Combined use of hyperthermia and radiation therapy for treating locally advanced cervical carcinoma (Withdrawn Paper, art. no. CD006377, 2010)

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[Intervention Review]

Combined use of hyperthermia and radiation therapy for treating locally advanced cervical carcinoma

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ABSTRACT

Background

Hyperthermia is a type of cancer treatment in which body tissue is exposed to high temperatures to damage and kill cancer cells. It was introduced into clinical oncology practice several decades ago. Positive clinical results, mostly obtained in single institutions, resulted in clinical implementation albeit in a limited number of cancer centres worldwide. Because large scale randomised clinical trials (RCTs) are lacking, firm conclusions cannot be drawn regarding its definitive role as an adjunct to radiotherapy in the treatment of locally advanced cervical carcinoma (LACC).

Objectives

To assess whether adding hyperthermia to standard radiotherapy for LACC has an impact on (1) local tumour control, (2) survival and (3) treatment related morbidity.

Search methods

The electronic databases of the Cochrane Central Register of Controlled Trials (CENTRAL), (Issue 1, 2009) and Cochrane Gynaecological Cancer Groups Specialised Register, MEDLINE, EMBASE, online databases for trial registration, handsearching of journals and conference abstracts, reviews, reference lists, and contacts with experts were used to identify potentially eligible trials, published and unpublished until January 2009.

Selection criteria

RCTs comparing radiotherapy alone (RT) versus combined hyperthermia and radiotherapy (RHT) in patients with LACC.

Data collection and analysis

Between 1987 and 2009 the results of six RCTs were published, these were used for the current analysis.

Main results

74% of patients had FIGO stage IIIB LACC. Treatment outcome was significantly better for patients receiving the combined treatment (Figures 1 to 3). The pooled data analysis yielded a significantly higher complete response rate (relative risk (RR) 0.56; 95% confidence interval (CI) 0.39 to 0.79; p < 0.001), a significantly reduced local recurrence rate at 3 years (hazard ratio (HR) 0.48; 95% CI 0.37 to 0.63; p

< 0.001) and a significanly better overall survival (OS) at three years following the combined treatment with RHT(HR 0.67; 95% CI 0.45 to 0.99; p = 0.05). No significant difference was observed in treatment related acute (RR 0.99; 95% CI 0.30 to 3.31; p = 0.99) or late grade 3 to 4 toxicity (RR 1.01; CI 95% 0.44 to 2.30; p = 0.96) between both treatments.

Authors' conclusions

The limited number of patients available for analysis, methodological flaws and a significant over-representation of patients with FIGO stage IIIB prohibit drawing definite conclusions regarding the impact of adding hyperthermia to standard radiotherapy. However, available data do suggest that the addition of hyperthermia improves local tumour control and overall survival in patients with locally advanced cervical carcinoma without affecting treatment related grade 3 to 4 acute or late toxicity.

PLAIN LANGUAGE SUMMARY

Combined use of hyperthermia and radiation therapy for treating locally advanced cervical carcinoma

Curative treatment for cervical carcinoma consists of complete surgical removal of the tumour or destruction of the tumour by means of radiation. If the tumour has grown beyond the boundaries of the cervix or has reached a size greater than 4 cm in diameter it is designated as a locally advanced cervical carcinoma. For these tumours surgery alone is considered inappropriate so radiotherapy is also given. Not all tumours are equally sensitive to radiation. Generally speaking, the likliehood that radiation alone is able to cure the tumour decreases with increasing tumour volume. In several clinical studies it was found that the liklehood of curing the tumour at the site of origin was increased by adding hyperthermia to radiotherapy. Hyperthermia is a treatment which kills tumour cells by increasing the normal body temperature (37 degrees celsius) up to around 42 to 43 degrees celcius at the area of the tumour for a one hour period. It is believed that hyperthermia may kill tumour cells that under certain conditions are resistant to radiation or that hyperthermia can turn tumour cells making them more sensitive to radiation. However, the results observed with this treatment are not consistent in subsequent clinical studies. Therefore we analysed the results of all clinical studies published so far comparing the treatment results of radiotherapy alone with those obtained with the combined treatment of radiotherapy and hyperthermia in patients with locally advanced cervical carcinoma. The results do suggest a better outcome for patients treated with the combination of radiotherapy with hyperthermia. Thus following treatment a complete disappearance of the tumour was observed more regularly, regrowth of the tumour at the site of origin during follow up was observed less frequently and more patients were still alive at three years after treatment. Treatment related side effects were not increased by the addition of hyperthermia to standard radiotherapy. However, the number of patients included in the clinical studies analysed is limited as the majority of patients had stage IIIB disease. The authors therefore conclude that hyperthermia may provide a clinically relevant improvement in treatment outcome for patients with locally advanced cervical carcinoma, in particular patients with stage IIIB disease. Additional clinical data are needed to warrant its use for all patients with locally advanced cervical carcinoma.

BACKGROUND

Description of the condition

For many years radiotherapy alone has been the treatment of choice in patients with LACC. Spread to the para-aortic lymph nodes has been recognised as the single most important prognostic factor (Fyles 1995; Stehman 1991). Nevertheless pelvic tumour control is a pre-requisite for cure (Haie 1988; Rotman 1995). Perez et al reported overall pelvic recurrences in 14%, 41%, 41% and 72%, whereas distant recurrences only were found in 12%, 18%, 16% and 21% of 1499 patients with FIGO stage I, II, III and IVA disease treated with radiotherapy (Perez 1998). Similarly, Horiot et al reported pelvic recurrences in 6%,17%,43% and 56% of 1383 patients with stage I, II, III and IVA, respectively, treated with radiotherapy (Horiot 1988).

Description of the intervention

Since 1987 the results of six randomised clinical trials (RCTs) have been published concerning the combined treatment of radiotherapy with hyperthermia (RHT) in patients with cervical carcinoma (Chen 1997; Datta 1987; Harima 2001; Sharma 1991; van der Zee 2000; Vasanthan 2005). Local tumour control and overall survival appeared to be improved by the addition of hyperthermia, although clinical observations were not unanimous. Possible explanations for the discrepancy may be found in the patient selection (e.g. with respect to stage or tumour volume) and other confounding factors such as treatment parameters (e.g. overall treatment time and hyperthermia technique). Therefore, the magnitude of any beneficial effect as well as the proper selection of patients for any combined treatment remains to be demonstrated.

How the intervention might work

In LACC the pelvis is the most common site of failure after treatment with radiotherapy. Several tumour characteristics have been related to the risk of pelvic failure following radiotherapy (Eifel 1994; Fyles 1995; Haensgen 2001; Hockel 1993; Horiot 1988; Lanciano 1991; Mendenhall 1984; Perez 1998; Stehman 1991; Stehman 1994; Thomas 2001; Tsang 1995; Werner 1995; West 1995). Probably the single most important of these is tumour volume (Fyles 1995; Perez 1998; Tsang 1995). Although tumour hypoxia is suggested to be an independent prognostic factor by some (Hockel 1999; Vaupel 2001) both animal (De Jaeger 1998; Khalil 1995; Milross 1997) and human data (Fyles 1998) have demonstrated an association between tumour volume and tumour hypoxia. Thus with increasing tumour volume, tumour necrosis increases and as a result oxygenation status worsens (De Jaeger 1998; Khalil 1995; Milross 1997). Metabolic processes will consequently be more anaerobic and tissue pH will decrease. It is under these circumstances that radioresistance increases whereas hyperthermia will be most effective. Hyperthermia is directly cytotoxic for cells that are less radiosensitive under these circumstances whereas tumour oxygenation will improve by increasing blood flow. Consequently the circumstances are then optimal for a therapeutic gain of the combination of both treatment modalities . In addition direct radiosensitization is another effect of hyperthermia.

Why it is important to do this review

The potential benefit of combining hyperthermia with radiotherapy in cervical carcinomaswas established several decades ago (Brady 1976), but RCTs are scarce. Furthermore, the number of patients included in the few available RCTs is small and are inconsistent regarding the beneficial effect of hyperthermia (Harima 2001; van der Zee 2000; Vasanthan 2005). Of importance also are the fundamental differences that exist in the heating techniques used, thus prohibiting any firm conclusion regarding the therapeutic benefit. The majority of published data deal with technical developments and do not provide treatment results. Despite these drawbacks, however, overall clinical data on the combined use of radiotherapy and hyperthermia suggest a therapeutic gain as compared to single modality treatment (Dinges 1998; Harima 2001; Hornback 1986;; van der Zee 2000; Vasanthan 2005). Therefore a systematic analysis on this treatment modality is required.

OBJECTIVES

This systematic review aims to provide a comprehensive and reliable summary of the effect of hyperthermia on LACC when applied concomitantly with radiotherapy. The specific aim is to review all prospective RCTs (phase II and phase III) which compare the effectiveness of combined hyperthermia and radiotherapy (RHT) with radiotherapy alone (RT) in patients treated for LACC.

METHODS

Criteria for considering studies for this review

Types of studies

RCTs (phase II or III).

Types of participants

Patients of any age with histologically proven LACC and with a WHO performance status 0 to 2 (WHO 1979). Cervical cancers with a central diameter equal or larger than 4 cm and/or FIGO stage IIB to IVA are considered locally advanced. Studies with less than 20 patients were excluded.

Types of interventions

Any regimen of radiotherapy for uterine cervical carcinoma consisting of (generally considered) curative doses of external beam radiotherapy (EBRT) with or without brachytherapy (BCT) given concurrently or not with hyperthermia. Only studies which used a minimum temperature of 40º celsius for hyperthermia were included. In case of concomitant use of chemotherapy and radiotherapy studies were included when hyperthermia was the only treatment variable. In that case no further distinction was made between different chemotherapy schedules.

Studies in which it was not possible to separate data on patients receiving combined hyperthermia plus radiotherapy (RHT) versus radiotherapy alone (RT), even after contacting the authors, were excluded.

Types of outcome measures

The following clinically relevant outcomes were studied:

- Complete tumour response (CR) at two months (that is no evidence of disease as assessed with clinical examination and/or any imaging technique).In cervical carcinoma a CR following radiotherapy is predictive for a durable pelvic tumour control.
- Local tumour recurrence (LR) at three years after treatment

- Overall Survival (OS) at three years
- Grade 3 to 4 acute toxicity (Tox acute; i.e. treatment related toxicity occurring during and/or lasting up to six weeks following treatment) and grade 3 to 4 late toxicity (Tox late; i.e. treatment related toxicity lasting or occurring more than six months after treatment).

Search methods for identification of studies

Electronic searches

For this review we identified the relevant trials in any language through electronic searches of the following databases:

- Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library Issue 1, 2009)
- Cochrane Gynaecological Cancer Groups Specialised Register (beginning to present)
- MEDLINE (1966 to present)
- EMBASE (1974 to present)
- CINAHL (1982 to present)

Furthermore, various trial databases were searched for the identification of recent completed and ongoing trials (metaRegister of Controlled Trials, Cancer Research UK, Cancer.gov, The Eastern Cooperative Oncology Group Trials Database). All studies identified until January 2009 were included in the present study.

For search strategies used see Appendix 1, Appendix 2 and Appendix 3

Search strategies have been developed and executed by the author team.

Searching other resources

Handsearching was performed in the following journals; International Journal of Radiation, Oncology, Biology and Physics,Radiotherapy and Oncology; Journal of Clinical Oncology; Clinical Oncology and the International Journal of Hyperthermia. In addition, published abstracts of the ASTRO, ESTRO and ESHO conference proceedings of the last three years were screened. We scrutinised reference lists from identified studies and reviews for additional studies. Colleagues, collaborators and other experts in the field were asked to identify missing and unreported trials.

Data collection and analysis

Selection of studies

All titles and abstracts of reports identified by electronic searches or handsearching were assessed to determine if they meet the eligibility criteria by three independent review authors (CVZ, DDH, LL). In a consensus meeting (DDH, GVM, JB, LL) discrepancies were discussed. Furthermore, if necessary the full journal papers were screened to identify study characteristics.

Data extraction and management

Two review authors (DDH, LL) screened the included studies for methodological quality according to pre-determined criteria (Assessment of risk of bias in included studies), the treatment characteristics (radiotherapy, hyperthermia, chemotherapy) and the results of outcome measures (Types of outcome measures). For time to event (OS or local tumour recurrence) data, we extracted the log of the hazard ratio [log(HR)] and its standard error from trial reports; if these were not reported, we estimated them from other reported statistics using the methods of Parmar 1998. We abstracted site of recurrence, where possible. For dichotomous outcomes (e.g. complete tumour response and adverse events), we extracted the number of patients in each treatment arm who experienced the outcome of interest and the number of patients assessed at endpoint, in order to estimate a risk ratio. We abstracted adverse events by grade of toxicity. The time points at which outcomes were collected and reported were noted.

In addition, the following data were collected from the manuscript: identifiers (authors, title of publication, journal name and citation), tumour characteristics (recurrent, primary, inoperable, metastasis and maximum tumour diameter), baseline characteristics of study population (age, WHO performance status at the time of randomisation, initial disease stage), treatment allocated and number of patients randomised. The results and discrepancies of the data extraction were discussed in different meetings (DDH, GVM, JB, LL). The quality of the hyperthermia treatment of the different studies was determined in a consensus meeting (CVZ, DDH, GVM, JB, LL).

Assessment of risk of bias in included studies

The risk of bias was assessed using the tool described in the Cochrane Handbook for Systematic Reviews of interventions (Higgins 2008) addressing the following six domains:

Sequence generation (1), allocation concealment (2), blinding (3), incomplete outcome data (4), selective reporting of outcomes(5) and other potential threats to validity (6).

Measures of treatment effect

A weighted estimate of the typical treatment effect across studies was computed for the study outcomes. The risk ratio (RR) was used as the effect measure. For time-to-event outcomes such as survival analysis, the HR was used as effect measure. For these analyses, p-values and total events were used and the randomization ratio was 1:1 (Tierney 2007). Tierney 2004 was used to facilitate the estimation of HRs from published summary statistics or data extracted from Kaplan-Meier curves.

Dealing with missing data

We did not impute missing outcome data; if only imputed outcome data were reported, we planned to contact trial authors to request data on the outcomes only among participants who were assessed.

Assessment of heterogeneity

Chi-square heterogeneity tests were used to test for statistical heterogeneity among trials. Since we anticipated that the trial results were heterogeneous, all analysis were performed using a random-effects model.

RESULTS

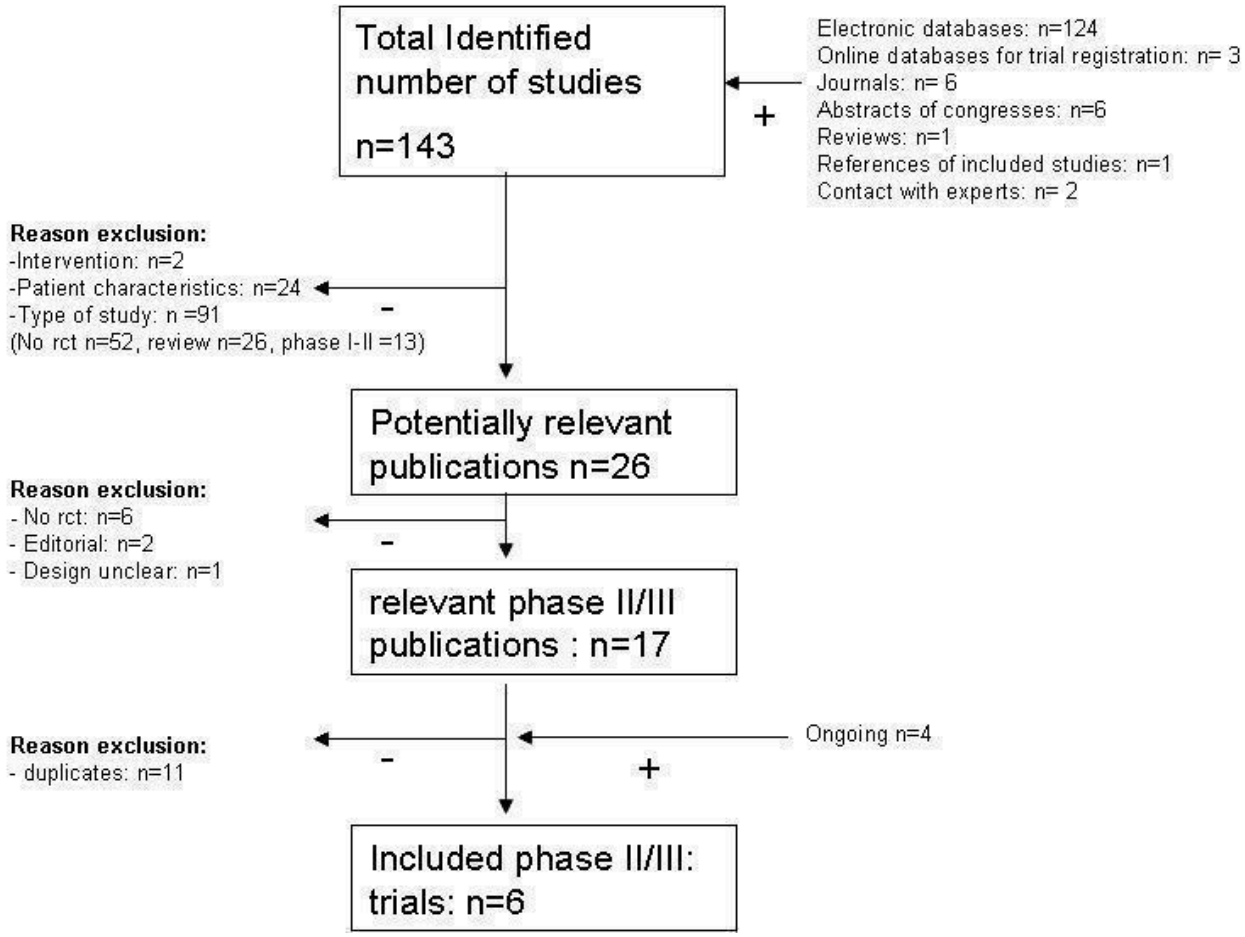
Description of studies

See:Characteristics of Included studies;Characteristics of Excluded studies.

Results of the search

The process of selecting the included studies for this review is summarized in Figure 1 . Of the 143 published abstracts that were selected by the performed search, we excluded 117 abstracts. The studies described in these abstracts did not evaluate the interventions of interest (n = 2) or did not contain data of cervical patient characteristics (n = 24). In addition, a total of 91 abstracts were excluded due to the study characteristics presented, i.e. no RCT (n = 52), a review (n = 26) or a phase 1-2 trial (n = 13). Of the remaining 26 abstracts the full journal papers were screened (if available). After screening, 6 studies appeared to be not randomised, 2 were editorial papers and 1 had an unclear design. The remaining 6 different trials (11 published papers: Franckena 2008; Chen 1997; Datta 1987; Harima 2000; Harima 2001; Sharma 1989; Sharma 1991; van der Zee 2000; van der Zee 2001; van der Zee 2002; Vasanthan 2005) were of RCTs (Phase 2 or 3) reporting radiotherapy together with a hyperthermia treatment (RHT) in one arm and radiotherapy only in the other arm. Of notice, the study of Chen et al included 120 patients with 4 treatment arms of which 2 treatment arms contained concomitant chemotherapy (Chen 1997). Since this analysis aimed to investigate the additional effect of hyperthermia on standard radiotherapy, we decided not to include the patients treated with concomitant chemotherapy in the pooled data analysis. Four ongoing studies that were identified from abstracts of congresses, online databases for trial registration and contact with experts (see table Characteristics of included studies) are not included in the present analysis.

Figure 1. Search Flow



Included studies

In 1987 Datta et al reported their results obtained in 53 patients with squamous cell cervical carcinoma, FIGO stage IIIB (Datta 1987). 64 Patients were randomly assigned to standard treatment only or combined treatment with local hyperthermia. Eleven patients were either lost to follow-up or received incomplete treatment leaving 53 assessable patients (RT n = 26; RHT n = 27)). No information concerning actually delivered therapy was provided by the authors. RHT yielded superior treatment results, i.e. 58% (15 out of 26) versus 74% (20 out of 27) CR, 46% (12 out of 26) versus 67% (18 out of 27) pelvic failure free survival and 27% (7 out of 26) versus 59% (16 out of 27) DFS at 2 years. The authors reported no increase of treatment related morbidity although detailed information was not provided.

In 1991 Sharma et al reported their results obtained in 50 patients with cervical carcinoma FIGO stage II-IIIB (Sharma 1991). Fifty patients were randomly assigned to RT or RHT. Two patients in each group were lost to follow-up whereas another 4 patients were not assessable for local tumour control after a minimal follow-up period of 18 months leaving 42 patients (i.e. 22 RT and 20 RHT group). No information concerning actually delivered therapy was provided by the authors. Strictly local tumour control was

evaluated, i.e. any pelvic side wall or distant recurrence was ignored. No details are provided on the duration of follow-up. RHT yielded superior treatment results , i.e. 50% (11 out of 22) versus 30% (6 out of 20) LR at 18 months for patients treated with RT and RHT, respectively. The authors reported no increase of treatment related morbidity although detailed information was not provided for late toxicity.

In 1997 Chen et al reported their results obtained in a study including 120 patients with cervical carcinoma, FIGO stage IIB - IIIB (Chen 1997). One hundred and twenty patients were randomly assigned to 1 of 4 treatment groups, no detailed information concerning the randomisation procedure was provided. Treatment consisted of RT, RHT, radiotherapy combined with chemotherapy (CRT) and radiotherapy combined with both hyperthermia and chemotherapy (TRIPLE). Vaginal applicators were used for the hyperthermia intervention but no further details were provided regarding the hyperthermia technique. No information concerning actually delivered therapy was provided by the authors. Treatment results were not significantly different , i.e. 46% (14 out of 30) versus 60% (18 out of 30) complete remission for the RT and RHT group. The authors reported no increase of acute treatment related rectal and bladder morbidity between the treatment groups although detailed information about the grade of toxicity was not provided.

In 2000 van der Zee et al reported their results obtained in a multicenter study including 114 patients with cervical carcinoma FIGO stage IIB-IVA (van der Zee 2000). Twenty-six patients did not complete radiotherapy treatment as planned because of insufficient tumour regression (n = 8 and n = 3), exceeding normal tissue dose constraints (n = 1 and n = 2), development of metastatic disease (n = 3 and n = 0), inability to access the cervical canal (n = 1 and n = 2), a cervical stump tumour (n = 0 and n = 2), intercurrent death (n = 1 and n = 1) and unknown (n = 3) in the control and experimental group, respectively. Median follow up was 43 months. RHT yielded superior treatment results i.e. 57% (32 out of 56) versus 83% (48 out of 58) CR, 41% versus 61% pelvic failure free survival and 27% versus 51% OS at 3 years for patients treated with RT and RHT, respectively. No difference in acute and late grade 3 to 4 treatment related rectal and/or bladder morbidity was observed.

In 2001 Harima et al reported their results obtained in a study including 40 patients with cervical carcinoma FIGO stage IIIB (Harima 2001). Mean follow-up was 25 (3.5 to 60.1) and 36 (5.9 to 64.3) months for the RT and RHT group, respectively. RHT yielded superior treatment results, i.e. 50% (10 out of 20) versus 80% (16 out of 20) CR; 50% versus 20% pelvic failure rate; 45% versus 64% DFS and 48% versus 58% OS at 3 years for patients treated with RT and RHT, respectively. Toxicity was not significantly different between treatment groups. However, in contrast to the RT group where no acute or late toxicity of any grade was observed, in the RHT group 1 patient had grade 3 acute bowel toxicity (RTOG score, Rubin 1995) and 2 patients developed grade 3 late bowel toxicity (obstructive colonic ileus and sigmoid-ileum fistula) after 1.5 and 2 years after treatment.

In 2005 Vasanthan et al reported their results obtained in a multicenter study in 110 patients with cervical carcinoma FIGO stage IIB -IVA (Vasanthan 2005). Median follow-up was 15.7 months for all patients and 17.2 months for surviving patients. Treatment results did not differ between RT and RHT groups. A subgroup analysis in 56 patients with stage IIB cervical carcinoma yielded a significantly worse survival for the RHT group whereas local control was similar for the 2 treatment groups. No details are provided concerning the cause of death or the location of disease recurrence. No significant difference in acute or late toxicity was observed. Grade 3 acute toxicity was observed only in 1 patient treated with RHT (grade 3 blister). Grade 3 bowel toxicity was equally distributed between treatment groups (n = 2 per group). One grade 4 bowel toxicity was observed in a patient treated with RT.

Quality of treatment

Radiotherapy

In general, state of the art treatment of LACC requires adequate EBRT combined with brachytherapy. Thus, EBRT doses between 45 to 50 Gy and cumulative doses between 70 to 90 Gy to 'Point A' are considered standard. Reported radiation doses delivered do not provide any information concerning the adequacy of tumour dose delivery. Except for the Datta study (Datta 1987), all standard radiotherapy protocols included combined treatment with EBRT and brachytherapy. To study the beneficial effect of any additional intervention to standard treatment ideally requires strictly standardized treatment protocols. Not surprisingly, taken the life span and geographical distribution of the 6 studies published, standard treatment varies significantly. Moreover, except for one study (Harima 2001) EBRT was not standardized within each study. Strictly adhering to the predefined quality criteria would mean that only three studies using hyperthermia treatment would qualify as adequate for review analysis. However, standard radiotherapy in these studies varied as well and would result in cancellation of the review. Taking this into account we decided to accept the variation in radiation therapy and hyperthermia techniques as well as the lack of description of the quality criteria in the manuscripts leaving 'randomised clinical study, including at least 20 patients' as major selection criterion. In doing so, we do realize that any outcome based on this analysis can only be suggestive and not conclusive.

Hyperthermia

The quality of the hyperthermia treatments is difficult to assess from the published information. Dose-effect relationships have been established for several hyperthermia dose parameters derived from the measured temperatures and the duration of heating, and taking into account the temperature distribution. In clinical practice, however, the number of thermometry sites is limited and in cervical cancer the thermometry probes are usually placed near the centre of the tumour. The temperature data are therefore not informative on what the hyperthermia dose has been in the entire tumour volume (van der Zee 2008). Other studies indicate that the applied energy distribution in the tumour volume can be used as a quality indicator (van der Zee 2008). The energy distribution can be estimated from the information provided in the publications. In five studies, electromagnetic (EM) radiation was used for heating. Chen et al used an intravaginal applicator with an unspecified source of energy, which may have been electromagnetic radiation as well. EM radiation was applied radiatively or capacitively (Chen 1997). Van der Zee et al used three different radiative EM systems with similar energy depositions in pelvis-sized phantoms (van der Zee 2000).

With EM radiation at a frequency of 70 to 120 MHz, energy input from around the pelvis and the use of interference, the energy is deposited widely in the pelvic region (Gellermann 2005; Sreenivasa 2003). In the other studies, capacitive heating systems were used.

With capacitive heating (8 to 27 MHz) between two large electrodes placed opposite on the patient's skin it is also possible to get energy deposition widely in the pelvic region, provided there is an appropriate patient selection and treatment procedure (van der Zee 2005). Subcutaneous fat tissue is preferentially heated by capacitive heating and must be cooled to allow for sufficient energy input into deeper seated tissues. Superficial skin cooling can limit the temperature increase in subcutaneous fat to an acceptable level to a depth of approximately 2 cm (Rhee 1991). With thicker subcutaneous fat layers, the high temperature in the deeper subcutaneous fat will limit the total power input. Further more, when a smaller (intravaginal) electrode is used in combination with one or two large external electrode(s) there will be a steep gradient of energy deposition with the maximum around the small electrode. The energy level normalized to maximum will fall below 25% within 1 to 2 cm from the intravaginal electrode (Hiraki 2000). With capacitive heating using an intravaginal electrode, only the central part of the tumour can be expected to be heated to therapeutic temperatures.

Datta 1987
Hyperthermia was given twice weekly before radiotherapy. The total number of treatments was not reported, it could have been 12 during 6 weeks of EBRT. The duration per treatment was 15 to 20 minutes after reaching a temperature of approximately 42.5°C, measured in the cervical canal. Hyperthermia was induced by a 27 MHz capacitive system with two external electrodes. The authors do not report subcutaneous fat thickness as an eligibility criterion, nor skin cooling, nor the applied power.

Sharma 1991
Hyperthermia was given 3 times per week for a total of 12 treatments of 45 minutes duration, before radiotherapy. A 27 MHz capacitive heating system was used with a large external and an intravaginal electrode. Temperatures were measured by a thermocouple attached to the intravaginal electrode. In most patients, the intravaginal temperature was 43°C for 30 minutes.

Chen 1997
Hyperthermia was given twice weekly after radiotherapy for a total of 6 treatments of 45 minutes at a temperature of 42° with an intravaginal technique. Further details of treatment are not reported.

van der Zee 2000
Hyperthermia was applied by three centres which all used a radiative hyperthermia system. Hyperthermia was given once a week after radiotherapy, for a total of 5 treatments of 60 minutes after reaching 42°C, or maximum 90 minutes. The mean power input and achieved intraluminal (rectal, bladder and vaginal) temperatures were reported by the centre recruiting the most patients and were reported separately: average 706 Watts and 40.6°C (Fatehi 2007).

Harima 2001
Hyperthermia was given once a week after RT, for a total 3 treatments of 60 minutes duration. Hyperthermia was induced with the Thermotron 8 MHz capacitive system with two external electrodes. Patients with subcutaneous fat layer of less than 4 cm were eligible.The authors do not report to have used pre-cooling. The applied power was 800 to1500 W. Intratumour temperature measurements were done with 4-point thermocouple probes; an average temperature of 40.6°C was achieved.

Vasanthan 2005
Five centres participated in this study. Hyperthermia was given once weekly before or after radiotherapy, for a total of 5 treatments of 60 minutes duration.

The description of applied heating techniques is incomplete. All centres used a 8 MHz capacitive heating system with, probably in the majority of patients, an intravaginal electrode (van der Zee 2005). A subcutaneous fat thickness of up to 3 cm was accepted; pre-cooling of skin was reported by only one centre. The level of power input was reported by only one centre: a mean of 520 W, which is relatively low. Centrally measured average temperatures ranged between 38.1 and 42°C.

The hyperthermia techniques using radiative electromagnetic heating or capacitive heating with external electrodes only can be considered adequate (Datta 1987; Harima 2001; van der Zee 2000). In the study of Sharma et al the effect on the central tumour was the main endpoint, for which the used intravaginal heating can be considered adequate (Sharma 1991). In the studies by Chen et al and Vasanthan et al the applied intravaginal heating (in the majority of patients) must be considered inadequate for treatment of the advanced tumours included in their studies (Chen 1997; Vasanthan 2005).

Excluded studies

From the retrieved studies, eight studies were excluded for this review mainly because of the used study design (El Sharouni 1997; Fujiwara 1987; Gupta 1999; Hasegawa 1989; Hornback 1986; Kohno 1990). One study was not assessable due to limited data (Li 1993) and one study could not be included because the trial is still ongoing (Prosnitz 2002).

Risk of bias in included studies

The methodological quality of the included studies is shown in the table 'Characteristics of included studies' and is summarized in Figure 2 and Figure 3.

Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

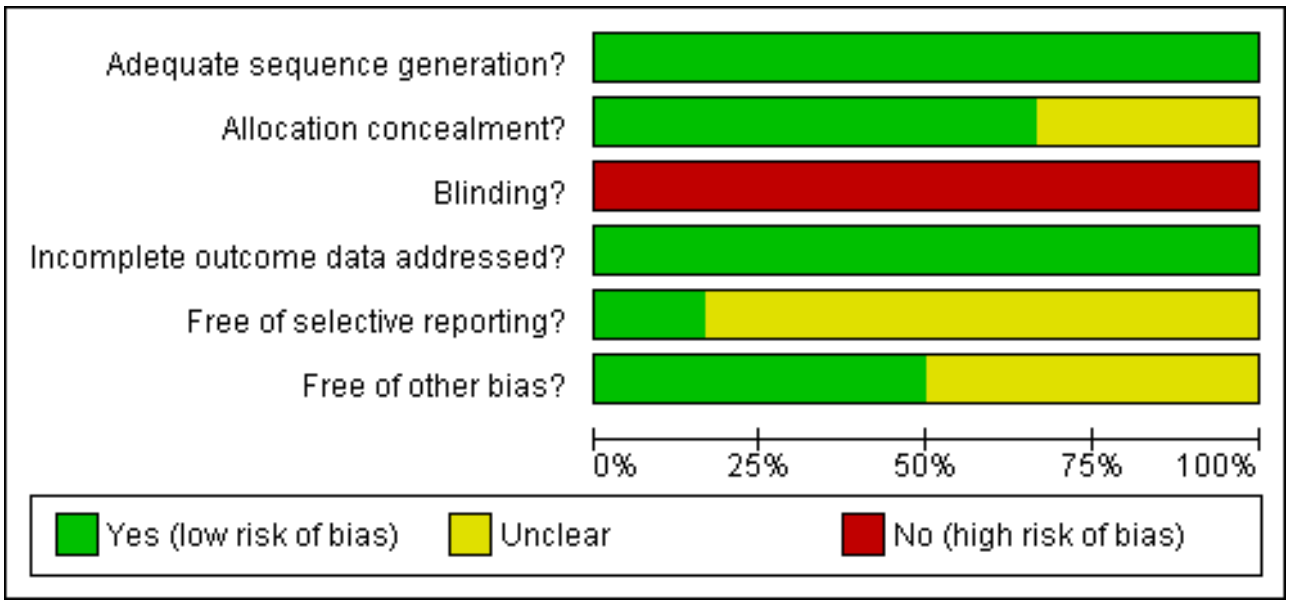
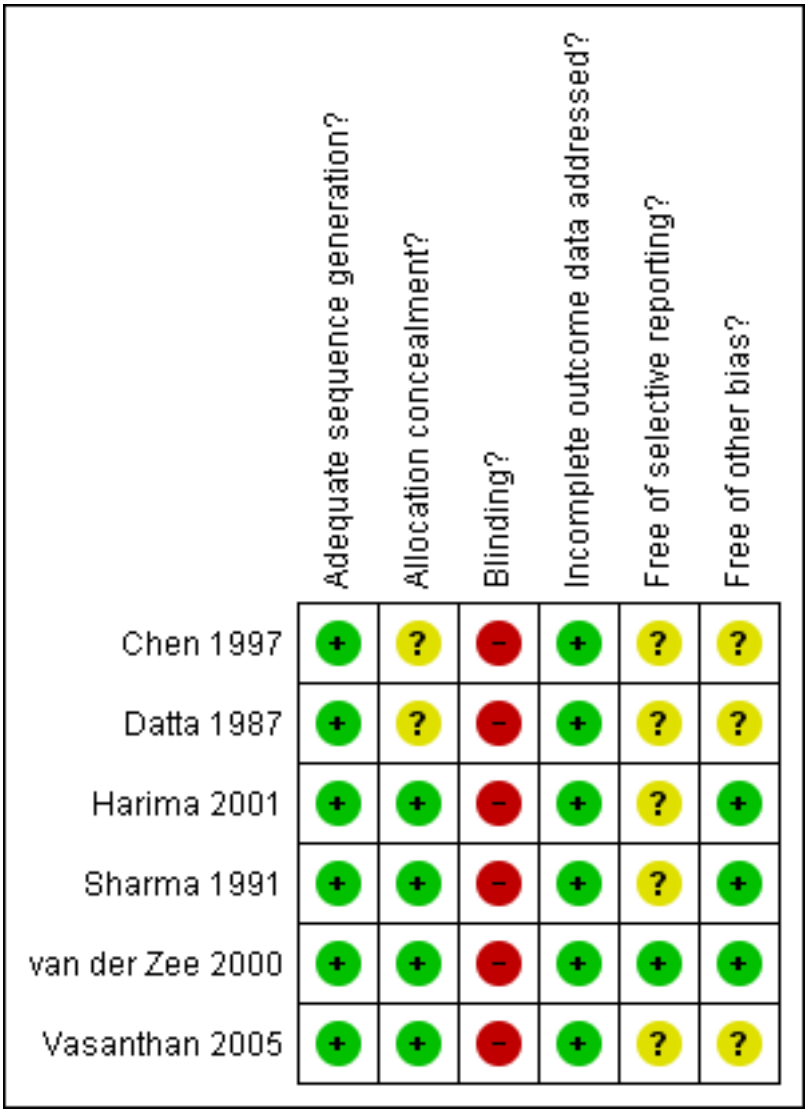


Figure 3. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



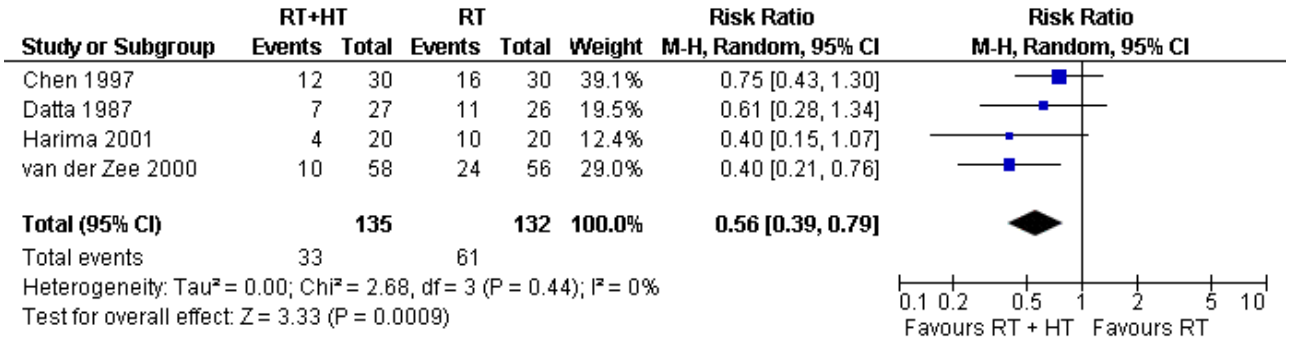
All six included studies reported on a randomisation process. In one study (Chen 1997) allocation concealment might be questionable. Although there was no blinding in any study, this is unlikely to affect outcome. In four studies there were no missing outcome data (Chen 1997; Harima 2001; van der Zee 2000; Vasanthan 2005) whereas in two studies the number of missing outcome data was limited and equally distributed between intervention groups (Datta 1987; Sharma 1991). No other problems were detected in any of the six studies that might have introduced a serious risk of bias. However, several other issues have to be considered. Of importance, uniformity in treatment was far from optimal, both for hyperthermia and radiotherapy. For example in hyperthermia the sequencing of radiotherapy and hyperthermia and the interval between radiotherapy and hyperthermia differed between and within (Vasanthan 2005) the studies. Similarly the radiation technique, the total radiation dose applied and overall treatment time differed between and within the studies (van der Zee 2000; Vasanthan 2005). Also the time point chosen for reporting of outcome parameters varies such that for the different outcome measures only three or four out of six studies can be used for pooled data analysis. Finally, overall the number of patients included in these six studies is small whereas the majority (i.e. 74%) had FIGO stage IIIB LACC.

Effects of interventions

Complete response

Using complete tumour response at the end of treatment as endpoint in the pooled data analysis including 267 study patients yields a significantly better treatment outcome following RHT (RR 0.56 (95% CI 0.39 to 0.79); $p < 0.001$; Figure 4; Analysis 1.1).

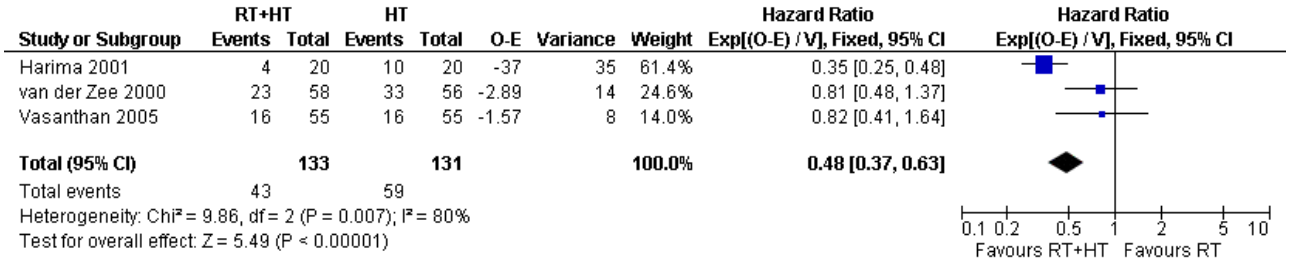
Figure 4. Forest plot of comparison: 1 RT + HT versus RT: all studies, outcome: 1.1 complete tumour response.



Local recurrence

Using local recurrence as endpoint in the pooled data analysis including 264 study patients yields a significantly reduced local recurrence rate at 3 years (HR 0.48 (95% CI 0.37 to 0.63); p < 0.001; Figure 5; Analysis 1.2) .

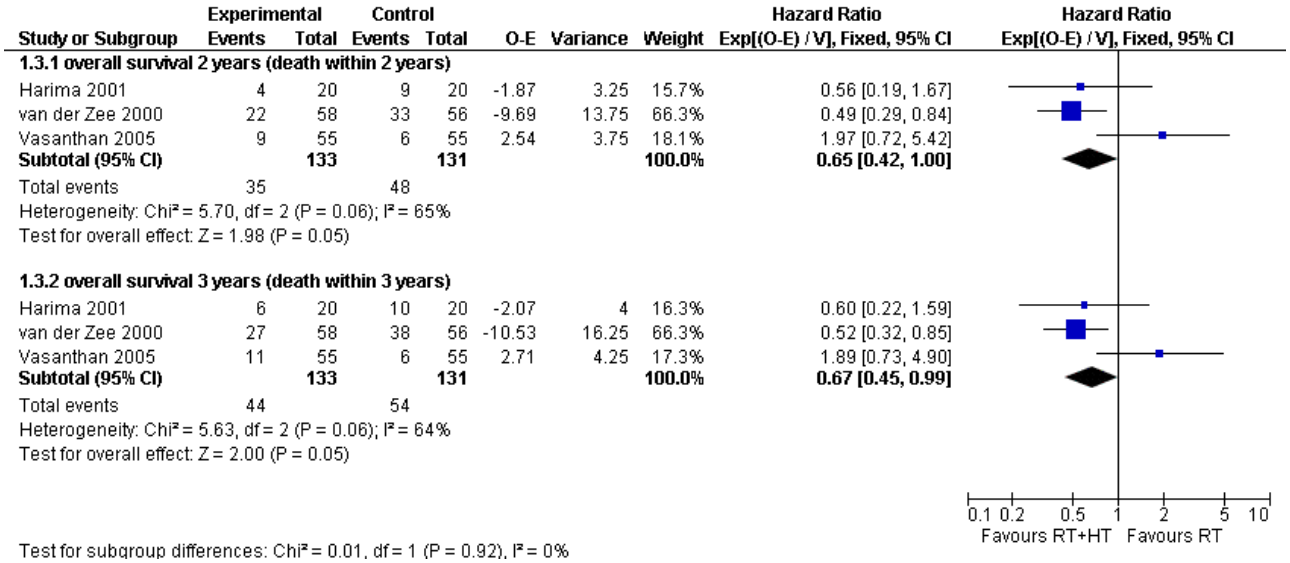
Figure 5. Forest plot of comparison: 1 RT + HT versus RT: all studies, outcome: 1.3 local tumour recurrence 3y_HR.



Overall survival

Using overall survival at three years as endpoint in the pooled data analysis including 264 study patients yielded a significantly better survival for the combined treatment group (RHT) (HR 0.67; 95% CI 0.45 to 0.99; p = 0.05; Figure 6; Analysis 1.3).

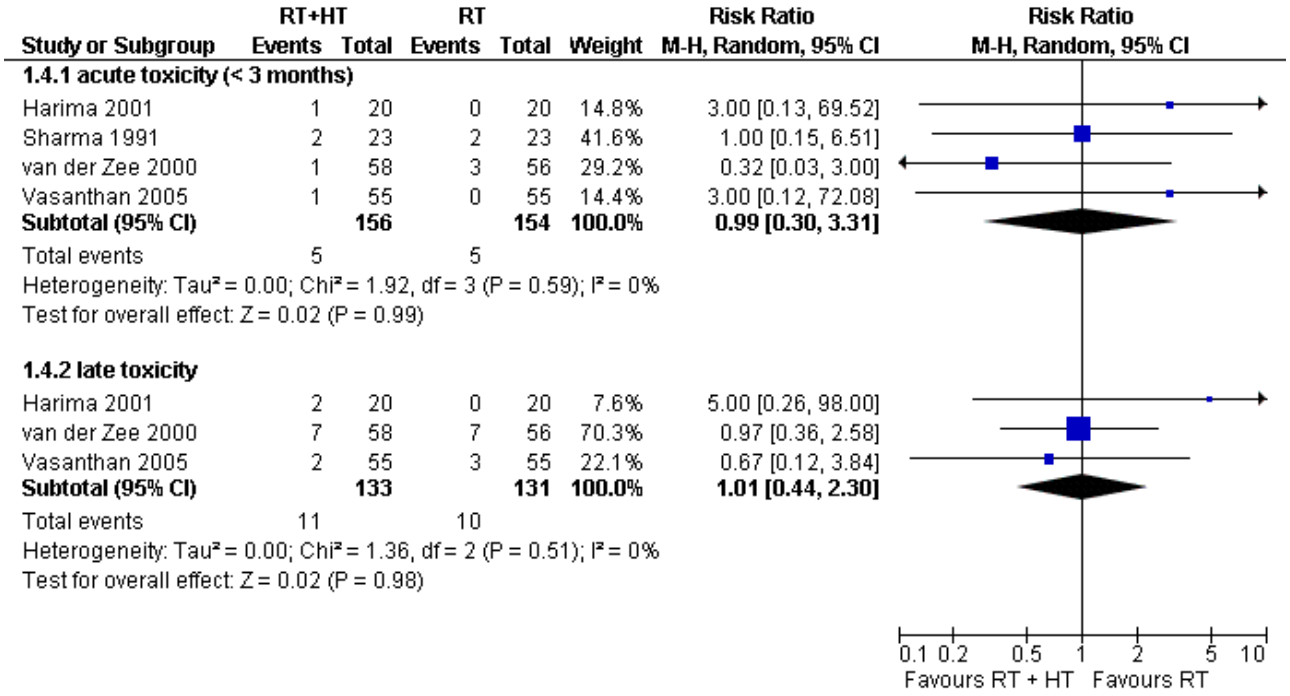
Figure 6. Forest plot of comparison: 1 RT + HT versus RT: all studies, outcome: 1.5 overall survival_HR (2 and 3 years).



Toxicity

Using acute toxicity as endpoint in the pooled data analysis including 310 study patients yielded no difference in acute treatment related toxicity between both treatment groups (RR 0.99 (95% CI 0.30 to 3.31); p = 0.99; Figure 7; Analysis 1.4). Similarly, the pooled data analysis using late toxicity as endpoint including 264 study patients yielded no difference in late toxicity between both treatment groups (RR 1.01 (CI 95% 0.44 to 2.30); p = 0.98.

Figure 7. Forest plot of comparison: 1 RT + HT versus RT: all studies, outcome: 1.7 toxicity (acute and late).



DISCUSSION

The results of the present analysis with respect to the endpoints studied, i.e. complete response rate following treatment, local recurrence, OS and treatment related toxicity grade 3 to 4 indicates a significant improvement of local (pelvic) tumour control and overall survival at three years following the combined treatment modality (RHT) whereas acute and late toxicity was not significantly different between both treatment groups. In four of six studies (Datta 1987; Harima 2001; Sharma 1991; van der Zee 2000) a significantly improved treatment outcome was observed by adding hyperthermia to standard radiotherapy, whereas in two studies no significant difference between both treatments was observed (Chen 1997; Vasanthan 2005).

In contrast, in one study (Vasanthan 2005) an inferior survival was observed in a subgroup of patients with FIGO stage IIB treated with RHT, although no further information is provided on the cause of death, whereas local tumour control was similar for both treatment groups. Sharma et al report on an increased rate of distant metastases in the RHTgroup although the difference is not significant and no survival data are provided (Sharma 1991). Of interest, the patient population differed significantly between these studies as the percentage of patients with FIGO stage IIIB disease varied between 38 to 77 % (Chen 1997; Vasanthan 2005) and between 70 to 100% (Datta 1987; Harima 2001; Sharma 1991; van der Zee 2000) in the two studies showing no difference and the four studies showing a beneficial effect of hyperthermia.

Regarding treatment related toxicity, all but one study (Chen 1997) did report treatment related toxicity. Two studies (Datta 1987; Sharma 1991) found no effect on normal tissue toxicity, although no further details were provided. Two trials (van der Zee 2000;Vasanthan 2005) reported no increased toxicity of any kind. One trial (Harima 2001) observed an increased late bowel toxicity in 2 out of 20 patients treated with RHT as compared to 0 out of 20 patients treated with RT.

AUTHORS' CONCLUSIONS

Implications for practice

Taken the limited number of patients available for this analysis, the over-representation of FIGO stage IIIB disease and the methodological flaws as discussed, it is not possible to draw definite conclusions regarding the beneficial effect of hyperthermia added to standard radiotherapy. Treatment related severe toxicity, i.e. grade 3 to 4 seems not to be affected by the addition of hyperthermia to standard radiotherapy treatment. However, the available data do suggest that superior local tumour control rates and overall survival can be achieved in patients with LACC by adding hyperthermia to standard radiotherapy. Although the available data mainly apply for patients presenting with FIGO stage IIIB disease, radiobiological considerations suggest a possible benefit for its use in other locally advanced stages as well. Based on the results of several recent RCTs investigating the role of adding chemotherapy to radiotherapy this treatment combination is currently considered standard in LACC. Considering the results of

this analysis and the finding that the effect of adding chemotherapy to radiotherapy on survival seems to decrease with increasing tumour stage hyperthermia should be considered as an alternative in case chemotherapy is contra-indicated, especially in higher tumour stages.

Implications for research

Taken the therapeutic benefit obtained, that is almost doubling of a durable local control with an associated increase in overall survival, without affecting treatment associated toxicity and the relatively low costs per patient, a limited number of clinical restrictions for its application, further investigation of the role of hyperthermia in a large scaled randomised trial is warranted. In case of a substantiated therapeutic gain this treatment modality should become available to all patients with this life threatening but potentially curable disease.

ACKNOWLEDGEMENTS

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Ongoing study 01-11-06.

Prosnitz *{published data only}*

Cisplatin and Radiation Therapy With or Without Hyperthermia Therapy in Treating Patients With Cervical Cancer. Ongoing study 01-06-04.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Chen 1997

Methods	Single centre RCT (arms = 4) randomisation procedure: adequate, ITT: unknown, baseline characteristics similar: unknown, eligibility criteria specified: yes, losses to follow up fully accounted for: unknown, bias due withdrawal/drop-out rate: unknown, co-interventions influenced results: no
Participants	Cervical cancer patients: E: 30, C: 30. FIGO stage: IIB (E:7, C:7);IIIB (E:23, C: 23) Age: E: unknown (32-70), C: unknown (32-70) WHO performance:0-1
Interventions	HT: Vaginal applicators. Timing: from the second week of EBRT. Duration: 45 minutes. Sequence: 1 hour after EBRT. Frequency:twice weekly with 48 to 72 hour interval. Total number: 6. RT: Standard EBRT: linear accelerator or telecobalt. Two parallel opposed fields. Primary tumour and pelvic draining lymphatics. A total dose of 20 Gy in 10 fractions in 2 weeks and an additional dose of 20 Gy in 10 fractions with a central block. Brachytherapy: Co-60. Timing: From the second week of EBRT. Dose per fraction: 5 to 10 Gy to 'Point A'. Frequency: weekly. Total number: 5-6. CT: yes (groups were not included in analysis)
Outcomes	CR (end of treatment)
Notes	2 arms (n = 60) with CT were not included in review

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Quote: "A randomised Trial".
Allocation concealment?	Unclear risk	Quote: "The patients were orderly grouped according to clinical stages". Taken the fact that it is a randomised trial this probably refers to a stratification procedure although this is not clear from the text.
Blinding? All outcomes	High risk	No blinding. However, the outcome measurements are not likely to be influenced.
Incomplete outcome data addressed? All outcomes	Low risk	There were no missing outcome data.
Free of selective reporting?	Unclear risk	No protocol available. An expected outcome measure was reported.

Chen 1997 *(Continued)*

Free of other bias?	Unclear risk	The study is published in a Chinese Journal. The English language used for reporting the material & method and result section is rather poor. Consequently important details may be missing.

Datta 1987

Methods	Multi centre RCT (arms = 2, centre = 3) randomisation procedure: unknown, ITT:no, baseline characteristics similar: unknown, eligibility criteria specified: yes, losses to follow up fully accounted for: yes, bias due with-drawal/drop-out rate: no, co-interventions influenced results: no Total quality score: 2
Participants	Cervical cancer patients: E: 33, C: 31. FIGO stage IIIB. Histology: squamous cell carcinoma: 64. Age: E: unknown (33-67), C: unknown (28-74) WHO performance:unknown
Interventions	HT: Capacitative applicators consisting of 2 plates. Duration: 15-20 minutes. Sequence: immediately preceding EBRT. Frequency: twice weekly with 72 hour interval. Total number: unknown. RT: Standard EBRT: telecobalt. Four field box-technique. Primary tumour and pelvic draining lymphatics. Total dose of 50 to 55 Gy in 25 to 28 fractions in 5 to 5½ weeks. An additional dose to the local tumour using antero-posterior opposed fields delivering a 10-15 Gy in 5-8 fractions in 1-1½ week. Brachytherapy: no CT: no
Outcomes	CR (4 weeks after treatment) LR (2Y) DFS (2Y)
Notes	No details on statistical analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Quote: "All cases were randomised and divided into two groups".
Allocation concealment?	Unclear risk	Insufficiently described.
Blinding? All outcomes	High risk	No blinding. However, the outcome measurements are not likely to be influenced.
Incomplete outcome data addressed? All outcomes	Low risk	The number of missing outcome data is equally distributed across the intervention groups with similar reasons for missing.
Free of selective reporting?	Unclear risk	No protocol available. Expected outcome measurements are reported.
Free of other bias?	Unclear risk	11 patients were not included in the analysis due to 1) lost to follow-up or 2) incomplete treatment. It is not stated how many patients per treatment group are due to either reason. Consequently exclusions for reasons related to the interventions cannot be ruled out.

Harima 2001

Methods	single centre RCT (arms = 2) randomisation procedure: adequate, ITT: unknown, baseline characteristics similar: yes, eligibility criteria specified: yes, losses to follow up fully accounted for: yes, bias due withdrawal/drop-out rate: no, co-interventions influenced results: no Total quality score:4
Participants	Cervical cancer patients: E: 20, C: 20 FIGO stage IIIB (n=40) Histology: Squamous cell carcinoma (n=35); Adenocarcinoma (n=5). Tumour diameter (mean): E 5.9 (+/- 2.2), C; 6.1 (+/- 1.8) Age: E: 64.9 (unknown), C: 61.6 (unknown) WHO performance: unknown
Interventions	HT: Capacitative applicators with 2 plates. Timing: after 3rd of 4th fraction of EBRT. Duration: 60 minutes. Sequence: within 30 minutes after EBRT. Frequency: once weekly. Total number: 3. RT: Standard EBRT: 6 MV linear accelerator. No details provided concerning radiation technique. Primary tumour and pelvic draining lymphatics. Total dose of 30.6 Gy in 17 fractions of 1.8 Gy, 5 times a week, with an additional dose of 52.2 Gy to the parametria with central shielding. EBRT to primary tumour and lymphatics 30.6 Gy/ 17 f, additional dose central block 52.2 Gy Brachytherapy: Ir-192 (High Dose Rate). Timing: unknown. Dose per fraction: 7.5 Gy to 'Point A'. Frequency: once weekly during EBRT. Total number: 4. CT: no
Outcomes	CR (at least 1 month after treatment) LR (3Y) DFS (3Y) OS (3Y) TOX acute and late
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Quote: "Randomization to treatment groups".
Allocation concealment?	Low risk	Quote: "Randomization was performed by a computer generated random number list before the start of treatment".
Blinding? All outcomes	High risk	No blinding. However, the outcome measurements are not likely to be influenced.
Incomplete outcome data addressed? All outcomes	Low risk	There were no missing outcome data.
Free of selective reporting?	Unclear risk	No protocol available. Expected outcome measures are reported.
Free of other bias?	Low risk	

Sharma 1991

Methods	single centre RCT (arms = 2) randomisation procedure: adequate, ITT: no, baseline characteristics similar: yes, eligibility criteria specified: yes, losses to follow up fully accounted for: yes, bias due withdrawal/drop-out rate: no, co-interventions influenced results: no Total quality score: 4
Participants	Cervical cancer patients: E: 25, C: 25 FIGO stage IIA (n=3); IIB (n=4) andIIIB (n=43) Histology: squamous cell carcinoma (n=50) Tumour diameter: 2-4 cm (E: 7; C 6); >4 cm (E: 18; C 19) Age: E: 50 (unknown), C: 48 (unknown) Karnofsky > 60
Interventions	HT: Specially designed capacitative intraluminal radiofrequency heating system, consisting of a small intravaginal applicator and a large extracorporeal electrode. Timing: from start of EBRT. Duration: 30 minutes. Sequence: within 30 minutes preceding EBRT. Frequency: on alternate days 3 times per week. Total number: 12. RT: Standard EBRT: linear accelerator or telecobalt. Two parallel opposed fields. Primary tumour and pelvic draining lymphatics. Total dose 45 Gy in 20 fractions in 4 weeks. If brachytherapy not feasible an additional EBRT dose of 20 Gy in 10 fractions using same fields. Brachytherapy: if feasible. Cs-137 (Low Dose Rate). Timing: following EBRT. Dose per fraction: 35 Gy to 'Point A' . Total number: 1. CT: no
Outcomes	LR (18 MO) DFS (18 MO) OS (18 MO) TOX acute and late
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Quote: "The patients were randomised blindly into 2 groups of 25 each".
Allocation concealment?	Low risk	For randomisation the sealed envelope technique was used.
Blinding? All outcomes	High risk	No blinding. However, the outcome measurements are not likely to be influenced.
Incomplete outcome data addressed? All outcomes	Low risk	The number of missing outcome data is equally distributed across the intervention groups with similar reasons for missing.
Free of selective reporting?	Unclear risk	No protocol available. Expected outcome measurements are reported.
Free of other bias?	Low risk	

van der Zee 2000

Methods	Multi centre RCT (arms = 2, centre = 9) randomisation procedure: adequate, ITT: yes, baseline characteristics similar: yes, eligibility criteria specified: yes, losses to follow up fully accounted for: yes, bias due withdrawal/drop-out rate: no, co-interventions influenced results: no Total quality score: 5
Participants	Cervical cancer patients: E: 58, C: 56 FIGO stage IIB (n=22); IIIA (n=1); IIIB (n=80) and IVA (n=11). Histology: squamous cell carcinoma (n=97); adenocarcinoma (n=11); other (n=6) Tumour diameter: < 6cm (E 13; C 12); 6-8 cm (E 26; C 27); > 8 cm (E 19; C 13); unknown (E 0; C 4). Age: E: 51 (26-75), C: 50 (30-82) WHO performance:<2
Interventions	HT: Regional (deep) hyperthermia was applied in 3 different centres using the BSD-2000 system, the 4-waveguide applicator system and the coaxial TEM applicator, respectively. Timing: from the first week of EBRT on. Frequency: once weekly. Duration: 60-90 minutes. Sequence: 1-4 hours after EBRT. Total number: 0 (n=7);1-3 (n=11) and 4-6 (n=40). RT: Standard EBRT: linear accelerator. No details concerning radiation technique. Primary tumour and pelvic draining lymphatics with or without the para-aortic lymph nodes. Total dose 46-50.4 Gy in 23-28 fractions. An additional dose to the pelvic sidewall was delivered in case of residual parametric tumour. If brachytherapy was not feasible an additional dose with EBRT was delivered to the tumour region. EBRT to primary tumour and lymphatics 46-50.4 Gy/ 23-28 f Brachytherapy: if feasible.(1) Ir-192 (High Dose Rate; n=38); Timing: following EBRT. Dose per fraction: 8.5 Gy to 'Point A'. Frequency: weekly. Total number: 2. (2) Cs-137 (Low Dose Rate; n=53); Timing: following EBRT. Dose per fraction: 20-30 Gy to 'Point A'. CT: no
Outcomes	CR (at least 1 month after treatment) LR (3Y) OS (3Y) TOX acute and late
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Quote: "Patients were randomly assigned treatment".
Allocation concealment?	Low risk	Quote: "Randomisation was done centrally by telephone and stratified by centre, tumour site and stage in variable block size".
Blinding? All outcomes	High risk	No blinding. However, the outcome measurements are not likely to be influenced.
Incomplete outcome data addressed? All outcomes	Low risk	There were no missing outcome data.
Free of selective reporting?	Low risk	The study protocol is available. All of the study's pre-specified outcome measures were reported.

van der Zee 2000 *(Continued)*

Free of other bias?	Low risk

Vasanthan 2005

Methods	Multi centre RCT (arms = 2, centre = 5) randomisation procedure: adequate, ITT: yes, baseline characteristics similar: yes, eligibility criteria specified: yes, losses to follow up fully accounted for: yes, bias due withdrawal/drop-out rate: no co-interventions influenced results: no Total quality score: 5
Participants	Cervical cancer patients: E: 55, C: 55 Figo stage IIB (n=56); IIIA (n=9); IIIB (n=42) and IVA (n=3). Histology: squamous cell carcinoma (n=103); adenocarcinoma (n=4); other (n=3). Tumour volume (median): E: 60 cm^3 ; C 50 cm^3. Age: E: 45 (27-72), C: 50 (22-71) WHO performance:<2
Interventions	HT: Capacitative applicators with 2 plates were used for generating local hyperthermia. In at least half of the patients this was combined with an intravaginal electrode. Protocols varied per centre. Timing: not available. Frequency: once weekly. Duration: 60 minutes. Sequence: immediately after EBRT (three centres); immediately before EBRT (one centre) Not available (one centre). Total number: 3-6. RT: Standard EBRT: 6-18 MV linear accelerator or telecobalt. Primary tumour and pelvic lymphatics. (n = 54) A total EBRT dose of 50 Gy in 2 Gy fractions in 5 weeks. Four field box technique. Two patients received an additional EBRT dose of 20 Gy instead of brachytherapy. Brachytherapy: Low Dose Rate. Timing: following EBRT. Dose per fraction: 20-22 Gy to 'Point A'. Total number: 1. (n = 28) A total EBRT dose of 14-18 Gy in 2 Gy fractions followed by an additional dose of 24-32 Gy using central shielding. Parallel opposed fields. Brachytherapy: High Dose Rate. Timing: unavailable. Dose per fraction: 5 Gy to 'Point A'. Frequency: unknown. Total number: 10. (n = 18) A total EBRT dose of 50.4 Gy in 1.8 to 2 Gy fractions, in 5 to 6 weeks. Four field box technique. An additional parametrial boost of 5.4 Gy in 3 fractions with central shielding. Brachytherapy: Co-60 (High Dose Rate). Timing: following EBRT dose of 50.4 Gy. Dose per fraction: 3 Gy to 'Point A'. Frequency: 3 times weekly. Total number: 7-13. (n = 9) A total EBRT dose of 30 Gy in 2 Gy fractions, 5 times a week followed by an additional dose of 20 Gy with central shielding. Four field box or parallel opposed fields. Brachytherapy: High Dose Rate. Timing: concomitantly with EBRT. Dose per fraction: 6 Gy to 'point A'. (n = 1) EBRT to primary tumour and lymphatics 30 Gy/wk, Brachytherapy: A total EBRT dose of 30 Gy in 2 Gy fractions. Brachytherapy: High Dose Rate. Timing: unavailable. Dose per fraction: 6 Gy to 'point A'. Frequency: twice weekly. Total number: 4. CT: no
Outcomes	LR (3Y) OS (3Y)

Vasanthan 2005 *(Continued)*

	TOX acute and late
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Quote: "Patients were registered and randomized".
Allocation concealment?	Low risk	Probably central allocation since (quote) "patients were stratified by institution".
Blinding? All outcomes	High risk	No blinding. However, the outcome measurements are not likely to be influenced.
Incomplete outcome data addressed? All outcomes	Low risk	There were no missing outcome data.
Free of selective reporting?	Unclear risk	No protocol available. Not all expected outcome measures are reported.
Free of other bias?	Unclear risk	The study was terminated after including 110 patients instead of 258 patients originally planned due to 1) the results of a preliminary analysis showing no difference between both treatment arms and 2) the slow accrual rate.

Figure 8

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
El Sharouni 1997	no RCT
Fujiwara 1987	no RCT
Gupta 1999	no RCT
Hasegawa 1989	no RCT
Hornback 1986	no RCT
Kohno 1990	no RCT
Li 1993	not able to contact author
Prosnitz 2002	RCT, ongoing

RCT = Randomized clinical trial

Characteristics of ongoing studies *[ordered by study ID]*

Harima

Trial name or title	Multicenter trial (6 centres)
Methods	
Participants	Cervical cancer
Interventions	RT+HT RT+ CT RT+HT+ CT
Outcomes	unknown
Starting date	unknown
Contact information	Department of Radiology, Kansai Medical University, Moriguchi, Osaka 570-8507, Japan. Y. Harima, principal investigator Email: harima@takii.kmu.ac.jp
Notes	closed after inclusion 62 pts,

Piotrkowicz

Trial name or title	
Methods	
Participants	Cervical cancer
Interventions	RT RT + HT (Int)
Outcomes	side effects
Starting date	01-11-06
Contact information	Brachytherapy dept. N. Piotrkowicz , principal investigator Center Oncology M.S.C. Memorial Institute Warsaw, Poland
Notes	

Prosnitz

Trial name or title	Cisplatin and Radiation Therapy With or Without Hyperthermia Therapy in Treating Patients With Cervical Cancer
Methods	
Participants	Cervical cancer (n = 400) Figo Stage IIB-IVA

Prosnitz *(Continued)*

	Figo Stage IA, IB, or IIA with positive pelvic lymph nodes or parametria by imaging OR pathologically involved at time of surgery
Interventions	RT+ CT RT+ CT+ HT
Outcomes	LRC failure-free survival OS
Starting date	01-06-04
Contact information	Dr. A.M. Westermann Afdeling Medische Oncologie Academisch Medisch Centrum AMC Universiteit van Amsterdam) Meibergdreef 9 1105 AZ Amsterdam Postadres AMC Postbus 22660 1100 DD Amsterdam
Notes	Phase III update of Phase II Westerman et al.

RADCHOC

Trial name or title	RADCHOC
Methods	
Participants	376 cervical cancer figo stage IB-IIA (> similar to 4 CM and IIB-IVA)
Interventions	RT + HT (Reg) RT + CT
Outcomes	EFS LRC OS QoL Costs
Starting date	24-11-03
Contact information	Erasmus MC - Daniel den Hoed Cancer Center Cobi van der Zee, MD,PhD, Cobi van der Zee P.O. Box 5201, Rotterdam, The Netherlands Ph: *31 10 7041470 Email: j.vanderzee@erasmusmc.nl
Notes	

RT = radiotherapy, HT = Hyperthermia, Reg = regional, Int = interstitial, CT = , TOX acute = toxicity acute , TOX late = Toxicity late, EFS = Event Free Survival , LRC = LocoRegional Control, OS = Overall Survival, QoL = Quality of Life, pts = patients, CisPt = cisplatin,

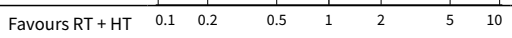
DATA AND ANALYSES

Comparison 1. RT + HT versus RT: all studies

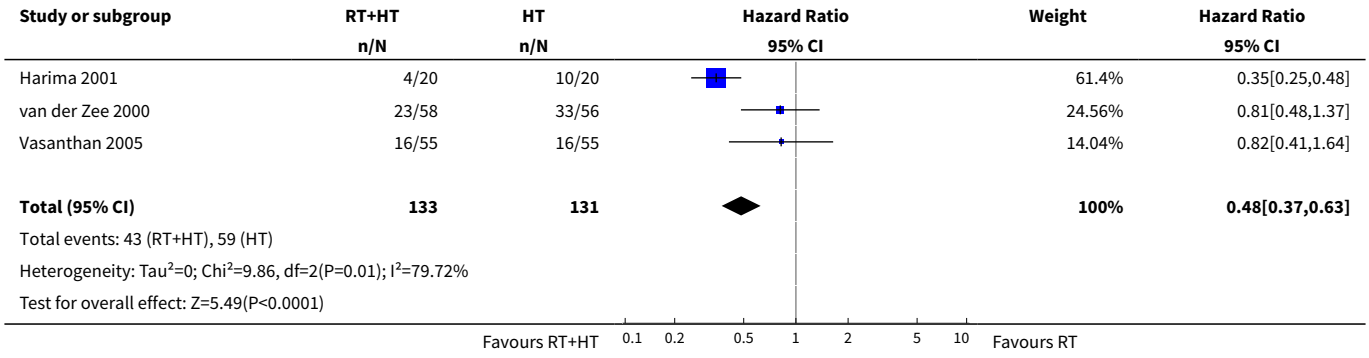
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 complete tumour response	4	267	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.39, 0.79]
2 local tumour recurrence 3y_HR	3	264	Hazard Ratio (95% CI)	0.48 [0.37, 0.63]
3 overall survival_HR (2 and 3 years)	3		Hazard Ratio (95% CI)	Subtotals only
3.1 overall survival 2 years (death within 2 years)	3	264	Hazard Ratio (95% CI)	0.65 [0.42, 1.00]
3.2 overall survival 3 years (death within 3 years)	3	264	Hazard Ratio (95% CI)	0.67 [0.45, 0.99]
4 toxicity (acute and late)	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 acute toxicity (< 3 months)	4	310	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.30, 3.31]
4.2 late toxicity	3	264	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.44, 2.30]

Analysis 1.1. Comparison 1 RT + HT versus RT: all studies, Outcome 1 complete tumour response.

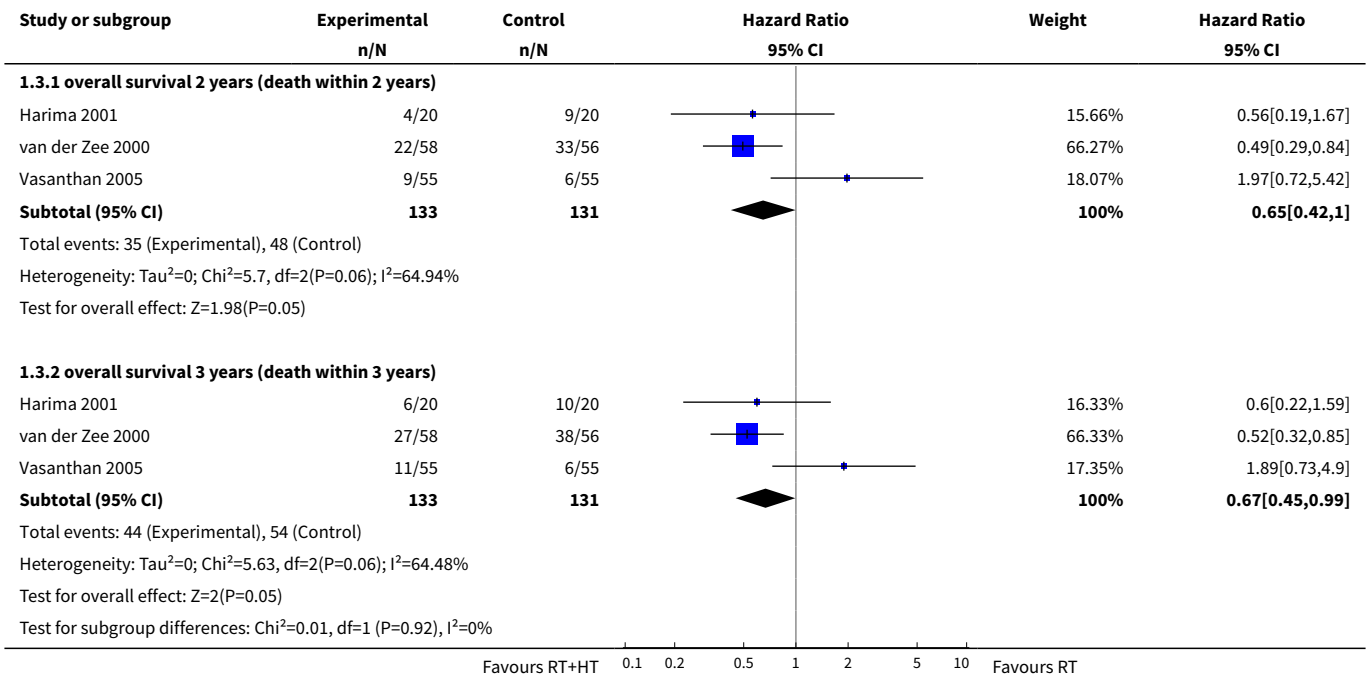
Study or subgroup	RT+HT n/N	RT n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Chen 1997	12/30	16/30		39.07%	0.75[0.43,1.3]
Datta 1987	7/27	11/26		19.54%	0.61[0.28,1.34]
Harima 2001	4/20	10/20		12.37%	0.4[0.15,1.07]
van der Zee 2000	10/58	24/56		29.02%	0.4[0.21,0.76]
Total (95% CI)	**135**	**132**		**100%**	**0.56[0.39,0.79]**
Total events: 33 (RT+HT), 61 (RT)					
Heterogeneity: Tau^2=0; Chi^2=2.68, df=3(P=0.44); I^2=0%					
Test for overall effect: Z=3.33(P=0)					



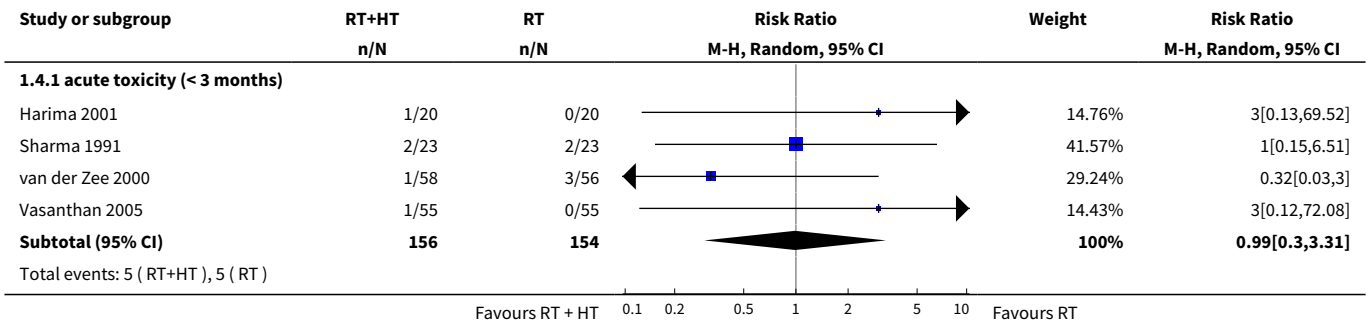
Analysis 1.2. Comparison 1 RT + HT versus RT: all studies, Outcome 2 local tumour recurrence 3y_HR.

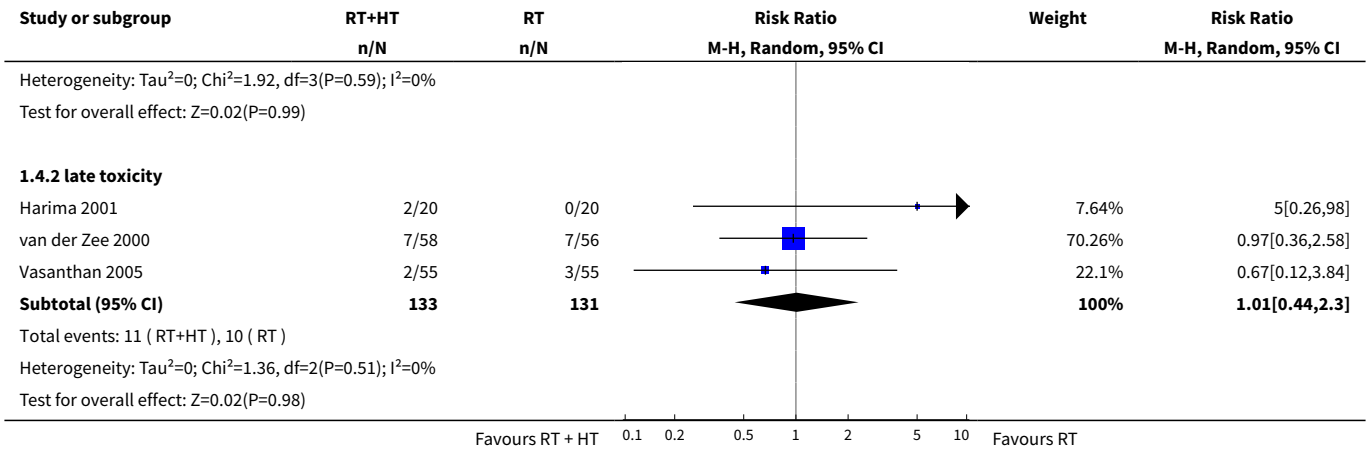


Analysis 1.3. Comparison 1 RT + HT versus RT: all studies, Outcome 3 overall survival_HR (2 and 3 years).



Analysis 1.4. Comparison 1 RT + HT versus RT: all studies, Outcome 4 toxicity (acute and late).





APPENDICES

Appendix 1. MEDLINE

#1 RANDOMIZED-CONTROLLED-TRIAL in PT
#2 CONTROLLED-CLINICAL-TRIAL in PT
#3 RANDOMIZED-CONTROLLED-TRIALS
#4 RANDOM-ALLOCATION
#5 DOUBLE-BLIND-METHOD
#6 SINGLE-BLIND-METHOD
#7 #1 or #2 or #3 or #4 or #5 or #6
#8 (TG=ANIMALS) not (TG=HUMAN and TG=ANIMALS)
#9 #7 not #8
#10 CLINICAL-TRIAL in PT
#11 explode CLINICAL-TRIALS/ all subheadings
#12 (clin* near trial*) in TI
#13 (clin* near trial*) in AB
#14 (singl* or doubl* or trebl* or tripl*) near (blind* or mask*)
#15 (#14 in TI) or (#14 in AB)
#16 PLACEBOS
#17 placebo* in TI
#18 placebo* in AB
#19 random* in TI
#20 random* in AB
#21 RESEARCH-DESIGN
#22 #10 or #11 or #12 or #13 or #15 or #16 or #17 or #18 or #19 or #20 or #21
#23 (TG=ANIMALS) not (TG=HUMAN and TG=ANIMALS)
#24 #22 not #23
#25 #24 not #9
#26 TG=COMPARATIVE-STUDY
#27 explode EVALUATION-STUDIES/ all subheadings
#28 FOLLOW-UP-STUDIES
#29 PROSPECTIVE-STUDIES
#30 control* or prospectiv* or volunteer*
#31 (#30 in TI) or (#30 in AB)
#32 #26 or #27 or #28 or #29 or #31
#33 (TG=ANIMALS) not (TG=HUMAN and TG=ANIMALS)
#34 #32 not #33
#35 #34 not (#9 or #25)
#36 #9 or #25 or #35
#37explode Cervical-Intraepithelial-Neoplasia (MeSH all)

#38 explode Uterine-Cervical-Neoplasms (MeSH all)
#39 cervi*
#40 cancer or tumor or tumour or malignan* or oncol* or carcinom* or neoplas* or growth or adenom* or cyst*
#41 #39 and #40
#42 #37 or #38 or #41
#43 radiother*
#44 radiat*
#45 explode Radiotherapy (MeSH all)
#46 explode Radiotherapy-Computer-Assisted (MeSH all)
#47 #43 or #44 or #45 or #46
#48 Hyperther*
#49 explode Hyperthermia-Induced (MeSH all)
#50 #48 or #49
#51 #42 and #47 and #50
#52 #51and #36

Appendix 2. EMBASE

#34 #33 and #17
#33 #32 and #28 and #23
#32 #31 or #30 or #29
#31 explode "hyperthermic-therapy" / all SUBHEADINGS in DEM,DER,DRM,DRR
#30 explode "hyperthermia-" / all SUBHEADINGS in DEM,DER,DRM,DRR
#29 Hyperther*
#28 #24 or #25 or #26 or #27
#27 explode "computer-assisted-radiotherapy" / all SUBHEADINGS in DEM,DER,DRM,DRR
#26 explode "radiotherapy-" / all SUBHEADINGS in DEM,DER,DRM,DRR
#25 radiat*
#24 radiother*
#23 # 18 or #19 or #20 or #21 or #22
#22 (cervi*) and (cancer or tumor or tumour or malignan* or oncol* or carcinom* or neoplas* or growth or adenom* or cyst*)
#21 cancer or tumor or tumour or malignan* or oncol* or carcinom* or neoplas* or growth or adenom* or cyst*
#20 cervi*
#19 explode "uterine-cervix-tumor" / all SUBHEADINGS in DEM,DER,DRM,DRR
#18 explode "uterine-cervix-carcinoma-in-situ" / all SUBHEADINGS in DEM,DER,DRM,DRR
#17 #12 not #16
#16 #14 not #15
#15 #13 and #14
#14 (ANIMAL or NONHUMAN) in DER
#13 HUMAN in DER
#12 #9 or #10 or #11
#11 (SINGL* or DOUBL* or TREBL* or TRIPL*) near ((BLIND* or MASK*) in TI,AB)
#10 (RANDOM* or CROSS?OVER* or FACTORIAL* or PLACEBO* or VOLUNTEER*) in TI,AB
#9 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
#8 "SINGLE-BLIND-PROCEDURE"/ all subheadings
#7 "DOUBLE-BLIND-PROCEDURE"/ all subheadings
#6 "PHASE-4-CLINICAL-TRIAL"/ all subheadings
#5 "PHASE-3-CLINICAL-TRIAL"/ all subheadings
#4 "MULTICENTER-STUDY"/ all subheadings
#3 "CONTROLLED-STUDY"/ all subheadings
#2 "RANDOMIZATION"/ all subheadings
#1 "RANDOMIZED-CONTROLLED-TRIAL"/ all subheadings

Appendix 3. CENTRAL

#1 Cervical Intraepithelial Neoplasia
#2 MeSH descriptor Uterine Cervical Neoplasms explode all trees
#3 cervi*
#4 cancer or tumor or tumour or malignan* or oncol* or carcinom* or neoplas* or growth or adenom* or cyst*
#5 (#3 AND #4)
#6 (#1 OR #2 OR #5)
#7 radiother*
#8 radiat*

#9 MeSH descriptor Radiotherapy explode all trees
#10 MeSH descriptor Radiotherapy, Computer-Assisted explode all trees
#11 (#7 OR #8 OR #9 OR #10)
#12 Hyperther*
#13 MeSH descriptor Hyperthermia, Induced explode all trees
#14 (#12 OR #13)
#15 (#6 AND #11 AND #14)

HISTORY

Protocol first published: Issue 1, 2007
Review first published: Issue 1, 2010

Date	Event	Description
24 July 2008	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

L Lutgens provided background information, methodology support and co drafted the review. M Pijls-Johannesma designed the literature search strategy, developed methodology and co-drafted review. J van der Zee provided expertise on hyperthermia and co-drafted the review. G van Mastrigt, D de Haas, J.Buijsen, G.Lammering, D De Ruysscher, and P Lambin co-drafted review.

DECLARATIONS OF INTEREST

none

SOURCES OF SUPPORT

Internal sources

- New Source of support, Not specified.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There were several discrepancies between the methods published in the protocol and those used in the actual review.

Firstly, as a consequence of limited data, sensitivity analyses and subgroup analyses could not be performed.

A second discrepancy was the presentation of the outcomes for overall survival, disease free survival and local regional tumour control. According to the protocol this should have been in terms of 2-year and 5-year ratios, however we were only able to extract the 2-year and 3 year figures. Due to the marginal availability of data in this review, these two measures were combined into one ratio (3-year). Moreover, due to limited reporting on disease free survival we were not able to perform analyses for this outcome.

Finally, in order to determine the risk of bias we planned to assess the quality of the included studies by the following criteria:

- Was the randomisation process adequate?
- Was there adequate allocation concealment?
- Was the analysis performed according to intention to treat?
- Were the groups similar at baseline for the most important prognostic indicators?
- Were eligibility criteria specified?
- Were losses to follow up fully accounted for?
- Was the withdrawal/drop-out rate unlikely to cause bias?
- Were co-interventions which may have influenced the results controlled for?

However, in the present review the risk of bias was assessed using the tool described in the Cochrane Handbook for Systematic Reviews of interventions (Higgins 2008) addressing the following 6 domains: Sequence generation (1), allocation concealment (2), blinding (3), incomplete outcome data (4), selective reporting of outcomes (5) and other potential threats to validity (6).

See Figure 8 for list of abbreviations used throughout this review.

Figure 8. Abbreviations

CRT	Chemo-radiotherapy
CT	Chemotherapy
d	day
DFS	Disease Free survival
EBRT	Standard external beam radiotherapy
f	fraction
Gy	Gray
HDR	High dose rate
HRT	Hyperthermy + radiotherapy
HT	Hyperthermia
ITT	Intention to Treat
LC	Loco-regional Control
LDR	Low dose rate
mins	minutes
not analyzed	reported data not analysed in review
Not used	Data not included in analysis
OS	Overall Survival
QoL	Quality of Life
RCT	Randomized clinical trial
RT	Radiotherapy
TOX acute	Toxicity acute
TOX late	Toxicity late
wk	week
ys	years

INDEX TERMS

Medical Subject Headings (MeSH)

Combined Modality Therapy [methods]; Hyperthermia, Induced [*methods]; Randomized Controlled Trials as Topic; Tumor Burden; Uterine Cervical Neoplasms [pathology] [radiotherapy] [*therapy]

MeSH check words

Female; Humans