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Original article

Radiation therapy combined with hyperthermia versus cisplatin for locally advanced cervical cancer: Results of the randomized RADCHOC trial

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ABSTRACT

Background: Chemoradiation (RT-CT) is standard treatment for locally advanced cervical cancer (LACC). This study tried to establish if radiotherapy combined with hyperthermia (RT-HT) should be preferred in bulky and/or FIGO-stage ⩾III.

Methods: In this open-label, multicenter randomized trial, patients with LACC were randomly assigned by a computer-generated, biased coin minimization technique to RT-CT or RT-HT. Central randomization was done with stratification by FIGO-stage, tumour diameter and nodal status. Primary endpoint was event free survival (EFS). Secondary endpoints were pelvic recurrence free survival (PRFS), overall survival (OS) and treatment related toxicity. Analysis was done by intention to treat.

Results: The trial was closed prematurely (87 of 376 planned patients enrolled: 43 RT-CT; 44 RT-HT). Median follow-up time was 7.1 years. The cumulative incidence of an event was 33% in the RT-CT group and 35% in the RT-HT group. The corresponding hazard rate (HR) for EFS was 1.15 (CI: 0.56–2.36, $p = 0.7$). Also the hazards for PRFS (0.94; CI 0.36–2.44) and OS (1.04; CI 0.48–2.23) at 5 years were comparable between both treatment arms as was grade ⩾3 radiation related late toxicity (6 RT-CT and 5 RT-HT patients).

Conclusion: After 25% of intended accrual, data suggest comparable outcome for RT-CT and RT-HT.

Radiotherapy combined with cisplatin-based chemotherapy (RT-CT) is considered standard treatment for locally advanced cervical cancer (LACC) following publication of several randomized trials [1–4]. The beneficial effect of chemotherapy seemed less obvious in patients with FIGO-stage III–IV disease [1] whereas similar improved outcome was demonstrated mainly in stage III and bulky disease by adding regional hyperthermia to radiotherapy (RT-HT) [5]. The question has been raised whether treatment choice could be better individualized according to specific tumour characteristics such as FIGO-stage and/or tumour bulk. This phase III study was thus designed, the main hypothesis being that RT-HT might be more effective than RT-CT for FIGO-stage ⩾III and/or bulky disease (>6 cm) and vice versa RT-CT more effective than RT-HT for FIGO-stage ⩽IIB and/or non-bulky disease (⩽6 cm). The trial was closed prematurely due to poor accrual. We here report long term results of 84 eligible patients enrolled in the study.

Materials and methods

Eligibility

The study protocol and consent procedure were approved by the Medical Ethics Review Board of participating centres. Patients with a biopsy proven cervical carcinoma FIGO-stage IB–IIA (⩾4 cm) or IIB–IVA, negative para-aortic lymph nodes (CT-scan short axis diameter ⩽ 1 cm), suitable to undergo radical radiotherapy combined with chemotherapy and/or hyperthermia and able to undergo brachytherapy, were eligible.

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Clinical staging included pelvic examination under anaesthesia; pelvic MR-scan; abdominal CT-scan and chest radiography. CT-guided fine needle aspiration was recommended for enlarged lymph nodes (short axis diameter > 1 cm). Retroperitoneal lymph node dissection of enlarged nodes was allowed.

After obtaining informed consent patients were randomly assigned to radiotherapy combined with cisplatin (RT-CT) or hyperthermia (RT-HT).

Radiation treatment

For external beam radiation (EBRT) the target volume was defined using CT imaging to include all gross tumour, the uterine corpus, the proximal 2/3 of the vagina, parametrial tissues and iliac vessels. In case of negative pelvic lymph nodes the cranial level was set at L5–S1. In case of positive lymph nodes at least 2 additional negative levels were included, the maximal cranial level set at L3–L4. A dose of 50 Gy was delivered in 25 daily fractions, 5 days a week. Dose specification and homogeneity requirements were according to ICRU-50.

Brachytherapy was scheduled in the final weeks of EBRT delivering a dose to point A of 21 Gy in 3 weekly fractions (HDR) or 32 Gy in 1–2 weekly fractions (LDR 40–70 cGy/h or PDR 40–70 cGy/pulse) or 29 Gy in 1–2 weekly fractions (MDR 70–110 cGy/h or PDR 70–110 cGy/pulse). For brachytherapy an intra-uterine tandem and vaginal ovoids were used not allowing modifications in applicators (e.g. extra interstitial needles). For dose description, definitions according to the classical Manchester system were used. For normal tissue the ICRU bladder (BRP) and rectal (RRP) reference points were obtained.

An additional EBRT boost to parametrial tissues and/or involved pelvic lymph nodes was allowed. The EQD2 dose constraint for the BRP and RRP was 75 and 80 Gy, respectively, and 60 Gy for small bowel. Overall treatment time was not allowed to exceed 49 days and in case of an EBRT boost 56 days.

Chemotherapy

Patients randomized to RT-CT were treated weekly during EBRT with 40 mg/m^2 cisplatin intravenously. Haemoglobin level (Hb), WBC-count, platelets and serum creatinine were checked weekly. Hb was kept $\geqslant$7.5 mmol/l, if necessary by means of red blood cells.

Chemotherapy was administered at the department of medical oncology of the respective participating centres.

Regional pelvic hyperthermia

Patients allocated to RT-HT were treated weekly with regional hyperthermia during EBRT with a planned total of 5 treatments, delivered 1–4 h after radiotherapy in accordance with ESHO quality guidelines for regional hyperthermia [6]. All hyperthermia treatments were applied at the Erasmus MC Rotterdam BSD-2000 system, (BSD Medical Corporation, Salt Lake City, USA). Each treatment was planned to last 60 min after 30 min of heating time. The power output was increased up to patients' tolerance.

Toxicity

Adverse effects were scored according to the Common Toxicity Criteria guidelines version 2.0 [7].

Follow-up

Two months after treatment a follow-up visit was planned to assess local tumour response by physical examination. Thereafter, patients were seen for regular follow-up visits 3 monthly for 3 years, 6 monthly during the fourth and fifth years, and annually up to 10 years.

Endpoints

Primary endpoint was event free survival (EFS), i.e. time from randomization to the date of first event, defined as an incomplete response, any pelvic or distant relapse, or death due to tumour progression or toxicity. Secondary endpoints were pelvic recurrence free survival (PRFS, i.e. within the irradiated volume), overall survival (OS), and radiation treatment related toxicity. Time to any event was calculated from the date of randomization to the date of event, censoring patients alive and event-free at date of last follow-up. Following RT-CT an EFS rate at 3 years of 65% and 31% was expected for small and large tumours, respectively. Taken an expected prevalence of 20% and 80% of small and large tumours, based on previous studies [5], a relative hazard rate of 0.68 for the RT-HT arm was hypothesized corresponding to an overall increase of EFS at 3 years of 13%. To detect this difference with $\alpha = 0.05$ (two-sided) and 80% power, 216 events had to be observed. The accrual goal was thus set at 376 patients in 5 years.

Randomization

For randomization the radiation oncologist contacted the central Data Centre (Erasmus MC, Rotterdam) by phone. Patients were stratified with respect to FIGO-stage (IB–IVA), tumour diameter (physical exam; cutoff 6 cm), clinical nodal status (N0 versus N+) and treating centre. Patients were randomly assigned by a computer-generated, biased coin minimization technique to RT-CT or RT-HT in a proportion of 1:1. The outcome of allocation was computer generated and subsequently unmasked.

Statistical methods

Analysis was done by intention to treat. SPSS for Windows software version 23.0 was used. Independence between variables was assessed with the Chi-Square test or with Fisher's exact test, depending upon the number of patients and/or events tested. EFS was estimated with the product limit method of Kaplan–Meier. Comparison of survival was done using the log-rank test. Cox's proportional hazards model was used to test the joint effect of previously screened prognostic factors.

Results

This trial was closed prematurely because of poor accrual after 87 patients being enrolled between 2003 and 2009 (23% of 376 patients planned). Three patients were excluded from analysis: two with PAO lymph node metastases and one with distant metastasis. Intention to treat analyses encompassed 84 patients: 42 patients in the RT-CT arm and 42 patients in the RT-HT arm (Fig. 1). Patient and tumour characteristics were comparable (Table 1).

Outcome

At the time of analysis median follow-up time was 7.1 years (range 0.3–10.0). Twenty-six patients (31%) had died: 22 patients (26%) from cervical cancer, 1 patient (1%) from treatment related morbidity and 1 patient (1%) immediately following her 1st brachytherapy session (no autopsy was performed).

The cumulative incidence of an event was 33% (14/42) in the RT-CT group and 35% (15/42) in the RT-HT group. The corresponding hazard rate for event free survival (EFS) was 1.15; 95% CI 0.56–2.39. $p = 0.7$ (Fig. 2). A pelvic treatment failure (i.e. within the

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