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Combined use of hyperthermia and radiation therapy for treating locally advanced cervical cancer.
Cochrane Database of Systematic Reviews 2007, Issue 1. Art. No.: CD006377.
DOI: 10.1002/14651858.CD006377.

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[Intervention Protocol]

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

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Editorial group: Cochrane Gynaecological, Neuro-oncology and Orphan Cancer Group.
Publication status and date: Unchanged, published in Issue 4, 2009.

Citation: Lutgens L, Lammering G, Pijls-Johannesma M, van der Zee J, Lambin P, De Ruysscher DKM, Deneufbourg JM. Combined use of hyperthermia and radiation therapy for treating locally advanced cervical cancer. *Cochrane Database of Systematic Reviews* 2007, Issue 1. Art. No.: CD006377. DOI: 10.1002/14651858.CD006377.

ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

This systematic review and meta-analysis aims to provide a comprehensive and reliable summary of the effect of hyperthermia on locally advanced cervix carcinoma when applied concomitantly with radiation therapy. The specific aim is to review prospective phase II and phase III trials evaluating the effect of combined hyperthermia and radiation therapy on tumor control and normal tissue, respectively, in patients treated for cervix carcinoma.

BACKGROUND

For many years radiotherapy alone has been the treatment of choice in patients with locally advanced cervix carcinoma. Spread to the para-aortic lymph nodes has been recognised as the single most important prognostic factor (Fyles 1995; Stehman 1991). Nevertheless pelvic tumor control is a pre-requisite for cure (Haie 1988; Rotman 1995). Perez et al (Perez 1998) 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. Similarly, Horiot et al (Horiot 1988) reported pelvic recurrences in 6%,17%,43% and 56% of 1383 patients with stage I, II, III and IVA, respectively, treated with radiotherapy.

In 1999 and 2000 the results of several randomised clinical trials (RCTs) were published concerning the combined treatment of radiotherapy with chemotherapy (Keys 1999; Morris 1999; Rose 1999; Whitney 1999) or hyperthermia (van der Zee 2000) in patients with cervical carcinoma. However, the therapeutic gain obtained with the addition of either chemotherapy or hyperthermia was not confirmed in more recently published RCTs (Pearcey 2002; Vasanthan 2005). Possible explanations for this discrepancy may be found in the patient selection (e.g. with respect to lymph node status) and other confounding factors such as treatment parameters (e.g. overall radiotherapy 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. Despite this, several groups have initiated a next step in the combined treatment strategy, that is the evaluation of a triple therapy (Westermann 2005).

Several tumor 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 tumor volume (Fyles 1995; Perez 1998; Tsang 1995). Although tumor 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 tumor volume and tumor hypoxia. Thus with increasing tumor volume, tumor 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 hyperthermia will be most effective. The potential benefit of combining hyperthermia with radiotherapy or chemotherapy in cervix carcinomas has been pointed out several decades ago (Brady 1976), but RCTs are scarce. Furthermore, the number of patients included in the few RCTs was small and were 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. However, despite these drawbacks, overall clinical data on the combined use of radiotherapy and hyperthermia suggest a therapeutic gain as compared to radiotherapy used as a single treatment modality (De Wit 1999; Dinges 1998; Harima 2001; Hornback 1986; Rietbroek 1997; van der Zee 2000; Vasanthan 2005). Therefore a systematic analysis on this subject seems justified.

OBJECTIVES

This systematic review and meta-analysis aims to provide a comprehensive and reliable summary of the effect of hyperthermia on locally advanced cervix carcinoma when applied concomitantly with radiation therapy. The specific aim is to review prospective phase II and phase III trials evaluating the effect of combined hyperthermia and radiation therapy on tumor control and normal tissue, respectively, in patients treated for cervix carcinoma.

METHODS

Criteria for considering studies for this review

Types of studies

Prospective phase II or III trials, fully published in journals and those identified from other sources (abstracts and proceedings of relevant scientific meetings and contacts with investigators) for which full details are available from investigators.

Types of participants

Patients of any age with histological proven locally advanced cervical cancer and performance status 0 to 2. Cervical cancers with a central diameter equal or larger than 4 cm and/or FIGO stage IIB to IVA are considered locally advanced.

Studies in which it is not possible to separate data on patients receiving combined hyperthermia plus radiotherapy versus radiotherapy alone, even after contacting the authors, will be excluded.

Types of interventions

Any regimen of cervical (chemo)radiotherapy consisting of curative doses of external beam radiotherapy and brachytherapy given concurrently or not with any hyperthermia regimen. Analyses will be stratified according to radiotherapy dose, overall treatment time of radiotherapy, combined chemotherapy or not and hyperthermia quality parameters. With respect to the concomitant use of chemotherapy and radiotherapy no further distinction is made between different chemotherapy schedules.

Only studies which used a minimum temperature of 41° Celsius for hyperthermia will be included. Studies with less than 20 patients with a mean or median follow-up of less that 12 months will be excluded.

Types of outcome measures

Clinically relevant outcomes will be studied:

- Local tumour recurrence at two and five years
- Acute and late severe normal tissue toxicity
- Clinical complete response at two months (i.e. no evidence of disease as assessed with clinical exam and/or any imaging technique)
- Survival two and five years overall survival (OS)

Search methods for identification of studies

Electronic searches

A search for identification of studies on the review topic will be undertaken of the following electronic databases: The Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library Issue 3, 2006), EMBASE (Webspirs) (1980 to present), MEDLINE(1980 to present). Further, the Cochrane Gynaecological Cancer Groups Specialised Register.

Searches will be performed without restricting the language of studies retrieved.

Search History
#1 explode "Randomized-Controlled-Trials" / all SUBHEADINGS in MIME,MJME,PT
#2 explode "Controlled-Clinical-Trials" / all SUBHEADINGS in MIME,MJME,PT
#3 explode "Random-Allocation" / WITHOUT SUBHEADINGS in MIME,MJME,PT
#4 explode "Double-Blind-Method" / WITHOUT SUBHEADINGS in MIME,MJME,PT
#5 explode "Single-Blind-Method" / WITHOUT SUBHEADINGS in MIME,MJME,PT
#6 #1 or #2 or #3 or #4 or #5
#7 (TG=animals) not ((TG=human) and (TG=animals))
#8 #6 not #7
#9 explode "Clinical-Trial" / WITHOUT SUBHEADINGS in MIME,MJME,PT
#10 clinical-trial in pt
#11 (clin* near trial*) in Ti
#12 (clin* near trial*) in a
#13 (singl* or doubl* or trebl* or tripl*) near (blind* or mask*)
#14 (#13 in ti) or (#13 in ab)
#15 placebos
#16 placebo* in TI
#17 placebo* in AB
#18 random* in TI
#19 random* in AB
#20 research design
#21 #9 or #10 or #11 or #12 or #14 or #15 or #16 or #17 or #18 or #19 or #20
#22 (TG=animals) not ((TG=human) and (TG=animals))
#23 #21 not #22
#24 tg=comparative-study
#25 explode "Evaluation-Studies" / all SUBHEADINGS in MIME,MJME,PT
#26 follow-up studies
#27 prospective studies
#28 control* or prospective* or volunteer*
#29 (#28 in TI) or (#28 in AB)
#30 #24 or #25 or #26 or #27 or #29
#31 (tg=animals) not ((tg=human) and (tg=animals))
#32 #30 not #31
#33 #8 or #23 or #32
#34 (explode "Cervical-Intraepithelial-Neoplasia" / all SUBHEADINGS in MIME,MJME,PT) or (explode "Uterine-Cervical-Neoplasms" / all SUBHEADINGS in MIME,MJME,PT)
#35 cancer or tumor or tumour or malignan* or oncol* or carcinom* or neoplas* or growth or adenom* or cyst*
#36 radiother*
#37 radiat*
#38 (explode "Radiotherapy-" / all SUBHEADINGS in MIME,MJME,PT) or (explode "Radiotherapy-Computer-Assisted" / all SUBHEADINGS in MIME,MJME,PT)
#39 #36 or #37 or #38
#40 #34 and #35 and #39
#41 Hyperther*
#42 explode "Hyperthermia-Induced" / all SUBHEADINGS in MIME,MJME,PT
#43 #41or #42
#44 #33 and #40 and #43

Searching other resources

Reference lists from identified studies will be scrutinised for any other additional studies. The electronic searches for clinical trials will be complemented with manual searches of the following oncology journals: International Journal of Radiation, Oncology, Biology and Physics; Radiotherapy and Oncology; Journal of Clinical Oncology; Clinical Oncology; International Journal of Hyperthermia. Abstracts from the principal oncology conferences not older than three years, will also be hand searched. Colleagues, collaborators and other experts in the field will be asked to identify missing and unreported trials.

Data collection and analysis

Selection of studies

Two review authors (LL and GL) will independently check the titles and abstracts retrieved in the databases searches.
Phase II and III studies identified by the search will be assessed to determine if they meet the inclusion criteria. They will be assessed by three independent authors (LL, GL, DDR) both for the quality of the methods against pre-determined criteria (see below) and for the results of key outcomes, which will be identified and tabulated.

Two review authors (LL, GL) will extract the data independently to ensure validity and discrepancies will be resolved by a third review author (DDR). All data extracted from the include studies will be included in this analyses.
The following data will be collected from the manuscript:

- Identifiers
- Gender
- Age
- Performance status at the time of randomisation
- Initial disease stage
- Definition of chemotherapy regimen
- Induction treatment that led to a complete response
- Start date of induction treatment
- Randomisation date
- Treatment allocated
- Overall treatment time of irradiation according to the protocol and updated information on survival
- Metastasis
- Loco-regional recurrence

Assessment of risk of bias in included studies

This will be assessed according to the following criteria:

Was the randomisation process adequate?Was there adequate allocation concealment?Were the analyses 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 and was the withdrawal/drop-out rate unlikely to cause bias?Were co-interventions which may have influenced the results controlled for?

These single quality criteria will be summarized to a summary quality score for each identified study.

Data synthesis

A weighted estimate of the typical treatment effect across studies will be computed for two-year survival data as well as five-year survival data, local control and toxicities. The risk ratio (RR) will be used as the effect measure. The hazard ratio (HR), will be used as effect measure for the survival analyses. Chi-square heterogeneity tests will be used to test for statistical heterogeneity among trials. As we anticipate that the trial results will be heterogeneous, all analyses will be performed using a random-effects model.Potential causes of heterogeneity will be explored by performing sensitivity and subgroup analysis (see below). In addition, in case of proven heterogeneity, random effects meta-regression will be explored, if there are enough studies to sustain such analysis. This procedure gives an indication of the robustness of the results.Sensitivity and subgroup analysis will be restricted to primary outcome measures using the following factors if appropriate:
Tumour stageHyperthermia techniqueChemotherapy or notRadiation schedule

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CONTRIBUTIONS OF AUTHORS

L Lutgens and GL Lammering provided background information, methodology support and helped draft the protocol. M Pijls-Johannesma designed the literature search strategy, developed methodology and co-drafted protocol. J van der Zee provided expertise on hyperthermia and co-drafted the protocol. P Lambin, JM Deneufbourgh and D De Ruysscher helped co-draft the protocol.

DECLARATIONS OF INTEREST

None

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

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