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CLINICAL INVESTIGATION **Cervix**

LONG-TERM IMPROVEMENT IN TREATMENT OUTCOME AFTER RADIOTHERAPY AND HYPERTHERMIA IN LOCOREGIONALLY ADVANCED CERVIX CANCER: AN UPDATE OF THE DUTCH DEEP HYPERTHERMIA TRIAL

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Purpose: The local failure rate in patients with locoregionally advanced cervical cancer is 41–72% after radiotherapy (RT) alone, whereas local control is a prerequisite for cure. The Dutch Deep Hyperthermia Trial showed that combining RT with hyperthermia (HT) improved 3-year local control rates of 41–61%, as we reported earlier. In this study, we evaluate long-term results of the Dutch Deep Hyperthermia Trial after 12 years of follow-up.

Methods and Materials: From 1990 to 1996, a total of 114 women with locoregionally advanced cervical carcinoma were randomly assigned to RT or RT + HT. The RT was applied to a median total dose of 68 Gy. The HT was given once weekly. The primary end point was local control. Secondary end points were overall survival and late toxicity.

Results: At the 12-year follow-up, local control remained better in the RT + HT group (37% vs. 56%; $p = 0.01$). Survival was persistently better after 12 years: 20% (RT) and 37% (RT + HT; $p = 0.03$). World Health Organization (WHO) performance status was a significant prognostic factor for local control. The WHO performance status, International Federation of Gynaecology and Obstetrics (FIGO) stage, and tumor diameter were significant for survival. The benefit of HT remained significant after correction for these factors. European Organization for Research and Treatment of Cancer Grade 3 or higher radiation-induced late toxicities were similar in both groups.

Conclusions: For locoregionally advanced cervical cancer, the addition of HT to RT resulted in long-term major improvement in local control and survival without increasing late toxicity. This combined treatment should be considered for patients who are unfit to receive chemotherapy. For other patients, the optimal treatment strategy is the subject of ongoing research. © 2008 Elsevier Inc.

Radiotherapy, Hyperthermia, Cervical cancer, Randomized study, Long-term outcome.

INTRODUCTION

Radiotherapy (RT) is the mainstay in the management of patients with locoregionally advanced cervix carcinoma. After RT alone, locoregional failure rates for the more advanced stages ranged from 41–72% (1, 2). Local control is a prerequisite for cure, and locoregional failure generally indicates a fatal course of the disease. If locoregional tumor control can be achieved definitively, the potential gain in survival is estimated to be 50–60% (3, 4).

Several large trials showed an advantage of combining RT with chemotherapy (CT) in terms of both improved local tumor control and better overall survival. Similar advantages were found in trials that combined RT with hyperthermia (HT) (5).

Hyperthermia, the artificial increase in tissue temperature to 40°C – 44°C, is an effective cytotoxic agent, especially in cells that are in a hypoxic nutrient-deprived low-pH environment. These conditions are commonly found in malignant tumors and make cells relatively resistant to RT (6). In addition to directly killing cells at temperatures of 40°C – 44°C, HT also increases the cytotoxic effect of RT. Experimental studies showed that it interfered with the cellular repair of

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radiation-induced DNA damage, thereby enhancing the cytotoxic effect of RT (7). Hyperthermia also increased blood flow, which may improve tissue oxygenation and make cells more sensitive to RT (8). Several randomized studies showed an increase in response rate and tumor control in various tumor sites when RT was combined with HT (9–12).

In 1990, the Dutch Deep Hyperthermia Trial (DDHT) started investigating the effect of the addition of HT to standard RT in patients with locally advanced rectal, bladder, and cervical cancer. The first results were published in 2000 (13, 14). A significant improvement in response rate and local control was found with the addition of HT. Overall survival also significantly improved after adjustment for prognostic factors. For patients with primary or recurrent rectal cancer, no improvement in local control or survival could be shown, and for patients with bladder cancer, the initial gain in local control disappeared during follow-up. Although there were no significant interactions between treatment group and tumor site for complete response, local control, and overall survival, the subgroup of patients with locally advanced cervical cancer appeared to benefit most from the addition of HT. However, at a median of 43 months, follow-up time was relatively short. In this study, we report on long-term pelvic control, overall survival, and toxic effects in patients with locally advanced cervical cancer who were treated in the DDHT.

METHODS AND MATERIALS

Patients

Patients were eligible for the trial if they required primary standard RT for cervical cancer International Federation of Gynaecology and Obstetrics (FIGO) Stages IIB (with extension to the lateral parametrium), IIIB (fixation to the pelvic wall or ureter obstruction causing hydronephrosis), or IVA (invasion of the bladder or rectum). In all patients, diagnosis was confirmed by means of histopathologic examination. Patients needed to be in reasonable general condition, defined as World Health Organization (WHO) performance status less than 2 and expected survival exceeding 6 months. Patients with a pacemaker or metal implant in the pelvic region larger than 10 cm were excluded because these are absolute contraindications for HT.

The study was approved by the local medical ethics committees of all participating hospitals.

Following informed consent, patients were randomly assigned to receive standard RT or standard RT plus HT.

Radiotherapy

External beam RT was given in 23–28 fractions of 2.0–1.8 Gy to a total dose of 46.0–50.4 Gy (mean external beam dose, 48.3 $\pm$ 5.9 [SD] Gy) using a four-field box technique with 6–10-MV photons. In the Daniel den Hoed Cancer Center, para-aortal lymph nodes were routinely included in the external RT field. In the other institutes, the para-aortal region was included only if there were metastases in the common iliac or para-aortal lymph nodes. Fifty-two women (46%) underwent para-aortal irradiation, 27 (48%) in the RT group and 25 (43%) in the RT + HT group. In patients with inguinal lymph node metastases, the inguinal regions were included.

In the Rotterdam area, high-dose-rate brachytherapy was given to 50 women (70%) to either a total dose of 17 Gy applied in two fractions of 8.5 Gy or to 18 Gy in three fractions of 6.0 Gy to point A. In the Amsterdam area, 36 women (84%) received a single brachytherapy application of 20–30 Gy at 1-Gy/h medium dose rate to achieve a total dose of 70 Gy to point A. At randomization, stratification was by radiation institute; therefore, brachytherapy schedules were equally distributed over both arms of the study.

An additional external beam sidewall boost was given to 34 patients with residual tumor in the parametrium at the time of the first brachytherapy application. These patients received three to seven boost fractions of 1.8–2 Gy, up to a total pelvic side-wall dose of 60 Gy by using two small opposed 6–10-MV photon fields. Of these, 14 patients were randomly assigned to the RT group, and 20 to the RT + HT group. Patients with involved lymph nodes received a similar boost to a total dose of 60 Gy.

Dose specifications and target-volume definition were according to the International Commission on Radiation Units and Measurements report 50. Median overall treatment times were 48 days in the RT + HT group (range, 35–116 days) and 50 days in the RT group (range, 35–121 days).

Hyperthermia

Deep locoregional HT was prescribed once weekly to a total of five times during the 5 weeks of external beam RT.

Of 90 minutes' treatment time, a maximum of 30 minutes was used for warming up to intratumor temperatures greater than 42°C. In the next 60 minutes, intrapelvic temperatures were kept as high and homogeneous as patient tolerance permitted. Patients were carefully instructed to mention any uncomfortable feelings that could be suggestive of hot spots during treatment. If symptoms occurred, treatment settings such as phase, amplitude, frequency, and power were adjusted accordingly.

For thermometry in Rotterdam, Bowman probes were placed in the bladder, rectum, and vagina. Thermal mapping was performed every 5 minutes with a step size of 1 cm and a maximum map length of 14 cm. Pulse rate and blood pressure were measured automatically before and every 5 minutes during treatment, and oral temperature was measured at 0, 15, 30, 60, and 90 minutes. In the two other centers, multisensor thermocouple probes were read out during the power-off pulse of the heating system.

Patients were recruited by 11 RT institutes in The Netherlands. Radiotherapy was given in the recruiting institute, and for their weekly HT treatment, patients were referred to one of three institutes with HT facilities. In the Daniel den Hoed Cancer Center, the BSD-2000 system was used (BSD Medical Corp., Salt Lake City, UT). In the other centers, custom-built systems were used: a four-waveguide applicator system was used in the Academic Medical Center Amsterdam, and a Coaxial TEM applicator was used in University Medical Center Utrecht. For the three systems, the energy distribution in a human pelvic-size phantom is the same (15).

Study design

Primary end points of the trial were complete response and pelvic tumor control. Follow-up visits were scheduled 1 month after treatment, once every 3 months during the first 2 years, and every 4–6 months thereafter. After the first 2 years, follow-up visits were planned in accordance with the Association of Cancer Centers Guidelines. Generally, patients visited a gynecologic oncologist and a radiation oncologist alternately.

A complete response was defined as disappearance of all tumor in the irradiated volume, established 3 months after treatment. Response was assessed by using anamnestic information, physical