

Comment to C.A. Minnaar's results
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The quality of the study design is an important issue. Per my view, the applied full protocol of radiotherapy by high-brachytherapy, with dose 74 Gy and increased cisplatin - in principle, is the best international protocol for cervix carcinoma. In this study, made by Dr. C. Minnaar, Oncothermia shows significantly better local control after evaluating 100 patients (42%). Differences in survival rates approaching the level of confidence is already at 6 months (when the differences are usually minimal), and an advantage in the quality of life is definitely significant (0.7-3% chance of error). The results are quite remarkable, especially considering the factor of proper control.

In previous hyperthermia studies for advanced cervix cancer of van der Zee (2000) and Harima (2001), the radiotherapy dose was less than 60 Gy. Accordingly, no significant differences were shown against control, whereas in comparison with the proper therapy (dose > 70 Gy) results in bimodal thermo-radio-therapy in Harima's and van der Zee's research were worse. The international multicenter study Vasanthan (2005) revealed these problems. Vasanthan's study used an adequate radiotherapy (72 Gy, but without amplification) and the most effective hyperthermia (average temperature in 41.8°C in the tumors, while it was 40-41°C in the study of van der Zee). Vasanthan's result was negative: hyperthermia worsened survival and in group IIB deterioration was significant. At the same time, the control of the RT group Vasanthan's research showed remarkable results: 4-year survival rate was 80%, which significantly exceeded the results of Harima and van der Zee, and it reliably and exceeded the results of RT-controls (50% and from 28% Harima in van der Zee), Fig. 1.

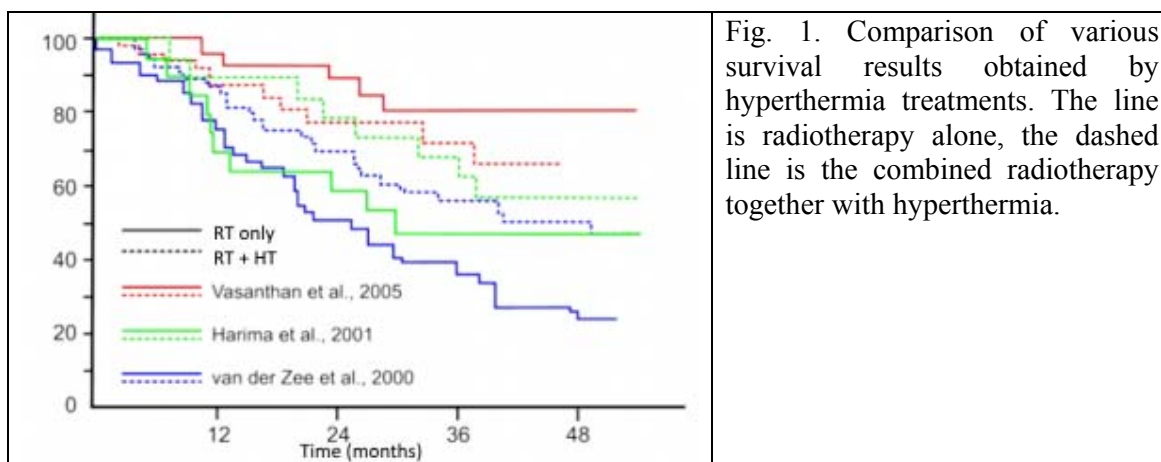


Fig. 1. Comparison of various survival results obtained by hyperthermia treatments. The line is radiotherapy alone, the dashed line is the combined radiotherapy together with hyperthermia.

Given the distortions, no study on hyperthermia radio-modification in cervical cancer, of course, can be considered successful.

Thus, the South-African study by Dr. Minnaar's onco-thermo-radio-therapy has all chances to become the first in the history of successful research on physical radio-modification in locally advanced cervical cancer.

The newest study of the van der Zee group (Lutgens LCHW et al, 2016) shows no difference between the bimodal radiotherapy + cisplatin and radiotherapy + hyperthermia. The event-free survival is shown on Fig. 2.

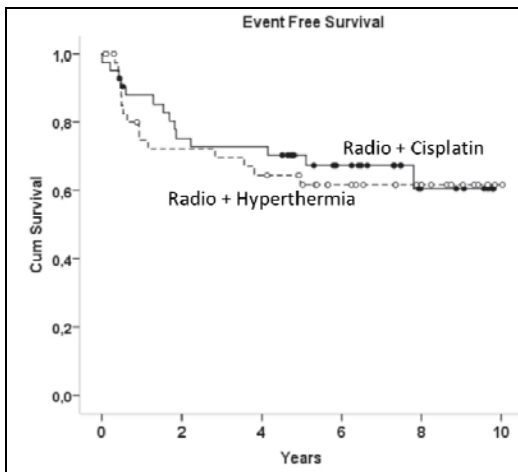


Fig. 2. The event free survival in the latest result of hconventional hyperthermia study for locally advanced cervix carcinoma. (From Lutrens LCHW et al 2016).

The complete comparison of the cervix results is shown on Fig. 3. The new radiotherapy plus hyperthermia results has remarkable correspondence with the same type of treatment earlier by Vasanthan et al.

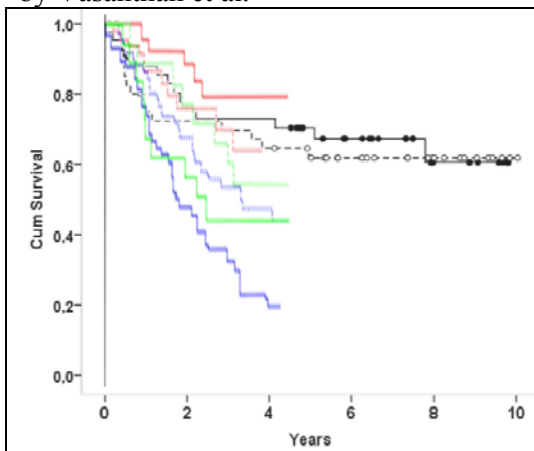


Fig. 3. Comparison of various survival results obtained by hyperthermia treatments. The line is radiotherapy alone and with cisplatin in case of black line, and the dashed line is the combined radiotherapy together with hyperthermia. The black patterns are from (Lutrens LCHW et al 2016), the others are equivalent with Fig. 1.

Noteworthy characteristic pattern of oncothermia effect is its definite difference from conventional hyperthermia. In all the conventional hyperthermia researches it shows the gain of complete remission, in some cases, the survival time does not increase parallel, but oppositely it decreases with growing local control. Oncothermia complete remission usually shows parallel gain of local control survival time and quality of life as well.

van der Zee J, González González D, van Rhoon GC, et al. Comparison of radiotherapy alone with radiotherapy plus hyperthermia in locally advanced pelvic tumours a prospective, randomised, multicentre trial. Dutch Deep Hyperthermia Group. *Lancet*. 2000; 355 (9210) 1119-25.

Harima Y, Nagata K, Harima K, et al. A randomized clinical trial of radiation therapy versus thermoradiotherapy in stage IIIB cervical carcinoma. *Int J Hyperthermia*. 2001; 17 (2) 97-105.

Vasanthan A, Mitsumori M, Park JH, Zhi-Fan Z, Yu-Bin Z, Oliynychenko P, Tatsuzaki H, Tanaka Y, Hiraoka M. Regional hyperthermia combined with radiotherapy for uterine cervical cancers a multi-institutional prospective randomized trial of the international atomic energy agency. *Int J Radiat Oncol Biol Phys*. 2005; 61 (1); 145-53.

Ludy C.H.W. Lutgens, Peter C.M. Koper, Jan J. Jobsen, et al. Radiation therapy combined with hyperthermia versus cisplatin for locally advanced cervical cancer Results of the randomized RADCHOC trial. *Radiotherapy and Oncology*. 2016; 120(3) 378-382.