

## **Oncothermia in HIV positive and negative locally advanced cervical cancer patients in South Africa**

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# Oncothermia in HIV positive and negative locally advanced cervical cancer patients in South Africa

## *Abstract*

**Aim:** Investigate the clinical, economic and cellular effects of the addition of oncothermia to standard treatment for HIV positive and negative locally advanced cervical cancer patients in public healthcare in South Africa. **Objectives:** Evaluate the effect that the addition of oncothermia has on local disease control, progression free survival, overall survival at 2 years, treatment toxicity, quality of life, economic impact and HIV status of participants. Radiobiology investigations will evaluate thermo-radiosensitivity and the molecular markers for thermo-radiosensitivity. **Methodology:** Phase III randomised clinical trial involving 236 HIV negative and positive stage IIb-III locally advanced cervical cancer patients. Treatment includes cisplatin, external beam radiation and brachytherapy. The study group will receive oncothermia treatments. Participants will be monitored for two years after completion of treatment. **Hypothesis:** The addition of oncothermia to standard treatment protocols will result in improved clinical response without increasing treatment toxicity in HIV positive patients or raising healthcare costs.

## *Introduction*

More than 80% of hospital patients in Africa receive treatment in public healthcare facilities where resources and funding are limited.<sup>1</sup> The economic impact of cancer extends from the financial costs of treatment, rehabilitation, end-of-life care and loss of life to the economic costs of days off work, loss of productivity and the social-economic pressures on the family and community of cancer patients.<sup>2</sup> Sub-Saharan Africa has the highest HIV prevalence in the world.<sup>3</sup> It is a growing concern that the HIV status of a person and the anti-retroviral medications increase the patients' sensitivity to toxicity from radiation therapy and chemotherapy.<sup>4,5,6</sup> There is therefore a strong need for the investigation and application of technologies which can increase cancer treatment efficacy without increasing the treatment costs in Africa. Research from the Netherlands indicates that hyperthermia technology may increase the treatment efficacy whilst lowering the healthcare costs of cervical cancer patients.<sup>7</sup> The investigation of the use of affordable hyperthermia technology is therefore warranted.

## *Background*

Cervical cancer is classified as an AIDS defining illness by the World Health Organisation. Over 80% of the 555 000 new cervical cancer diagnoses globally per year will occur in developing countries where HIV is prevalent.<sup>8</sup> Cervical Cancer is the second most prevalent female cancer in South Africa with around 5 000 new cases diagnosed per year. This was 16.24% of all new cancer diagnoses in 2001, the year in which the last official national cancer statistics were published.<sup>9</sup> Although recent statistics on cervical cancer in South Africa are lacking, doctors at the Charlotte Maxeke Johannesburg Academic hospital estimate that 20% of radiation oncology patients have cancer of the cervix, 60% of which are in stage IIIb at the time of diagnosis. An estimated 30% of the cervical cancer patients in public healthcare facilities are HIV positive.<sup>10</sup> cancer in South Africa with around 5 000 new cases diagnosed per year. This was 16.24% of all new cancer diagnoses in 2001, the year in which the last official national cancer statistics were published. <sup>9</sup>Although recent statistics on cervical cancer in South Africa are lacking, doctors at the Charlotte Maxeke Johannesburg Academic hospital estimate that 20% of radiation oncology patients have cancer of the cervix, 60% of which are in stage IIIb at the time of diagnosis. An estimated 30% of the cervical cancer patients in public healthcare facilities are HIV positive.<sup>10</sup>

## *Aim*

To investigate the clinical, economic and cellular effects of the addition of oncothermia to standard treatment protocols for HIV positive and negative locally advanced cervical cancer patients in public healthcare in South Africa.

## ***Methodology***

**Study-design:** Phase III randomised clinical trial. **Sample:** 236 HIV negative and HIV positive stage IIIb-III locally advanced cervical cancer patients will be recruited. This is based on the estimated required sample size for a two-sample comparison of survivors' function at two years. The statistical significance is defined as a two-sided alpha  $<0.05$  for a log-rank test, with a constant Hazard ratio of 0.5693, a statistical power of 90%, a 15% withdrawal rate and an estimated 140 events. We anticipate at least 50% of recruited participants will be in Stage III of the disease and around 30% of participants will be HIV positive. **Randomisation:** The participants will be divided into a control group (N=118) and a study group (N=118) and the sampling method used will be stratified random sampling (stratum: HIV status). Location: Charlotte Maxeke Johannesburg Academic Hospital, Gauteng, South Africa. **Treatment:** Participants from both groups will receive 3 doses of cisplatin (80mg/m<sup>2</sup>) administered three weeks apart, external beam radiation (50Gy administered over 25 fractions of 2Gy) and 3 HDR intracavitary brachytherapy treatments of 8Gy each. The study group will receive two 60 minute modulated electro-hyperthermia (oncothermia) treatments per week during the external beam radiation therapy (total 10 treatments). **Duration:** The study is scheduled to start in early 2013 and the recruitment period is expected to take two years. Participants will be monitored for two years after completion of treatment protocols. The total study duration is expected to be four years. Preliminary results for the local disease control and radiobiology research are expected to be available within the first three years. **Radiobiology Research:** Radiobiology research will be conducted on tissue and tumour samples in order to study the effect that heating tumours has on the systemic and local response and toxicity resulting from treatment with ionising radiation.

## ***Objectives***

**Primary Objectives:** Evaluate the effect that the addition of oncothermia has on local disease control at 6 months (assessed by PET scans); progression free survival at 12, 18 and 24 months and overall survival at 2 years (and the cause of death) in HIV positive and negative cervical cancer patients. **Secondary Objectives:** To evaluate the adverse effects that can be directly attributed to oncothermia treatments. To evaluate the effects of oncothermia on tolerability and toxicity of the prescribed treatments. To evaluate the economic impact of the addition of oncothermia to standard treatment protocols in public healthcare (based on quality adjusted life years). To evaluate the effect of the addition of oncothermia on the quality of life of patients (EuroQOL EQ-5D-5L questionnaire and the EORTC QLQ-CX23 cervical carcinoma specific questionnaire). To evaluate the effect, if any, of oncothermia treatments on the HIV disease status of HIV positive participants by assessing the CD4 count; HIV viral load and the concurrent AIDS-defining conditions. To describe cervical cancer recurrence patterns in both groups by loco-regional and distant recurrences and by initial stage and suspicion for nodal metastasis pre-treatment. **Radiobiology:** To evaluate thermo-radiosensitivity by measuring DNA damage (double strand breaks) in lymphocytes in response to ionising radiation combined with oncothermia. Haematological samples will be taken from patients in all four groups before and after the administration of radiation therapy. Double strand breaks will be measured using Micronucleus (MN) assays and the results will be analysed in order to determine whether the addition of oncothermia had an effect on the systemic toxicity of ionising radiation therapy in HIV positive and HIV negative cancer patients. To investigate the molecular markers for thermo-radiosensitivity. This will be done by comparing gene expression profiles of cells extracted from biopsies of thermo-radiosensitive and thermo-radio-resistant tumours. Gene profiling of tumour samples will be used to identify potential molecular markers in the tumour cells which are associated with increased response or with resistance to radiochemotherapy combined with oncothermia.

## ***Expected outcomes***

It is expected that the addition of oncothermia to standard treatment protocols will result in improved local disease control and improved two year survival rates without increasing the treatment toxicity. We hypothesise that the addition of oncothermia will result in a reduction in healthcare costs associated with the treatment of cervical cancer.

## ***Study rationale***

This will be the first trial to date to investigate the effects of hyperthermia on HIV positive cancer patients and will be the first hyperthermia trial to be conducted in Africa. This will be the first phase III trial investigating oncothermia in cervical cancer patients and the first phase III trial investigating the trimodality treatment of cervical cancer patients. The study will investigate the economic impact of the addition of oncothermia to public healthcare protocols in Africa. The radiobiology research and genetic profiling is also unique in the field.

## ***Acknowledgements***

The hyperthermia device being used is the EHY2000 Plus which is being supplied by Oncotherm GmbH.

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