%) were node-negative and 296 (40.5%) node-positive. Tumour width at diagnosis was assessed clinically in 603/731 patients (82.5%, median 5 cm, range 1–10 cm) and on MRI in 581/731 patients (79.5%, median 4.7 cm, range 1–10.5 cm).

**Table 1**
Patient and tumour characteristics.

| Variable | | No of patients *n*/% |
|---|---|---|
| Median age (years) | 53 (23–91) | 731 |
| FIGO stage | 1B | 123 (16.8%) |
| | 2A | 42 (5.6%) |
| | 2B | 368 (50.3%) |
| | 3A | 23 (3.1%) |
| | 3B | 145 (19.8%) |
| | 4A | 23 (3.1%) |
| Histology | Squamous cell Ca | 591 (84.7%) |
| | Adenocarcinoma | 9.3% |
| | Others | 6% |
| Median tumour width at diagnosis | Clinically: 50 mm | MRT: 46 mm |
| Nodal status | N+ | 40% |
| | N− | 60% |
| CHT | Yes: 566 (76.5%) | No: 165 (22.5%) |

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