First Results of Triple-Modality Treatment Combining Radiotherapy, Chemotherapy, and Hyperthermia for the Treatment of Patients with Stage IIB, III, and IVA Cervical Carcinoma

Anneke M. Westermann, M.D., Ph.D.[1]
Ellen L. Jones, M.D.[2]
Baard-Christian Schem, M.D.[3]
Elzbieta M. van der Steen-Banasik, M.D.[4]
Peter Koper, M.D.[5]
Olav Mella, M.D.[3]
Apollonia L. J. Uitterhoeve, M.D.[6]
Ronald de Wit, M.D., Ph.D.[7]
Jacobus van der Velden, M.D., Ph.D.[8]
Curt Burger, M.D., Ph.D.[9]
Clasina L. van der Wilt, M.Sc.[10]
Olav Dahl, M.D., Ph.D.[3]
Leonard R. Prosnitz, M.D.[2]
Jacoba van der Zee, M.D., Ph.D.[7]

[1] Department of Medical Oncology, Academic Medical Center, Amsterdam, The Netherlands.

[2] Department of Radiotherapy, Duke University Medical Center, Durham, North Carolina.

[3] Department of Radiotherapy, Haukeland Hospital, Bergen, Norway.

[4] Department of Radiotherapy, Arnheim Radiotherapy Institution, The Netherlands.

[5] Department of Radiotherapy, Erasmus Medical Center, Rotterdam, The Netherlands.

[6] Department of Radiotherapy, Academic Medical Center, Amsterdam, The Netherlands.

[7] Department of Medical Oncology, Erasmus Medical Center, Rotterdam, The Netherlands.

[8] Department of Gynecology, Academic Medical Center, Amsterdam, The Netherlands.

[9] Department of Gynecology, Erasmus Medical Center, Rotterdam, The Netherlands.

[10] Comprehensive Cancer Center, Amsterdam, The Netherlands.

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Address for reprints: Anneke M. Westermann, M.D., Ph.D., Department of Medical Oncology, F4-224, Academisch Medisch Centrum, Postbus 22660, 1100 DD Amsterdam, The Netherlands; Fax: (011) 31 206919743; E-mail: a.m.westermann@amc.uva.nl

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BACKGROUND. Patients with advanced cervical carcinoma are treated routinely with radiotherapy and cisplatin-containing chemotherapy. It has been shown that hyperthermia can improve the results of both radiotherapy and cisplatin. In the current study, the feasibility and efficacy of the combination of all three modalities was studied in previously untreated patients with cervical carcinoma.

METHODS. Patients with advanced cervical carcinoma were registered prospectively in the U.S., Norway, and the Netherlands. External-beam radiotherapy and brachytherapy were administered for a biologically effective dose $\geq$ 86.7 gray. At least 4 courses of weekly cisplatin (40 mg/m^2) and 4 sessions of weekly locoregional hyperthermia were added to radiotherapy.

RESULTS. Sixty-eight patients with a median age of 45 years were enrolled. Full-dose radiotherapy was delivered to all patients according to plan. At least 4 courses of chemotherapy were received by 97% of patients, and at least 4 courses of hyperthermia treatment were received by 93% of patients. Toxicity was fully comparable to that described for chemoradiotherapy alone, and the median total treatment time was 45 days. Complete remission was achieved by 61 patients (90%). After a median follow-up of 538 days, 74% of patients remained alive without signs of recurrence, and the overall survival rate was 84%.

CONCLUSIONS. The combination of full-dose radiotherapy, chemotherapy, and hyperthermia was feasible and effective in a multicenter international setting among patients with advanced cervical carcinoma. A Phase III study comparing this novel triplet with standard chemoradiation, designed to show at least a 15% improvement in overall survival, has been launched. ***Cancer*** **2005;104:763–70.**

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Cervical carcinoma is a common malignancy with a yearly incidence of 10 per 100 000 women in the U.S., with 5-year survival ranging from > 90% for patients with Stage IA disease to < 40% for patients with Stage IIIB disease.[1] Radical surgery is reported to be successful in patients with early-stage cervical carcinoma, but patients who have more extensive disease are treated with cisplatin-containing chemoradiation, the efficacy of which has been demonstrated to date in five large, randomized studies.[2–7]

Hyperthermia (HT), which is defined as an artificial elevation of tissue temperature to > 40 °C, is synergistic with radiotherapy (RT) in a number of tumors.[8] Two Phase III trials randomizing between RT and RT plus HT as primary treatment in patients with locally advanced cervical carcinoma showed both improved complete response rates and improved overall survival for the combination treatment.[9,10] HT also enhances the activity of chemotherapy, most notably that of cisplatin.[11] The combination of cisplatin and locoregional HT increased response rates and survival in patients with recurrent cervical carcinoma without added toxicity.[12,13]

In view of the fact that both concurrent chemotherapy and concurrent HT add to the efficacy of RT in patients with cervical carcinoma, we hypothesized that combining all three modalities would improve outcomes further. Preclinical studies have supported this trimodality approach[14] as well as a Phase I/II study in patients with advanced malignancies.[15]

Based on these data, three similar but separate Phase II studies of the efficacy and toxicity of adding deep, locoregional HT to cisplatin and RT in patients with advanced cervical carcinoma were initiated independently in the U.S., Norway, and The Netherlands. In 2001, we decided to gather and analyze the data centrally and to present the results in this combined report.

MATERIALS AND METHODS

Setting

Three prospective, Phase I–II studies were carried out in the U.S., Norway, and The Netherlands. The patients in the U.S. were treated at Duke University Medical Center (Durham, NC) between August 1998 and December 2000. The Norwegian study was performed at Haukeland University Hospital (Bergen) between April 2000 and May 2002. The Dutch patients were treated at different RT institutions (Rotterdam, Amsterdam, Arnhem, and Enschede) and in the Hyperthermia Departments at the Academic Medical Center (Amsterdam) or the Erasmus Medical Center (Rotterdam) between May 2000 and June 2002. The studies were performed in accordance with the Declaration of Helsinki, all studies were approved by the local Institutional Review Board, and all patients provided written informed consent. Patients were registered prospectively at the local data center (U.S. and Norway) or at the Comprehensive Cancer Center in Amsterdam (all Dutch patients). A report on 12 patients from the U.S. has been published previously[16]: Ten of those 12 patients (the patients with primary tumors) also are part of the current data set of 13 patients in the U.S. The data from all patients from all locations were registered on case record forms that were designed for this assessment and were collected in Amsterdam, where they were analyzed at the Comprehensive Cancer Center.

Patients

Eligible patients were age > 18 years with previously untreated, histologically confirmed, invasive carcinoma of the uterine cervix. Adenocarcinoma, planocellular carcinoma, and mixed histology were allowed, but small cell histology was an exclusion criteria. Patients were staged according to the International Federation of Gynecology and Obstetrics (FIGO) with Stage IIB, Stage IIIA, Stage IIIB, or Stage IVA disease in all three countries or with inoperable Stage IB diseases (U.S. only). Paraaortic RT fields were permitted in the Norwegian and U.S. patients, but not in the Dutch patients. The performance status of each patient had to be Eastern Cooperative Oncology Group-Zubrod 0, 1, or 2. Adequate bone marrow function, demonstrated by leukocyte counts $> 3 \times 10^9$/L, an absolute neutrophil count $> 1.5 \times 10^9$/L, and platelets $> 100 \times 10^9$/L, was mandatory. Hemoglobin had to be at $\geq$ 7.0 mmol/L (11.2 g/100 mL) at the beginning of treatment and during treatment, and this could be accomplished with either erythropoietin or transfusion at the physician's discretion. Adequate renal function, defined as creatinine clearance calculated using the Cockroft formula of at least 60 ml/minute, was required. Locoregional HT had to be feasible technically. Serious concomitant disease or active infection was not allowed, and neither was previous malignancy that conceivably still could be active.

Treatment

RT

All patients received 15-megavolt (MV) external-beam RT to the whole pelvis to a total of 45.0–50.4 grays (Gy) in 5 fractions of 1.8–2.0 Gy per week using a 4-field box technique, according to local protocol, and also to the paraaortic nodes when indicated in the U.S. and Norway. Brachytherapy was administered according to local protocol, employing high-dose-rate brachytherapy (Rotterdam and Norway), low-dose-rate

brachytherapy (U.S., 0.5 Gy per hour; Amsterdam, 1.0 Gy per hour), or pulsed-dose-rate brachytherapy (Arnhem, 0.6 Gy per hour per pulse) up to a total biologically effective dose (BED) of at least 86.7 Gy ($\alpha/\beta = 10$ Gy) to Point A, except for 1 patient who received a BED of 71 Gy.[17–19] External side-wall boosts were given when appropriate to administer a minimal dose of 60 Gy to the side wall.

Chemotherapy

Patients were treated with weekly cisplatin at a dose of 40 mg/m^2 during external-beam RT, with an optional final course before brachytherapy in those centers at which brachytherapy was delivered the week after external RT. Only in the Netherlands did the first 6 patients received 30 mg/m^2 as a first dose level. Cisplatin was dissolved in NaCl 3% and administered over 90–180 minutes according to local preference, with appropriate prehydration and posthydration measures and antiemetics, typically including a 5-hydroxytripamine antagonist and a steroid. Weekly blood counts and serum creatinine were mandatory.

HT

Regional whole-pelvis HT was administered on a weekly basis, either concomitant with cisplatin chemotherapy (Amsterdam, Bergen, and Rotterdam), or independent from chemotherapy (U.S., and the patients in Rotterdam who received RT at another hospital), and before or after the RT of that day. Patients who were scheduled to receive cisplatin the day before brachytherapy were eligible to receive an optional final course of HT on that day. HT was not scheduled concurrent with brachytherapy. Five treatments were planned using a BSD 2000 annular phased array (BSD Medical Corp, Salt Lake City, UT) or the 4-waveguide applicator system (Amsterdam only). Thermometry catheters were placed in the rectum, bladder, and cervical os, vagina, or intratumoral space (Bergen) for thermal dose calculations. Power output was increased until the patient's tolerance threshold was reached, following appropriate adjustments of treatment settings. The objective of HT treatment was to continue treatment for 60 minutes after cervical os or vaginal measurements reached 40 °C (Norway, U.S.) or 41 °C (The Netherlands) or, if that temperature was not reached within 30 minutes, for a maximum of 90 minutes.

Statistical Analysis

The objective of the U.S. and Norwegian pilot series was to assess the feasibility and toxicity of trimodality therapy for cervical carcinoma. The Dutch trial was conducted according to the two-stage Simon design,[20] after no dose-limiting toxicity had occurred in the first six patients. The endpoint was the number of patients who were able to complete treatment, defined as full-dose RT, at least four cisplatin courses, and at least four HT courses. Acceptable was defined as $\geq$ 90% patients receiving full treatment, and unacceptable was defined as $<$ 70% of patients receiving planned treatment, with an α of 0.10 and a β of 0.10. In the first step, nine patients were treated and, if six or less patients were able to complete treatment, then the trial would be stopped and the treatment combination declared not feasible. In the second stage, the patient number was increased to 28 on the premise that, if 22 patients or less could finish treatment, then the combined-modality treatment would be abandoned. At the end of the trial, if the 95% confidence interval (95% CI) of the complete remission (CR) rate did not include 50%, then the regimen would be rejected for lack of efficacy.

RESULTS

Patient Characteristics

In total, 68 patients were treated with a combination of RT, cisplatin chemotherapy, and whole-pelvic HT in the 3 trials. The median patient age was 45 years (range, 26–75 years), and the majority of patients had a ECOG-Zubrod performance status 0 or 1. Sixty-two patients had squamous cell histology, 42 patients had FIGO Stage IIB disease, and 21 patients had Stage IIIB disease (Table 1). Paraaortic disease, which was allowed in the U.S. protocol only, was present in eight patients.

Treatment Characteristics

Full-dose, external-beam RT could be delivered according to plan to all patients. The median dose to the whole pelvis was 46 Gy, and 39 patients (57%) received an external boost to the pelvic side wall of 7.2 Gray (median). Brachytherapy was considered unsuitable for 3 Norwegian patients, who received higher dose external-beam RT (total pelvic doses of 73.4 Gy, 73.8 Gy, and 77.4 Gy, respectively). Brachytherapy was delivered at high dose rate in 32 patients, low dose rate in 27 patients, and at pulsed dose rate in 6 patients.

All but 2 patients received at least 4 courses of chemotherapy, and, in 10 courses, the dose was reduced by 25%, mainly due to nephrotoxicity or weight loss. Chemotherapy was withheld for one or more cycles because of toxicity or patient refusal in five patients.

It was feasible to heat all patients, but five patients received less than four courses, either because of toxicity or due to patient refusal. In addition, the range of achieved thermal doses varied. The average tempera-

TABLE 1
Patient Characteristics in the Three Different Trials and Combined Data

Characteristic	Netherlands	Norway	U.S.	Total
No. of patients	36	19	13	68
Age (yrs)				
Median	48	49	40	45
Range	30–75	34–64	26–57	26–75
Performance status[a]				
0	24	16[b]	5	45
1	12	2	7	21
2	—	—	1	1
FIGO stage				
Stage IB inoperable	—	—	3	3
Stage IIB	26	11	5	42
Stage IIIB	9	7	5	21
Stage IVA	1	1	—	2
Paraaortic lymph node involvement	—	—	8	8
Histology				
Squamous cell	33	18	11	62
Adenocarcinoma	3	1	1	5
Mixed	—	—	1	1

FIGO: International Federation of Gynecology and Obstetrics.
[a] Performance status was based on Eastern Cooperative Oncology Group-Zubrod score.
[b] One unknown.

TABLE 2
General Treatment Characteristics

Treatment	Netherlands (n = 36)	Norway (n = 19)	U.S. (n = 13)	Total (n = 68)
RT duration before boost				
Duration in days	35	43	43	40
Range (days)	30–46	19–61	40–65	19–65
No. > 49 days (%)	0	4	5	9 (13)
RT duration including side-wall boost				
Duration in days	37	46	52	45
Range (days)	30–56	36–61	40–73	30–73
No. > 49 days (%)	5	6	11	22 (32)
Median total BED RT (Gy)	87.7	87.3	89.4	—
No. of chemotherapy cycles				
< 4 cycles	1	—	1	2
≥ 4 cycles	35	19	12	66
HT courses				
< 4 courses	2	—	3	5
≥ 4 courses	34	19	10	63
Average T90 in °C	39.7	NA	38.6	39.4
Average T50 in °C (no. of treatments)	41.0 (161)	41.1 (84)	39.2 (52)	40.7 (297)

RT: radiotherapy; BED: biologically effective dose; Gy: grays; HT: hyperthermia; T90: the temperature that was equaled or exceeded by 90% of all measured points; NA: not available; T50: the temperature that was equaled or exceeded by 50% of all measured points.

TABLE 3
NCI Common Toxicity Criteria Grade 3–4 Acute Toxicity for 66 Patients[a]

Toxicity	Netherlands (n = 34)	Norway (n = 19)	United States (n = 13)	Total (%) (n = 66)
Leukopenia	5	2	1	8 (12.1)
Thrombopenia	0	2	0	2 (3.0)
Fatigue	3	0	0	3 (4.5)
Diarrhea	3	0	0	3 (4.5)
Nephrotoxicity	1	1	0	2 (3.0)
Other	5[b]	0	0	5 (7.6)

NCI: National Cancer Institute.
[a]The worst toxicity per patient was scored.
[b]Patients in this category included two patients with pain related to tumor, one patient with a skin reaction related to radiotherapy, one patient with thrombosis, and one patient with constipation.

ture that was equaled or exceeded by 90% of all measured points (T90) was 38.6 °C for the patients from the U.S. (n = 13 patients), 39.7 °C for the Dutch patients (n = 34), and 39.4 °C for the combined U.S. and Dutch data set. The average temperature that was equaled or exceeded by 50% of all measured points (T50) was 41.0 °C in The Netherlands, 41.1 °C in Norway, and 39.2 °C in the U.S., with an overall average T50 based on 297 treatments of 40.7 °C (Table 2).

Treatment duration for external-beam RT to the whole pelvis was a median 35 days, and it was a median of 40 days when brachytherapy was included. The median treatment time increased to 45 days when external-beam RT to the pelvic side wall was included. Total treatment time exceeded 49 days for only 9 of 68 patients when a side wall boost was not considered but extended beyond 49 days in 22 of 68 patients when a side wall boost was taken into consideration (Table 2).

The most common side effects were leukopenia, fatigue, nausea, emesis, and diarrhea. A minority of patients suffered renal toxicity. Specific HT-related side effects consisted of pain (n = 5 patients), Grade 1 (according to National Cancer Institute Common Toxicity Criteria) burns (n = 12 patients), and subcutaneous fatty necrosis (Grade 1–2; n = 5 patients). However, these never were reasons for withholding HT treatment (Table 3).

The median hemoglobin levels during treatment were 7.5 mmol/L, with slightly lower values in the patients in the U.S. (6.9 mmol/L; range, 5.1–8.3 mmol/L) than in the Norwegian patients (7.7 mmol/L; range, 6.1–8.8 mmol/L) and Dutch patients (7.7 mmol/L; range, 5.6–9.2 mmol/L). Eleven Dutch patients (31%) received blood transfusions, and 3 Dutch patients (8%) were treated with erythropoietin prompted by hemoglobin levels < 7.5 mmol/L (12.0 g/100 mL). Similar data are not available for the other countries.

Response Rate and Follow-Up

Sixty-one of 68 patients achieved clinical CR with trimodality treatment, for a CR rate of 90%. There was no

TABLE 4
Response Rate and Follow-Up of Trimodality Treatment in Three Trials

Response and follow-up	Netherlands (n = 36)	Norway (n = 19)	United States (n = 13)	Total (%) (n = 68)
Complete remission	32	18	11	61 (90)
Median follow-up (days)	538	496	1042	538
No. of patients lost to follow-up	2	—	—	2
Total no. of patients in follow-up	34	19	13	66
Alive	31	15	9	55 (83)
Ongoing remission	29	15	5	49 (74)
Alive with disease	2	0	4	6 (10)
Died of disease	3	4	4	11 (17)

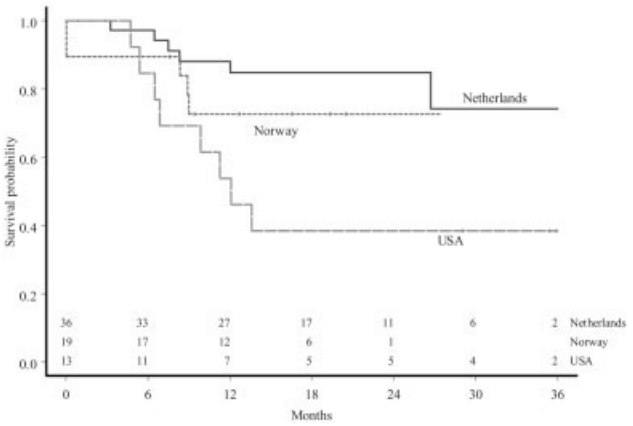

FIGURE 1. This chart illustrates disease-free survival by country. Solid line: the Netherlands; dotted line: Norway; dashed line: U.S.A.

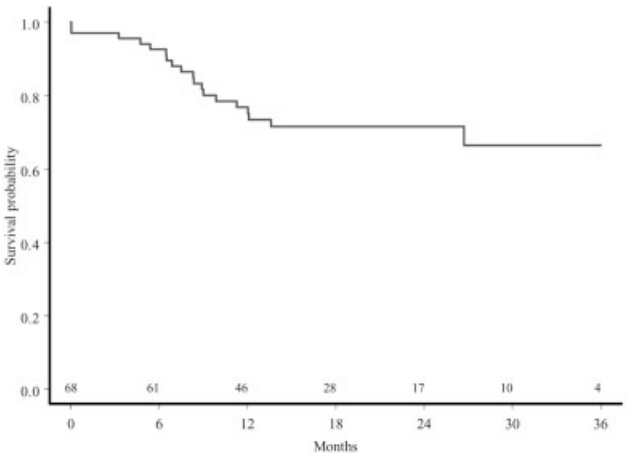

FIGURE 2. This chart illustrates results from the combined analysis of disease-free survival.

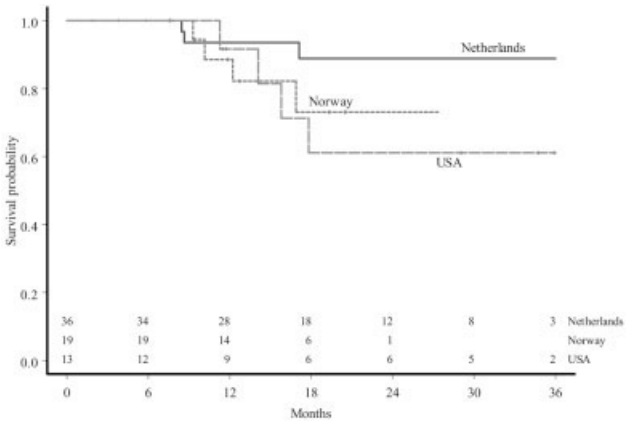

FIGURE 3. This chart illustrates overall survival by country. Solid line: the Netherlands; dotted line: Norway; dashed line: U.S.A.

significant difference in response rates between the countries. After a median follow-up of 538 days, 2 patients were lost to follow-up, because they remigrated to their country of origin. Of the remaining 66 patients, 11 died of disease, and 55 remained alive, including 6 patients with recurrent disease. The disease-free survival rate at 2 years (from the day of registration in the study) was 71.6% (95%CI, 55.1–82.8%), and the overall survival rate at 2 years was 78.5% (95%CI, 63.9–90.0%) (Table 4; Figs. 1–4). Explorative analyses demonstrated a significant difference in disease-free survival between the Netherlands and the U.S. (P = 0.01), but not for Norway and the U.S. or for the Netherlands and Norway. No significant differences were found in overall survival between the different countries.

DISCUSSION

In the current study, whole-pelvic HT was added to the current standard of care for patients with advanced cervical carcinoma, RT and chemotherapy. The activity of cisplatin-containing chemoradiotherapy in cervical carcinoma was established in 5 large, randomized studies of cisplatin-containing chemoradiation, which showed a reduction in the risk of recurrence of 40–60%.[2–6] In a sixth study, no statistically significant benefit was found for the addition of cisplatin to RT.[21] This discrepancy has engendered considerable discussion in the literature and speculation with regard to the reason. In the positive studies, the poor results of the RT only arms possibly may be explained by less-than-optimal RT, in which case, cisplatin may have corrected for the negative effects of suboptimal RT. An alternative explanation is that, in the negative study, patients in the cisplatin arm were significantly more anemic than patients in the control arm. Anemia is known as an adverse prognostic factor in RT-treated cervical carcinoma,[22] so the arms may

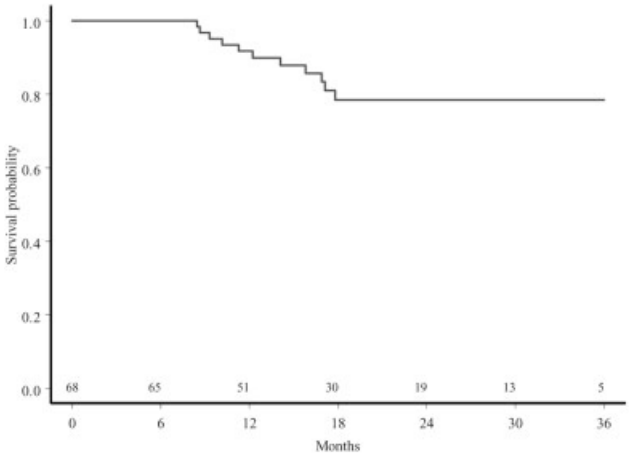

FIGURE 4. This chart illustrates results from the combined analysis of overall survival.

have been unbalanced. In addition, on statistical grounds alone, a single negative trial might be expected along with five other positive trials.[23] On balance, the available evidence definitely favors the use of combined chemotherapy and RT. Indeed, a clinical alert was issued by the National Cancer Institute strongly recommending this treatment.[7]

It is interesting to note that, when the addition of HT to CT was studied in 2 randomized trials, complete response rates and 3-year survival improved by the same magnitude as that observed in the chemoradiotherapy studies.[9,10] Although cisplatin significantly increases the side-effects of RT, HT does not change the toxicity profile of RT in a meaningful way. This heightens its appeal as an added modality to RT. However, the impressively high numbers of randomized patients in the chemotherapy studies (n = 2192 patients), compared with the limited patient numbers in the HT studies (n = 154 patients), and combined with the limited availability of HT, to date, have not led to a worldwide adaptation of HT in the treatment of cervical carcinoma.

Another possible advantage of combining RT, chemotherapy, and HT in cervical carcinoma lies in the additional synergy of cisplatin and HT, which has been documented in in vitro, in vivo, and clinical studies.[11–13] Although the feasibility of the triple combination has been suggested in Phase I studies,[14,15] we wanted to investigate the toxicity and efficacy in a uniform patient group with optimal RT in a uniform treatment protocol before proceeding to a randomized study.

The number of patients who were able to complete treatment (i.e., no dose reductions or interruptions of planned treatment due to toxicity) was chosen as the measure of feasibility. Full treatment was defined as 100% of the planned RT, at least 4 cisplatin courses, and at least 4 HT courses. Of the 68 patients in the study, all completed the planned RT treatment, although 3 patients did not receive brachytherapy because of tumor size. 66 patients (97%) received at least 4 courses of cisplatin, and 63 patients (93%) finished at least 4 HT treatments. This suggests that neither RT dose, nor cisplatin dose, nor HT dose was compromised in the study cohort. The recent studies using a weekly cisplatin schedule at a dose of 40 mg/m^2 for 6 weeks showed that roughly 90% of patients received at least 4 of 6 planned cisplatin courses.[2,5] The percentage of patients in this study who received at least 4 HT treatments also compares favorably with that of the randomized HT study (69%).[9]

To determine the quality of treatment, RT dose and treatment time were assessed. The RT equivalent BED was adequate, with a median dose of 86.7 Gy, and only 1 patient was treated at a substantially lower dose (71 Gy), apart from the 3 patients who could not receive brachytherapy because of tumor characteristics. Total treatment time, which is a prognostic feature in patients with cervical carcinoma, was acceptable, with a median of 45 days. Despite this, a substantial minority of patients (22 of 68 patients) had treatment time $>$ 49 days, mostly (in 13 of 22 patients) because a side-wall boost was administered at the end of external-beam and intracavitary RT. Hemoglobin, which is another independent determinant of outcome in patients with cervical carcinoma who are treated primarily with RT,[22] also was evaluated as a parameter of the quality of treatment. The hemoglobin levels measured weekly during treatment mostly were within the normal range, with a satisfactory median level of 7.5 mmol/L (12.0 g/100 mL). Almost 40% of patients (data from Dutch study only) were treated with transfusions or erythropoietin to achieve that goal, as expected.

The quality of HT, as documented by the thermometry data, suggests adequate heating for the majority of patients. Even though only T50 data are available for all patients, previous studies in breast carcinoma suggest a strong correlation between all calculated thermal dose parameters.[24,25]

The optimal sequencing of the three therapeutic modalities was not known. For maximum interaction between chemotherapy and HT, concurrent administration appears to be preferable; and, for maximum interaction between chemotherapy and RT, administration of cisplatin prior to RT appears to be preferable. It is not clear whether cisplatin interacts primarily with RT on the day on which the cisplatin is administered or whether there also is interaction with the

other four fractions of RT during a given week. Because of these considerations, the protocol advised (but did not command) the administration of chemotherapy and HT concurrently 1 hour prior to RT, but no more than 6 hours prior to RT. It was recognized that logistic issues at different institutions may require modification of this schedule. Although the actual sequencing in the current cohort was not recorded consistently, HT did not always precede RT on the same day, and a substantial number of patients did not receive chemotherapy concurrent with HT. This was considered acceptable, both because no clinical data exist on sequencing, and because the objective of the study was to develop a treatment schedule that realistically may be applied widely in the future. It is reassuring that, in the previously published studies of RT-chemotherapy and RT-HT, scheduling either was variable or was not mentioned at all. Nevertheless, all studies found a considerable and comparable advantage for bimodality treatment over RT alone. The magnitude of the treatment effect apparently is sufficiently large that it is not influenced by sequence variability.

The toxicity was fully comparable to that seen in the previous trials of RT and chemotherapy and, predictably, was greater than with RT alone. Although specific toxicity associated with HT was mild, treatment was refused by a number of patients, and it is noteworthy that this number was higher for HT than for chemotherapy.

Response rates and survival in this selected patient group were encouraging, with few recurrences from CR, once more confirming the predictive value of reaching CR in this disease. Follow-up is available for the majority of patients (97%), thus minimizing the chance of bias toward increased survival. The suggestion of a worse prognosis in the U.S. series, in all probability, is related to the presence of clinical paraaortic disease in $>$ 50% of those patients and to the longer follow-up compared with the European patients.

The results of the current study demonstrate that the addition of whole-pelvic HT to RT and chemotherapy for the treatment of patients with advanced cervical carcinoma is feasible without concessions to RT, chemotherapy, or HT dose compared with single-modality or combined-modality treatment. These results are reproducible in separate centers and countries and show encouraging response rates and survival data. Based on this study, an international, randomized, Phase III trial of chemoradiotherapy with or without HT has been launched. The study will randomize 400 patients so that it is powered to detect a 15% improvement in 5-year failure-free survival (i.e., from 50% to 65%) and overall survival (i.e., from 60% to 75%).

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