Articles

Comparison of radiotherapy alone with radiotherapy plus hyperthermia in locally advanced pelvic tumours: a prospective, randomised, multicentre trial

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Summary

Background Local-control rates after radiotherapy for locally advanced tumours of the bladder, cervix, and rectum are disappointing. We investigated the effect of adding hyperthermia to standard radiotherapy.

Methods The study was a prospective, randomised, multicentre trial. 358 patients were enrolled from 1990 to 1996, in cancer centres in the Netherlands, who had bladder cancer stages T2, T3, or T4, N0, M0, cervical cancer stages IIB, IIIB, or IV, or rectal cancer stage M0–1 were assessed. Patients were randomly assigned radiotherapy (median total dose 65 Gy) alone (n=176) or radiotherapy plus hyperthermia (n=182). Our primary endpoints were complete response and duration of local control. We did the analysis by intention to treat.

Findings Complete-response rates were 39% after radiotherapy and 55% after radiotherapy plus hyperthermia ($p<0{\cdot}001$). The duration of local control was significantly longer with radiotherapy plus hyperthermia than with radiotherapy alone ($p=0{\cdot}04$). Treatment effect did not differ significantly by tumour site, but the addition of hyperthermia seemed to be most important for cervical cancer, for which the complete-response rate with radiotherapy plus hyperthermia was 83% compared with 57% after radiotherapy alone ($p=0{\cdot}003$). 3-year overall survival was 27% in the radiotherapy group and 51% in the radiotherapy plus hyperthermia group. For bladder cancer, an initial difference in local control disappeared during follow-up.

Interpretation Hyperthermia in addition to standard radiotherapy may be especially useful in locally advanced cervical tumours. Studies of larger numbers of patients are needed for other pelvic tumour sites before practical recommendations can be made.

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Introduction

In patients with locally advanced tumours of the bladder, uterine cervix, and rectum, local-control rates after standard radiotherapy are disappointingly low. Local tumour control is an important goal of primary treatment, since local failure leads to major morbidity and, moreover, probably increases the risk of distant metastases. For such patients, local treatment failure generally suggests a fatal course of the disease. The potential gain in survival by definitive eradication of locoregional tumours in patients with gastrointestinal, cervical, and genitourinary cancer has been estimated to be about 50%.[1]

Experimental studies have shown that hyperthermia—artificial raising of temperature to 40–45°C—is an effective method of killing cells, especially for cells in hypoxic, nutrient-deprived, and low-pH environments, conditions that are specifically found in malignant tumours. The combination of radiotherapy with hyperthermia increases cytotoxic effects.[2] Several clinical randomised trials in different tumour sites have shown benefits from combined treatment.[3]

Two similar prospective randomised studies were started in the Netherlands in 1990 (the Academic Medical Center [AMC] study, Amsterdam, and the Daniel den Hoed Cancer Center [DHCC] study, Rotterdam), on the effect on local tumour control of standard radiotherapy plus hyperthermia in patients with locally advanced tumours of the bladder, cervix, or rectum. The hypotheses of the two studies were that the addition of hyperthermia to radiotherapy would result in higher locoregional control rates in all three tumour sites. Since it was anticipated that the absolute magnitude of the effect of hyperthermia could be different for the three tumour sites, subgroup analyses were planned in the two studies. The effect of locoregional control on overall survival was a secondary endpoint in each study.

The DHCC study was a multicentre study with ten participating centres, and the AMC was done at one centre. The data of the two studies were combined for analysis, because the inclusion criteria, treatment schedules, and objectives were similar. Here, we present the combined results.

Methods

Patients and randomisation

Patients were eligible for the trial after they were accepted for standard radiation treatment for: bladder cancer, stages T2 (AMC study only), T3 (>5 cm and inoperable), or T4, N0, M0; cervical cancer, FIGO stages IIB (with extension into the lateral parametrium), IIIB, or IV; or rectal cancer, locally advanced primary or recurrent, M0–1. In all patients, diagnosis was confirmed by histopathological assessment. Tumour staging was

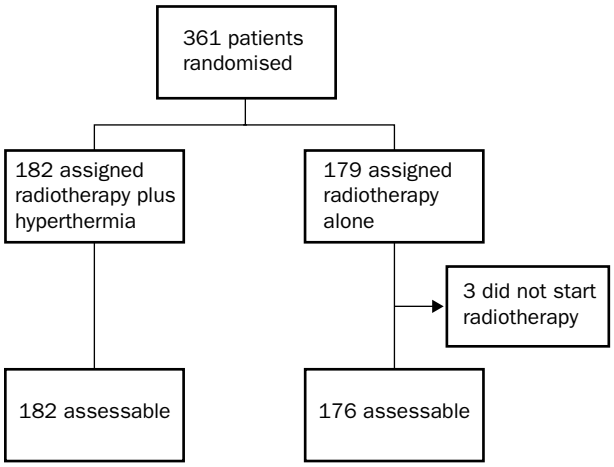

Figure 1: **Trial profile**

done according to the UICC-TNM classification of malignant tumours.[4] Expected survival had to be at least 6 months and WHO performance score less than 2. Patients who had pacemakers or metal implants in the pelvic region larger than 10 cm (eg, hip prostheses) were excluded, since these objects are absolute contraindications for radiofrequency-induced hyperthermia treatment.

Study design

The protocols and consent procedure were approved by the local medical ethics committees. After verbal informed consent had been obtained, patients were randomly assigned treatment with radiotherapy alone or radiotherapy plus hyperthermia (figure 1). Randomisation was done centrally by telephone and stratified by participating centre (AMC, DHCC, or other), tumour site, and stage, in variable block sizes.

Radiotherapy schedules were planned according to local standard schedules. External-beam radiotherapy was given in daily fractions. For rectal cancer, patients received total doses of 46–50 Gy in fractions of 1·8–2·3 Gy, administered directly to the tumour and regional pelvic lymph nodes, followed, if possible, by a boost of 10–24 Gy to the tumour mass. Several patients received total doses of 50 Gy with the intention of achieving resectability. In cervical cancer, 23–28 fractions of 1·8–2·0 Gy were given to the tumour and regional pelvic nodes. If feasible, a brachytherapy boost was delivered to a total dose of 17 Gy, applied in two high-dose-rate fractions (42 patients), or one low-dose-rate fraction of 20–30 Gy (49 patients) in point A located 2 cm lateral to the centre of the uterine canal and 2 cm from the mucous membrane of the lateral fornix in the place of the uterus. In the DHCC study, para-aortal nodes were routinely included in the external radiotherapy field. In bladder cancer, 66–70 Gy was prescribed in fractions of 2 Gy to the bladder, with the regional pelvic lymph nodes included in the field to a total dose of 40 Gy. Dose specifications and target volume definition were according to ICRU report 50.[5]

In the DHCC study, patients from institutes in which hyperthermia equipment was not available received radiotherapy in the original institution, and, if randomised to combined treatment, hyperthermia in Rotterdam.

Hyperthermia was prescribed once weekly during the period of external radiotherapy, 1–4 h after radiotherapy, to a total of five treatments. The three institutions in which deep hyperthermia was available used different systems: the BSD-2000 system in Rotterdam (BSD Medical Corporation, Salt Lake City, UT, USA), the 4-waveguide applicator system in Amsterdam and the coaxial TEM applicator in Utrecht (custom built systems). For each system, the distribution of energy in human-pelvic-size phantoms is similar.[6]

After preparation, including the introduction of thermometry probes[7] and positioning, heating was started. Patients were carefully instructed to mention any unpleasant sensation suggestive of hot spots, such as a burning sensation, a feeling of pressure, or any pain. Any symptom mentioned by the patient that disappeared within 1 min of power decrease was taken to show that the temperature was too high. Treatment settings were adjusted depending on observed temperatures and information from patients. Adjustments of treatment settings were changes in power output per channel, frequency or phase settings, or placement of additional water boluses. Power outputs were increased up to patients' tolerances. The aim was to continue treatment for 60 min after interstitially measured tumour temperature had reached 42°C, or (generally) for a maximum total duration of 90 min.

The primary endpoints of the trial were complete response and duration of local control. Follow-up visits were scheduled 1 month after treatment, once every 3 months during the first 2 years, and every 4–6 months thereafter. Generally, patients were seen alternately by radiation oncologists and gynaecologists, urologists, or surgeons. Complete response was defined as disappearance of all tumour in the irradiated volume and was established 3 months after treatment. In cervical cancer, response was assessed by gynaecological examination and cervical-smear cytology. In bladder cancer, cystoscopy and cytology of urine were done. In irresectable rectal cancer, a complete response was defined by absence of all pretreatment signs of local tumour, such as pain, tumour mass that was palpable, visible, or both, as well as increased concentrations of carcinoembryonic antigen. Patients treated postoperatively after gross incomplete resection

Characteristic	Radiotherapy plus hyperthermia (n=72)	Radiotherapy (n=71)
Sex (M/F)	35/37	37/34
Median (range) age (years)	62 (30–77)	64 (31–85)
WHO performance score		
0	51	50
1	16	16
2	2	5
3	3	. .
Haemoglobin (mmol/L)		
≤7	15	6
>7	34	40
Unknown	23	25
Tumour stage		
Primary/recurrent	12/60	12/59
Postoperative for gross residual	11	10
Preoperative	6	18
Irresectable	55	43
Histology		
Adenocarcinoma	72	70
Unknown	. .	1
Differentiation		
Good	6	10
Moderate	44	48
Poor	15	4
Unknown	7	9
Tumour maximum diameter (mm)		
<60	14	35
60–80	23	15
>80	34	14
Unknown	1	7
Metastatic disease (outside treatment volume)		
Yes	16	11
No	56	60
Radiotherapy*		
Mean (SD) dose (Gy)	56·2 (7·1)	56·7 (6·9)
Mean (range) overall treatment time (days)	42 (29–112)	42 (32–81)
Number of hyperthermia treatments		
0	. .	69
1–3	13	. .
4–6	59	2

*Restricted to patients with total dose ⩾40 Gy; n=71 radiotherapy plus hyperthermia, n=67 radiotherapy.

Table 1: **Characteristics of patients and treatment for rectal cancer**

of the rectal tumour were judged locally controlled while there was no tumour regrowth. In patients treated preoperatively, for whom the aim was to achieve radical operability, a complete response was defined as the finding of microscopically free margins in the surgical sample. Patients who did not show complete response were classified as local-treatment failures at day 0. Time to local failure was defined as the time between randomisation and date of local progression in the irradiated volume, or death because of toxicity. Patients who had complete responses with no evidence of local progression were censored at the date of last follow-up or death.

Secondary endpoints were overall survival, and toxic effects from radiotherapy or hyperthermia. Overall survival was measured from date of randomisation until the time of last follow-up or death. Acute and late toxic effects were scored according to Radiation Therapy Oncology Group and European Organisation for Research and Treatment of Cancer radiation morbidity scoring criteria.[8]

Statistical analysis

The AMC and DHCC studies were each designed to have a sample size of 180 patients to have power of at least 80% to detect a decrease in local-control failure rates from 30–75% after radiotherapy alone, dependent on tumour site, to 15–50% after radiotherapy plus hyperthermia, with a significance level of 5% (two-sided). The two studies expected accrual periods of 3–4 years. Interim analyses were planned after 60 and 120 patients had been assessed for a minimum of 6 months, with the possibility of stopping the trials if significant differences ($p<0·005$) appeared overall or in one of the subgroups.

Analysis was done by intention to treat. Odds ratios for risk of death for each tumour site were calculated with log-rank tests. The total and subtotals were calculated and are shown graphically with 95% CI in Forrest plots, according to the methods of the Early Breast Cancer Trialists Collaborative Group.[9] The same analysis was done for complete response, for which the odds ratios for risk of not reaching complete response were calculated.

Logistic regression was used to analyse differences in complete-response rates between the two treatment groups, and Cox's regression for difference in duration of local control and difference in survival. These preplanned analyses were adjusted for age and tumour size (rectum) or stage (cervix and bladder). Regression analysis were used to test for interaction between treatment effect and tumour site.

Results

In 1993, a pooled interim analysis was done based on 147 assessable patients from the two studies. This analysis showed a higher rate of complete response in the radiotherapy plus hyperthermia group (58 *vs* 37%, $p=0·003$). Although this result met one of the stopping rules, the trials were continued because the overall survival did not differ between treatment groups; longer follow-up was required to show whether an increase in complete-response rate could be maintained, whether the rate would translate into a survival advantage, and to be more specific about the value of additional hyperthermia for the different tumour sites, which is important for practical recommendations.

In September, 1996, entry to the trial was closed after 361 patients had been randomised.

Patients' baseline and treatment characteristics are shown in tables 1–3. The distribution of prognostic factors was equally balanced over the two treatment groups, except for rectal tumours, for which the proportions of tumours with a maximum diameter of more than 8 cm and irresectable tumours were larger in the radiotherapy plus hyperthermia group.

Characteristic	Radiotherapy plus hyperthermia (n=58)	Radiotherapy (n=56)
Median (range) age (years)	51 (26–75)	50 (30–82)
WHO performance score		
0	45	39
1	13	17
Haemoglobin (mmol/L)		
≤7	16	14
>7	37	38
Unknown	5	4
FIGO stage		
IIB-lateral	11	11
IIIA	· ·	1
IIIB	40	40
IVA	7	4
Nodal status		
N0	9	6
N1	16	19
Nx	33	31
Histology		
Squamous-cell carcinoma	51	46
Adenocarcinoma	4	7
Other	3	3
Differentiation		
Good	4	4
Moderate	21	29
Poor	23	15
Undifferentiated	1	· ·
Unknown	9	8
Tumour maximum diameter (mm)		
<60	13	12
60–80	26	27
>80	19	13
Unknown	· ·	4
Radiotherapy*		
Mean (SD)	67·2 (6·0)	66·2 (7·2)
Mean (range) overall treatment time (days)	48 (35–116)	50 (35–121)
Number of hyperthermia treatments		
0	7	56
1–3	11	· ·
4–6	40	· ·

*Restricted to patients with total dose ≥40 Gy; n=57 radiotherapy plus hyperthermia, n=54 radiotherapy.

Table 2: **Characteristics of patients and treatment for cervical cancer**

Three patients in the radiotherapy group did not start treatment because of rapid tumour progression and deterioration of general condition leading to death in 2 months (figure 1, tables 1–3), and were excluded from the analysis. The remaining 358 patients had a median follow-up time of 38 months (range 4–76). In 38 patients (radiotherapy 22, radiotherapy plus hyperthermia 16), of whom 26 had cervical cancer, the applied radiotherapy total dose was less than planned because of clinical circumstances, such as tumour progression outside or within the treatment volume. In patients who had cervical cancer, the main reason for not applying brachytherapy as planned was insufficient tumour regression after external radiotherapy (ten patients in the radiotherapy group, four in the radiotherapy plus hyperthermia group). Two patients in the radiotherapy group requested and received hyperthermia treatments. 16 patients in the radiotherapy plus hyperthermia group received no hyperthermia treatment because of: refusal after consent (ten), contraindications established after randomisation (three), and tumour progression inside (one) or outside (two) the treatment volume. Of the 182 patients in the radiotherapy plus hyperthermia group, 135 (74%) received at least four hyperthermia treatments. Generally, patients received fewer than the five planned treatments because of refusal.

Characteristic	Radiotherapy plus hyperthermia (n=52)	Radiotherapy (n=49)
Sex (M/F)	37/15	40/9
Median (range) age (years)	73 (51–87)	69 (37–89)
WHO performance score		
0	35	41
1	16	7
2	1	1
Haemoglobin (mmol/L)		
⩽7	1	3
>7	19	16
Unknown	32	30
Tumour stage		
T2	4	6
T3	22	19
T4	26	24
Nodal status		
N0	44	43
N1	7	5
Nx	1	1
Histology		
Transitional-cell carcinoma	44	48
Squamous-cell carcinoma	5	..
Other	3	1
Differentiation		
Moderate	5	3
Poor	34	30
Undifferentiated	..	2
Unknown	13	14
Tumour maximum diameter (mm)		
<60	23	28
60–80	14	10
>80	11	9
Unknown	4	2
Metastatic disease (outside treatment volume)		
Yes	1	..
No	51	49
Radiotherapy*		
Mean (SD) dose (Gy)	65·9 (3·3)	64·4 (6·4)
Mean (range) overall treatment time (days)	48 (36–127)	48 (21–90)
Number of hyperthermia treatments		
0	9	49
1–3	7	..
4–6	36	..

*Restricted to patients with total dose ⩾40 Gy; n=49 radiotherapy plus hyperthermia, n=48 radiotherapy.

Table 3: **Characteristics of patients and treatment for bladder cancer**

In 14 patients (13 with bladder cancer and one with rectal cancer) local tumour response was not assessed because of clinical complications due to tumour progression outside the treated volume. 12 of these patients died a median of 4·5 months after randomisation. These 14 patients were assessed as having local failure.

For all tumour sites, a higher rate of complete response was seen in the radiotherapy plus hyperthermia group than in the radiotherapy group, with an overall decrease in the odds of not reaching complete response of 59% (95% CI 40–75, p=0·0003; figure 2). For patients with cervical and bladder cancers, the complete-response rates differed greatly between treatment groups (26% [p=0·003] and 22% [p=0·01]). For the patients with rectal cancer, the overall probability of complete response was 18%, and the absolute increase in rate of complete response in the radiotherapy plus hyperthermia group was 6% and not significant. A test for interaction between treatment group and tumour site for probability of a complete response, however, was not significant (p=0·60). This finding implies that the differences are compatible with effect of hyperthermia on local control between the three tumour

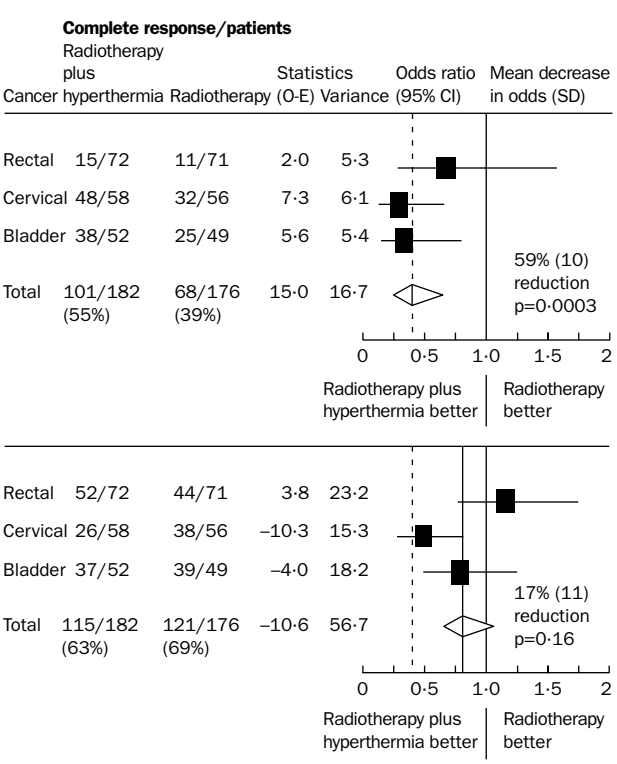

Figure 2: **Odds ratio for not reaching complete response and overall survival**
In these analyses, no adjustment for prognostic factors was applied.

sites are probably compatible with chance fluctuations. The frequency of complete response was higher in older patients than in younger patients (p=0·03) and in patients with less-advanced tumours than in patients with tumours at higher stages (p=0·007). Adjustment for these factors did slightly lower the odds ratio for not reaching a complete response from 0·41 to 0·33.

The actuarial duration of local control was, overall, worse in the radiotherapy group than in the radiotherapy plus hyperthermia group, in which there was a lower local-failure rate (relative hazard ratio 0·76 [95% CI 0·58–0·98], p=0·04; after adjustment for age and tumour size, 0·70 [0·54–0·92], p=0·01). For patients who had cervical cancer, the initial difference in local control was maintained during follow-up. For patients with bladder cancer, the difference in duration of local control between the two treatment groups was not significant. However, there was no significant interaction between treatment group and tumour site for duration of local control (p=0·44). At 3-year follow-up, the rates of local control in the radiotherapy plus hyperthermia group and the radiotherapy group, respectively, were 38% and 26% for all patients, 16% and 8% for rectal cancer, 61% and 41% for cervical cancer, and 42% and 33% for bladder cancer.

On average, the odds of death was slightly lower for radiotherapy plus hyperthermia than for radiotherapy alone (17% [95% CI –10 to 36], p=0·16; figure 2). After adjustment in the regression analysis for age, tumour site, tumour size or stage, and study, overall survival differed significantly between groups (relative hazard rate 0·74 [0·57–0·97], p=0·03). There was no significant interaction between tumour site and treatment for risk of death (p=0·12), although large differences between the tumour sites are apparent (figure 3). At 3-year follow-up,

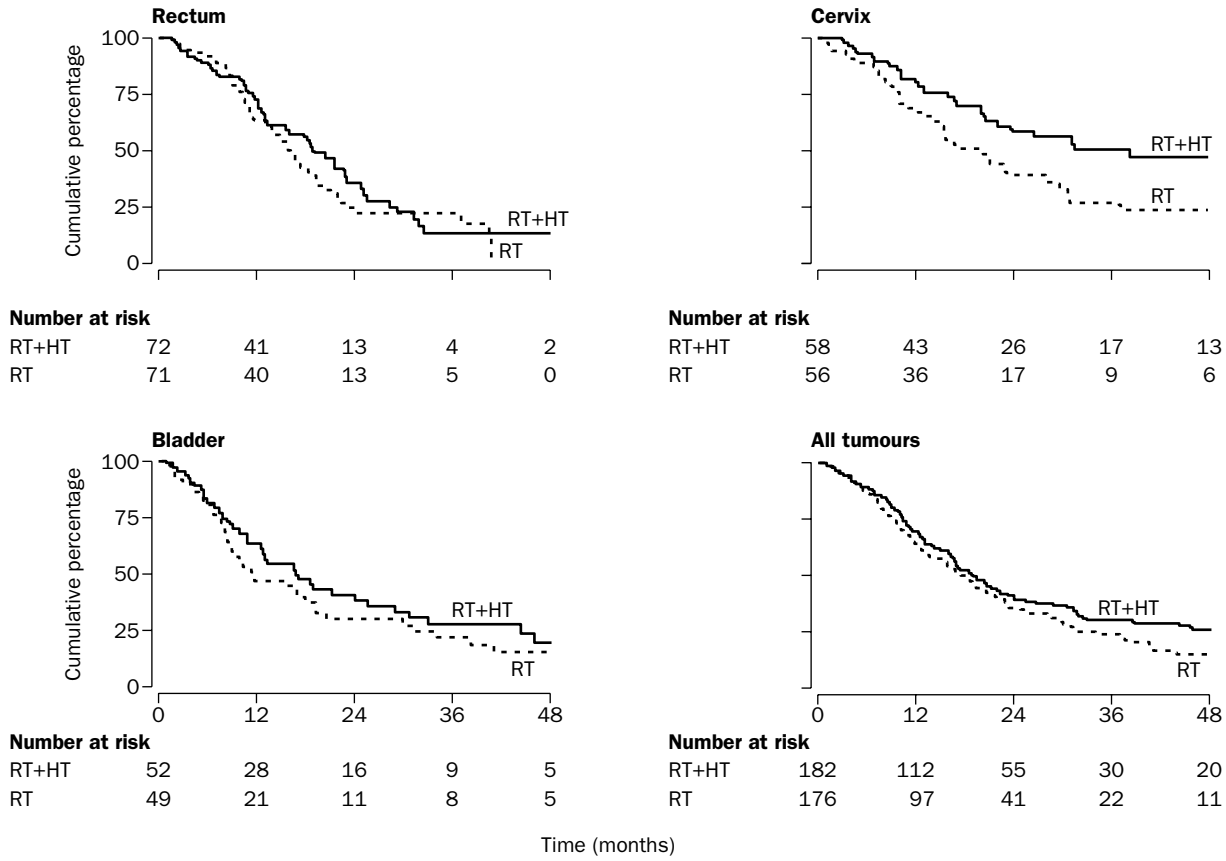

Figure 3: **Overall survival by tumour site and combined**
RT+HT=radiotherapy plus hyperthermia; RT=radiotherapy.

the overall survival in the radiotherapy plus hyperthermia group and in the radiotherapy group were 30% and 24% for all patients, 13% and 22% for rectal cancer (p=0·44), 51% and 27% for cervix cancer (p=0·009), and 28% and 22% for bladder cancer (p=0·33).

Hyperthermia treatment was generally well tolerated and admission to hospital was not required. Features of hyperthermia treatment that the patients found unpleasant were the introduction of thermometry probes and the long duration of treatment. Hyperthermia-related toxic effects were as follows. Subcutaneous burns—the clinical symptoms of which are a subcutaneous induration, leading to discomfort for generally less than 2 weeks' duration and disappearing spontaneously—occurred in 20 patients. Skin burns developed in five patients—one blister, healing within 2 weeks, and two third-degree burns healing after 2 months' conservative treatment. In two patients, deeper burns of skin and subcutaneous tissue developed, requiring conservative treatment of longer duration. Some patients developed infection after introduction of bladder catheters or intratumour thermometry catheters. Treatment was delayed for seven patients in the radiotherapy plus hyperthermia group, and for one in the radiotherapy group. These effects did not lead to differences in overall treatment time.

The frequency of acute or late radiation toxic effects did not differ between treatment groups. Acute grade 3–4 radiation-related toxic effects were seen in 4% of patients (2·2% in the radiotherapy plus hyperthermia arm, 5·9% in the radiotherapy arm). The actuarial cumulative incidence of grade 3–4 toxic effects from radiation at 2 years was 12% in each group. Two patients (one in each group) died because of late toxic effects—one in the radiotherapy plus hyperthermia group because of perforation of the small intestine secondary to an untreated ileus due to stenosis of the rectosigmoid, and one in the radiotherapy group postoperatively after resection of an ischaemic part of the small intestine.

Discussion

The addition of hyperthermia to radiotherapy can improve local control and overall survival in patients with advanced pelvic tumours. Complete-response rates were increased for all tumour sites and overall survival was improved for cervical and bladder cancer. The overall gain seemed higher in cervical and bladder cancer than in rectal cancer, although tests for interaction showed no significant difference in hyperthermia effect between the three tumour sites. The power of these tests was, however, limited because of the small numbers of patients in each tumour subgroup.

The improved local-control rates were not accompanied by increased toxic effects from radiation. This finding is similar to the results of randomised studies comparing radiotherapy plus hyperthermia with radiotherapy in superficially located tumours.[3] The objective tolerance of the hyperthermia treatment was generally good. 41% of patients refused to receive all five planned hyperthermia treatments, but refusal might be explained by their knowledge of the experimental nature of the treatment. Since September, 1996, hyperthermia has been administered in a standard way with radiotherapy to patients with advanced cervical cancer in the centres that had participated in the study. In the DHCC since that time, 80 (78%) of 102 patients treated with combined therapy received five hyperthermia

treatments, and 93% at least four. The main reason for patients receiving fewer than five treatments was logistic difficulties.

In our subgroup analysis, the results for rectal cancer were disappointing. Complete response was seen in 18% of patients, which was not significantly improved by the addition of hyperthermia. The 3-year local-control rate was only 8% in the radiotherapy group and 16% in the radiotherapy plus hyperthermia group. Given the advanced stages of tumours, our results for the radiotherapy group are in line with other complete-response rates of 9–20% for irresectable rectal tumours.[10,11] The absence of a beneficial effect from the addition of hyperthermia to radiotherapy in our trials can probably be explained by the relatively low doses of radiotherapy because of the mainly large recurrent tumours. Results of randomised trials of radiotherapy given at 50 Gy after surgery for microscopic tumour residual have shown only small improvements in local control and no gain in survival.[12,13] In experimental studies, combined hyperthermia and radiotherapy has had a more than additive effect. Whether much can be expected from a sensitising effect when hyperthermia is applied once weekly is, however, questionable. Probably the main gain of hyperthermia is a direct effect on the hypoxic tumour cells. This extra cell kill will be clinically relevant in a small proportion of patients only, and studies of more patients are required to establish such an improvement.

Results of combined radiotherapy and hyperthermia in colorectal cancer have been reviewed.[14] One small study compared radiotherapy plus hyperthermia with radiotherapy alone given to patients who were unsuitable for hyperthermia. The radiotherapy plus hyperthermia group had a higher response rate and longer local progression-free survival. Two randomised studies showed that, before surgery, radiotherapy plus hyperthermia was superior to radiotherapy alone and improved tumour response and survival. A phase II study showed promising results for patients with T3 and T4 tumours treated before surgery with combined radiotherapy, chemotherapy, and hyperthermia.[15]

The complete-response rate of 51% and 3-year local-control rate of 33% we saw for bladder cancer after radiotherapy alone, are within the range of those seen in other studies. Complete-response rates of 42–46% after 50–66 Gy in bladder tumours of stage T3–4 have been reported.[15,16] In our trial, the addition of hyperthermia significantly increased the complete-response rate from 51% to 73%. Unfortunately, long-term local control and overall survival were not significantly improved. Reports on radiotherapy alone in bladder cancer have shown that pelvic local control is frequently not long term, with local control of 3–4 years' duration in stages T1–4 in 25–50% of patients.[16–18] The shortage of good long-term results may be because radiotherapy, given alone or combined with hyperthermia, kills enough cells to establish a clinical complete response but does not sterilise all clonogenic tumour cells.

Other reports of radiotherapy and hyperthermia in bladder cancer are scarce and mostly inconclusive. The abstract of one small randomised study reported significant improvements in pelvic control and survival.[19]

In cervical cancer, we saw a striking therapeutic gain by addition of hyperthermia, with an increase in 3-year local control from 41% to 61%, and in 3-year overall survival from 27% to 51%. At this tumour site, the 3-year local-control rate of 41% and overall-survival rate of 27% after radiotherapy alone were lower than rates generally reported elsewhere. Several studies of large groups of patients with stage IIB–IV cancers, report 5-year local-control rates of about 60%,[20,21] and one reports a 10-year local-control rate of 68%.[22] There are several explanations for the relatively poor overall results seen in our patients.

First, many patients were selected because of an anticipated poor outlook. The median age was young at 50 years, and the maximum tumour diameter was at least 6 cm in 77% of patients. 69% of patients for whom computed-tomography scans were available had pathologically enlarged lymph nodes. Younger age, larger tumour size, and positive lymph nodes have all been associated with poorer results.[21–23] Magee and colleagues[24] reported a wide variation of tumour sizes in FIGO stages IIB and IIIB, and found that tumour size was a better predictor of local control than FIGO stage. They concluded that this finding has implications for the comparison of results from different centres, in which variation in treatment results may be partly because of differing tumour sizes.

Second, we assesssed all patients, including all those who did not complete the planned treatment schedule. In the subgroup of patients treated with a total dose that was thought to be inadequate (<63 Gy at point A), we found a higher complete-response rate in the radiotherapy plus hyperthermia group than in the radiotherapy group, although the observed initial differences in local control and overall survival were lost in the first 16 months of follow-up. The results in patients treated according to protocol were better than those who did not complete treatment.

Two small randomised studies comparing radiotherapy with radiotherapy plus hyperthermia in patients with cervical cancer FIGO stage IIIB showed improvements in local control and disease-free survival with the addition of hyperthermia.[25,26] In cervical cancer, the impact of the radioresistant tumour cells in the poorly perfused areas on locoregional control is suggested by previous results of radiotherapy applied under hyperbaric conditions.[27] Later studies showed that cervical tumours contain high proportions of hypoxic areas, and that hypoxia influences prognosis in a negative way.[28,29]

Investigators have shown that combined radiotherapy and cisplatin for cervical cancer improved disease-free and overall survival.[30] Since the addition of hyperthermia to radiotherapy did not increase the frequency of toxic effects from radiation, and application of hyperthermia to cervical tumours in addition to cisplatin was found to be safe as well,[31] a logical next step would be to study the three treatments together in these tumours.

Hyperthermia combined with radiotherapy is beneficial for patients with advanced pelvic tumours, especially for advanced cervical tumours. Since 1996, use of hyperthermia in standard treatment for cervical cancer was eased by financial considerations. There is a widely spread misconception that hyperthermia is an expensive treatment. Application of the treatment is labour-intensive and requires the availability of some substantial resources. The DHCC study, however, showed hyperthermia to be highly cost effective. In our institutions, combined radiotherapy and hyperthermia is the treatment of choice for patients with cervical cancer of FIGO stage IIB–IVA. For the other two tumour sites, evidence is required from

trials with more patients before practical recommendations can be made.

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Jacoba van der Zee, Dionisio González González, Gerard C van Rhoon, and Jan D P van Dijk were the project leaders and initiators of the Dutch Deep Hyperthermia Trial, and were all involved in the protocol design, data analysis, and preparation of the paper. Jacoba van der Zee and Dionisio González González were responsible for coordination of the two clinical studies. Gerard C van Rhoon and Jan D P van Dijk were the physicists responsible for hyperthermia quality control. Wim L J van Putten and Augustinus A M Hart were involved in protocol design and data analysis, did the statistical assessment, and were further involved in the interpretation of the results and preparation of the paper.

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