Chemoradiation in Cervical Cancer with Cisplatin and High-Dose Rate Brachytherapy Combined with External Beam Radiotherapy

Results of a Phase-II Study

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Background: In 1999, five randomized studies demonstrated that chemoradiation with cisplatin and low-dose rate (LDR) brachytherapy has a benefit in locally advanced cervical cancer and for surgically treated patients in high-risk situations. We evaluated the safety and efficacy of concomitant chemoradiation with cisplatin and high-dose rate (HDR) brachytherapy in patients with cervical cancer.

Patients and Method: 27 patients were included in our phase-II trial: 13 locally advanced cases (group A) and 14 adjuvant-therapy patients in high-risk situations (group B). A definitive radiotherapy was performed with 25 fractions of external beam therapy (1.8 Gy per fraction/middle shielded after eleven fractions). Brachytherapy was delivered at HDR schedules with 7 Gy in point A per fraction (total dose 35 Gy) in FIGO Stages IIB–IIIB. The total dose of external and brachytherapy was 70 Gy in point A and 52–54 Gy in point B. All patients in stage IVA were treated without brachytherapy. Adjuvant radiotherapy was performed with external beam radiotherapy of the pelvis with 1.8 Gy single-dose up to 50.4 Gy. Brachytherapy was delivered at HDR schedules with two fractions of 5 Gy only in patients with tumor-positive margins or tumor involvement of the upper vagina. The chemotherapeutic treatment schedule provided six courses of cisplatin 40 mg/m^2 weekly recommended in the randomized studies GOG-120 and -123.

Results: A total of 18/27 patients (66.7%) completed all six courses of chemotherapy. Discontinuation of radiotherapy due to therapy-related morbidity was not necessary in the whole study group. G3 leukopenia (29.6%) was the only relevant acute toxicity. There were no differences in toxicity between group A and B. Serious late morbidity occurred in 2/27 patients (7.4%). 12/13 patients (92.3%) with IIB–IVA cervical cancer showed a complete response (CR). 13/14 adjuvant cases (92.8%) are free of recurrence (median follow up: 19.1 months).

Conclusion: Concomitant chemoradiation with cisplatin 40 mg/m^2 weekly $\times$ 6 using HDR brachytherapy represents a promising treatment of cervical cancer with an acceptable toxicity.

Key Words: Chemoradiation · Cisplatin · Cervical cancer · HDR brachytherapy · Phase-II study

Strahlenther Onkol 2002;178:378–85
DOI 10.1007/s00066-002-0956-1

Simultane Radiochemotherapie beim Zervixkarzinom mit Cisplatin, kombiniert mit einer High-Dose-Rate-Afterloading-Brachytherapie und einer perkutanen Hochvolttherapie – Resultate einer Phase-II-Studie

Hintergrund: 1999 zeigten fünf randomisierte Studien, dass die simultane Radiochemotherapie mit Cisplatin und einer Low-Dose-Rate-Brachytherapie für Patientinnen mit einem lokal fortgeschrittenen Zervixkarzinom und in der adjuvanten Hochrisikosituation einen Überlebensvorteil bringt. Wir untersuchten die Sicherheit und Effektivität der simultanen Radiochemotherapie mit Cisplatin und High-Dose-Rate-Brachytherapie bei diesen Patientinnen.

Patientinnen und Methode: 27 Patientinnen wurden in unsere Phase-II-Studie eingeschlossen: 13 mit lokal fortgeschrittenen Zervixkarzinomen (Gruppe A) und 14 adjuvante Hochrisikopatientinnen (Gruppe B). Die primär radiochemotherapierten Fälle erhielten 25 Fraktionen einer perkutanen Hochvolttherapie des Beckens (1,8 Gy pro Fraktion/Einbringen eines Mittelblocks nach elf Fraktionen). Die Brachytherapie wurde bei den FIGO-Stadien IIB–IIIB nach dem High-Dose-Rate-Afterloading-Prinzip mit 7 Gy pro Fraktion in Punkt A (Gesamtdosis 35 Gy) appliziert. Die Gesamtdosis der kombinierten Therapie war 70 Gy in Punkt A und 52–54 Gy in Punkt B. Bei den FIGO-Stadien IVA erfolgte keine Brachytherapie. Bei der adjuvanten Strahlentherapie wurde die perkutane Hochvolttherapie des Beckens mit Fraktionen von 1,8 Gy bis zu einer Gesamtdosis von 50,4 Gy appliziert. Die High-Dose-Rate-Af-

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Received: October 18, 2001; accepted: January 25, 2002

terloading-Brachytherapie mit zwei Fraktionen von 5 Gy erfolgte nur bei Patientinnen, bei denen sich im Operationspräparat tumorbefallene Resektionsränder oder ein Befall der Scheide fanden. Das Chemotherapieregime mit 6 wöchentlichen Gaben von 40 mg/m² Cisplatin entsprach dem der Studien 120 und 123 der GOG.

Ergebnisse: 18 von 27 Patientinnen (66,7%) erhielten alle sechs Cisplatingaben. Eine Unterbrechung der Strahlentherapie aufgrund von Nebenwirkungen war in keinem Fall erforderlich. Die G3-Leukozytopenie (29,6%) war die einzige relevante Akuttoxizität; Toxizitätsunterschiede zwischen Gruppe A und B konnten nicht gesehen werden. Erhebliche späte Nebenwirkungen traten bei zwei der 27 Patientinnen (7,4%) auf. Zwölf von 13 Patientinnen (92,3%) mit einem Zervixkarzinom FIGO IIB–IVA zeigten eine Komplettremission (CR). 13 von 14 adjuvanten Fällen (92,8%) sind nach einer medianen Nachbeobachtungszeit von 19,1 Monaten rezidivfrei.

Schlussfolgerung: Die simultane Radiochemotherapie des Zervixkarzinoms mit 6 wöchentlichen Cisplatingaben 40 mg/m² und High-Dose-Rate-Afterloading-Brachytherapie stellt eine sichere und effektive Therapieform dar.

Schlüsselwörter: Simultane Radiochemotherapie · Cisplatin · Zervixkarzinom · HDR-Afterloading · Brachytherapie · Phase-II-Studie

Introduction

Cervical cancer, at present accounting for some 8,800 new cases in Germany each year, is one of the most common malignancies in women although the incidence is decreasing. In 1999 and 2000, five prospective randomized phase-III studies were published in the USA which demonstrated a statistically significant survival benefit for concurrent cisplatin chemoradiation as compared to radiation alone or chemoradiation with hydroxyurea in locally advanced inoperable cervical cancer and as an adjunct in operable high-risk cases [12, 14, 19, 23, 27]. Operable high-risk cases, according to the authors of the studies, were patients in FIGO stages I–II whose cancer showed such unfavorable prognostic factors as pelvic lymph node metastases, parametric tumor invasion or histologically positive surgical resection margins.

The fatality risk associated with cervical cancer was decreased by 30–50% with concurrent chemoradiation. On the basis of these results, simultaneous chemoradiation with cisplatin was established as a standard therapy in patients with cervical cancer and the above indications.

There is no evidence for a benefit of a sequential schedule of chemotherapy followed by radiation compared with radiation alone as a result of prospective randomized studies [5].

The question concerning the optimal treatment plan for concurrent chemotherapy has not been conclusively answered. In two randomized studies, a cisplatin dose of 40 mg/m² weekly × 6 was applied concurrently with radiation in the superior arm [12, 23]. The GOG-120 study demonstrated that a weekly dose of 40 mg/m² cisplatin × 6 was as effective as a combination of 50 mg/m² cisplatin d1+29, 4 g/m² 5-fluorouracil (96 hr) d1+29, and 2 mg/m² hydroxyurea twice weekly × 6 concurrently with radiotherapy, but that the latter was more toxic [23].

Before 1999 we generally used a combination of cisplatin/5-fluorouracil in postoperative adjuvant simultaneous chemoradiation of high-risk patients at our clinic [2, 3]. This treatment schedule is the only scheme that has so far demonstrated a survival benefit in a prospective randomized study compared with radiation alone [19]. The acute gastrointestinal toxicity (diarrhea) of this combination seems to be higher in contrast to chemoradiation with cisplatin alone. There is no strong evidence for a benefit of prophylactic drug application to prevent this acute side effect [10].

In contrast to most centers in Germany, brachytherapy in the above-cited US studies was applied as low-dose rate (LDR) brachytherapy with a total dose of 30–40 Gy in point A. As against that, Souhami et al [24] 1993 reported an unacceptable high rate of G3/G4 late sequelae in a phase-I/II study with percutaneous radiation fractions of 2 Gy and a concurrent dose of 30 mg/m² cisplatin weekly and a subsequent high-dose rate (HDR) brachytherapy [24]. While a complete clinical remission was achieved in 88% of 50 patients in stages IIA–IV, including 50% in stage IIIB, serious late bowel complications occurred in 13 patients (26%) a median 11 months after radiation, which the authors only observed in 7.5% of cases undergoing radiation alone according to this plan. Based on these findings, we conducted a phase-II study at our clinic in 1999 and 2000 with the aim of testing the safety and efficacy of a chemoradiation comprising six weekly doses of cisplatin 40 mg/m² under the radiation scheme used in our clinic with a course of high-dose rate brachytherapy.

Patients and Methods

In the framework of the phase-II study, 27 patients with cervical cancer underwent chemoradiation during 1999–2000. These included 13 women with locally advanced cancer in Stages IIB–IVA (group A) and 14 receiving adjuvant treatment after radical hysterectomy PIVER III in stages pT1b1–pT2b with parametric tumor infiltration and/or positive pelvic lymph nodes (group B).

The median age of patients in the whole study group was 47.1 years (range 33–69 years) with no differences between Group A (median age 47.8 years) and Group B (median age 46.5 years). 23 patients with squamous cell cancer, two with adenocancer and two with adenosquamous cancer were included in the study.

Of the 13 patients in group A seven were in FIGO stage IIIB and three each in FIGO stages IIB and IVA. Nine of the

14 adjuvant patients in group B showed a pelvic lymph node involvement; two were in stage pT1b1, three in pT1b2 and nine in pT2b. The patients' characteristics and individual treatment parameters of both groups are listed in Tables 1 and 2.

The criteria for inclusion and exclusion for concurrent chemoradiation with cisplatin in our study are described in Figures 1 and 2 while the treatment plan is shown in Figure 3.

Patients in stages IIB and IIIB were treated with a combination of 25 × 1.8 Gy external radiation with 15-MV photons

Table 1. Patients' characteristics and individual treatment parameters of locally advanced cases: group A ([a]patient died from tumor disease 10 months after therapy).

Tabelle 1. Patientencharakteristik und Therapiedaten der lokal fortgeschrittenen Fälle: Gruppe A.

No. of patient	Age (years)	Tumor stage FIGO classification	Group A Histologic subtype – Grading	Percutaneous radiotherapy (TD)	Brachytherapy (No. of fractions, dose per fraction)	No. of cisplatin courses	Duration of therapy (days)	Follow-up time (months) (n)
1	53	III B	Squamous cell cancer G3	45 Gy	5 × 7 Gy	6	36	17
2	47	III B	Squamous cell cancer G3	45 Gy	5 × 7 Gy	5	38	25
3	43	III B	Squamous cell cancer G3	45 Gy	5 × 7 Gy	6	36	24
4	54	II B	Squamous cell cancer G3	45 Gy	5 × 7 Gy	5	36	27
5	50	IV A	Squamous cell cancer G3	54 Gy		6	40	21
6	38	II B	Squamous cell cancer G2	54 Gy	5 × 7 Gy	6	48	17
7	55	III B	Squamous cell cancer G2	45 Gy	5 × 7 Gy	6	44	17
8	47	IV A	Squamous cell cancer G3	54 Gy	–	4	46	17
9	33	II B	Adenosquamous cancer G3	45 Gy	5 × 7 Gy	6	43	16
10	66	IV A	Squamous cell cancer G3	54 Gy	–	4	50	18
11	38	III B	adenocancer G2	50.4 Gy	3 × 7 Gy	6	51	–[a]
12	44	III B	Squamous cell cancer G2	45 Gy	5 × 7 Gy	6	45	13
13	33	III B	Squamous cell cancer G2	45 Gy	5 × 7 Gy	6	44	13

Table 2. Patients characteristics and individual treatment parameters of adjuvant high-risk cases: group B ([a]tumor-affected resection margins [R1-resection] in this case; all other cases with R0-resection).

Tabelle 2. Patientencharakteristik und Therapiedaten der adjuvanten Hochrisikofälle: Gruppe B.

No. of patient	Age (years)	Tumor stage FIGO classification	Group B Histologic subtype – Grading	Percutaneous radiotherapy (TD)	Brachytherapy (No. of fractions, dose per fraction)	No. of cisplatin courses	Duration of therapy (days)	Follow-up time (months) (n)
1	52	pT1b2 N1 M0	Squamous cell cancer G3	50.4 Gy	–	6	42	24
2	44	pT2b N0 M0	Squamous cell cancer G2	50.4 Gy	2 × 5 Gy	6	38	26
3	43	pT2b N0 M0	Squamous cell cancer G2	50.4 Gy	–	6	42	19
4	42	pT1b2 N1 M0	Squamous cell cancer G3	50.4 Gy	–	6	44	25
5	48	pT1b2 N1 M0	Squamous cell cancer G2	50.4 Gy	–	6	45	20
6	47	pT1b1 N1 M0	Squamous cell cancer G2	50.4 Gy	–	5	39	20
7	69	pT2b N1 M0	Adenosquamous cancer G3	50.4 Gy	2 × 5 Gy	3	44	21
8	41	pT2b N0 M0	Squamous cell cancer G2	50.4 Gy	2 × 5 Gy	4	44	23
9	41	pT2b N1 M0	Squamous cell cancer G3	50.4 Gy	2 × 5 Gy	6	45	23
10	33	pT2b N0 M0	Squamous cell cancer G2	50.4 Gy	–	6	37	16
11	56	pT2b N0 M0	Squamous cell cancer G3	50.4 Gy	–	6	36	15
12	48	pT2b N1 M0[a]	adenocancer G2	50.4 Gy	2 × 5 Gy	6	46	14
13	49	pT1b1 N1 M0	Squamous cell cancer G3	50.4 Gy	–	4	42	12
14	38	pT2b N1 M0	Squamous cell cancer G3	50.4 Gy	–	5	43	10

Patients with histologically confirmed, advanced cervical cancer without distant metastases, FIGO stages IIB–IVA

Cervical cancer pT1b1–pT2b as an adjunct after radical hysterectomy with positive pelvic lymph nodes and/or parametric infiltration in the surgical preparation

Age 18–70 years

Minimum life expectancy of 3 months

WHO performance status 0, 1 or 2

Adequate bone marrow, hepatic or renal function (platelet count ≥ 100 Gpt/l, leukocytes ≥ 3000 /ml, bilirubin i.s. ≤ 2 × normal value [N], transaminases i.s. ≤ 2 × N, alkaline phosphatase i.s. ≤ 3 × N, serum creatinine ≤ 1,25 × N)

Figure 1. Phase-II study on chemoradiation with cisplatin in cervical cancer: inclusion criteria.

Abbildung 1. Phase-II-Studie zur simultanen Radiochemotherapie beim Zervixkarzinom: Einschlusskriterien.

M1 situation

Positive paraaortic lymph nodes (imaging and/or histological examination)

Myocardial insufficiency ≥ NYHA 2, angina pectoris symptoms ≥ CCS II, myocardial infarction during past 6 months, AV block ≥ 2nd degree, ventricular cardiac arrhythmias ≥ Lown II

Uncontrolled arterial hypertension (RR diastolic > 95 mm Hg)

Acute infection

Known allergic reaction to cisplatin

Existing peripheral neuropathy or motor-sensory neurotoxicity ≥ CTC 2

Existing impairment of hearing ≥ CTC 2

Pregnancy

Figure 2. Phase-II study on chemoradiation with cisplatin in cervical cancer: exclusion criteria.

Abbildung 2. Phase-II-Studie zur simultanen Radiochemotherapie beim Zervixkarzinom: Ausschlusskriterien.

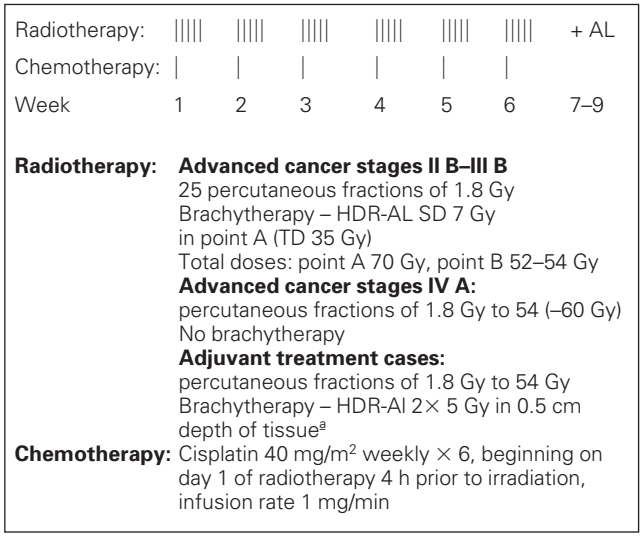

Figure 3. Therapeutic plan for phase-II study in simultaneous cisplatin chemoradiation in cervical cancer ([a] an adjuvant HDR-AL brachytherapy was only applied in patients with tumor involvement of upper vagina or tumor infiltration of resection margins).

Abbildung 3. Phase-II-Studie zur simultanen Radiochemotherapie beim Zervixkarzinom: Therapieplan.

via individually shaped ap/pa pelvic portals. Five weekly fractions of up to 19.8 Gy were given in the first 2 weeks of treatment. Patients then received additional HDR brachytherapy with Ir-192, single dose 7 Gy in point A, with a remote afterloading technique (Selectron/Nucletron®) once weekly (no external radiotherapy on days with brachytherapy), and five afterloading fractions were given. The volume of HDR brachytherapy was shielded after eleven fractions in the external radiation fields. During the last week of treatment, the patients were treated with two afterloading applications. The total dose of external and brachytherapy was 70 Gy in point A and 52–54 Gy in point B. The total doses to the bladder and rectum were kept below 60 Gy. In stage IVA, we generally treated patients with 54–60 Gy external radiotherapy without brachytherapy. The total length of treatment in most cases was 6 weeks, but never more than 7 weeks.

In the adjuvant treatment cases, brachytherapy was only given to patients in which the histological examination showed an involvement of the vaginal cuff or tumor-affected resection margins. In these patients, two fractions of 5 Gy were applied to the vaginal cicatrix at a tissue depth level of 0.5 cm. In addition, percutaneous irradiation with five fractions of 1.8 Gy per week up to a total dose of 50.4 Gy in the pelvic lymph outflow area was also generally performed.

Concurrently with percutaneous radiation, cisplatin chemotherapy was administered weekly, starting on day 1 of radiotherapy with a single dose of 40 mg/m² up to a total dose of 240 mg/m². The onset of infusion, which was performed at a rate of 1 mg/min, was 4 hours prior to irradiation. A sufficient pre- and post-hydratation of 500 ml NaCl solution was recommended. A prophylactic course of antiemetics with HT3 antagonists was also given.

The administration of cisplatin was halted at a leukocyte count ≤ 2.0 Gpt/l (ANC ≤ 1.0 Gpt/l) or a thrombocytopenia ≤ 75 Gpt/l and resumed after hematologic recovery. Cisplatin

was discontinued prematurely in the event of hepatic and renal dysfunction or an ototoxicity of CTC grade 2 [15].

The study was evaluated both with regard to efficacy and acute toxicity as well as chronic therapeutic sequelae.

To evaluate the therapeutic response in patients with locally advanced cancer (group A) undergoing primary chemoradiation, a computer tomography of the abdomen as well as MRI of the pelvis were performed in addition to the clinical examination before and 3 months after chemoradiation. We performed the same imaging procedures in addition to the clinical examination in all group B patients in the preoperative diagnostic setting and 3 months after adjuvant chemoradiation.

The acute side effects of therapy were classified and evaluated following CTC criteria according to the NCI Clinical Trials Group while the chronic therapeutic sequelae (≥ 91 days after therapy) were assessed according to the Late Radiation Morbidity Criteria of RTOG and EORTC, in order to ensure comparability with other studies [15, 18]. Based on the results of recently published retrospective multivariate analyses, we regarded every anemia with a Hb value < 11.0 g/dl (G1 NCI-CTC) under chemoradiation as worthy of treatment [8, 26].

Results

A total of 27 patients were evaluable with regard to therapeutic response and the toxicity of chemoradiation, including 13 patients with locally advanced cancer and 14 with postoperative adjuvant treatment. The median length of therapy was 42.8 days (range 36–51 days) for the patients in group A and 41.9 days (range 36–46 days) for patients receiving adjuvant therapy (group B). In group A we achieved a complete clinical remission in twelve of 13 cases (92.3%) and a partial remission in one case. The latter patient with a FIGO IIIB adenocancer already had advanced cancer 6 months after the start of therapy and died from her tumor disease 10 months after primary therapy. The other women are all in complete remission after a median follow-up period of 18.8 months (range 13–27 months).

In the adjuvant therapy group B 13 of 14 patients (92.8%) are free from recurrences after a median follow-up period of 19.1 months (range 10–26 months). One patient with a pT2bN1M0G3 adenocancer with tumor-affected resection margins developed a progressive tumor during adjuvant radiotherapy and also showed a parametric tumor growth which was histologically diagnosed as a tumor progression of the adenocancer of the cervix.

The therapy was well tolerated by all women. In no case did the radiotherapy have to be discontinued or interrupted because of relevant side effects, nor were there any therapy-related fatalities.

All patients received at least three subsequent weekly doses of cisplatin, 26 of 27 patients (96.3%) were given even four and more doses. The patient receiving only three weekly doses of cisplatin was a 69-year-old woman with breast cancer in whom, during a course of FEC chemotherapy, a squamous cell cancer of the cervix pT2bN1M0G3 was diagnosed and subsequently operated. The patient is recurrence-free 16 months after the onset of therapy.

All of the six scheduled weekly cisplatin infusions were given to 18 of 27 cervical cancer patients (66.7%). This meant that in nine cases (33.3%) the weekly administration of cisplatin had to be discontinued prematurely or in deviation from the treatment plan, the underlying reason being in eight cases a leukocytopenia CTC grade 3 and in one case a persisting enteritis CTC grade 2. The case of acute toxicity as classified according to the CTC criteria (NCI Clinical Trials Group 1988) is documented in Table 3. There are no differences in frequency of acute side effects of chemoradiation between group A and B.

Apart from a leukocytopenia in eight cases, we only observed one G3 acute toxicity as a non-hematologic toxicity: In a patient receiving adjuvant therapy, a posttherapeutic follow-up examination of the abdomen by computer tomography revealed a left renal vein thrombosis which was asymptomatic but required anticoagulation with fractionated heparines at therapeutic dosages. A computertomographic follow-up exam performed 3 months later showed a recanalization of the vessel.

An anemia with a Hb value < 11.0 g/dl in the nadir under therapy occurred in 15 of 27 patients (55.5%); only six patients (22.2%) had a CTC grade 2 anemia.

In nine of 27 patients (33.3%) an anemia already existed before therapy while a pre-therapy grade 2 anemia was diagnosed in three cases (11.1%), the latter all being in locally advanced stages. Ten of 27 patients (37.0%) were treated with an erythropoietin therapy at a dosage of 150 IU/kg × 3 per week s.c. and five of 27 patients (18.5%) received a transfusion.

Only two of 27 patients (7.4%) experienced relevant late sequelae of chemoradiation > G1 according to RTOG/EORTC score.

Table 3. Acute toxicity of simultaneous cisplatin chemoradiation according to CTC criteria of NCI-Clinical Trials Group 1988.

Tabelle 3. Akuttoxizität der simultanen Radiochemotherapie (nach den CTC-Kriterien der NCI Clinical Trials Group 1988).

Toxicity grading	G1	G2	G3	G4
White blood count	9	9	8	0
Hemoglobin	9	6	0	0
Platelets	6	0	0	0
Nausea	4	2	0	0
Vomiting	3	1	0	0
Diarrhea	4	7	0	0
Local skin	4	3	0	0
Urinary bladder	3	2	0	0
Hypokalaemia	4	0	0	0
Thrombosis	0	0	1	0

In a 33-year-old woman with a squamous cell cancer pT2bN1M0G3 of the uterine cervix, a surgical intervention became necessary 5 months after an adjuvant chemoradiation because of a small-bowel obstruction.

In another patient with a squamous cell cancer pT2bN1M0 G3 receiving adjuvant therapy, an asymptomatic left hydronephrosis due to a distal ureter stenosis was diagnosed 12 months after therapy, with neither clinical examination, nor sonography, abdominal computer tomography or pelvic MRI showing any signs of recurrence.

The median follow-up period of all patients was 19.0 months (range 10–27 months).

Discussion

We carried out a phase-II study on cisplatin chemoradiation in cervical cancer in 1999 despite the fact that the results of four prospective, controlled and randomized US studies published in the same year impressively demonstrated that a chemoradiation performed simultaneously with cisplatin was superior in terms of efficacy to radiotherapy alone both in the treatment of locally advanced cancer and as an adjunct in high-risk cases [12, 14, 19, 27]. It should be noted, however, that in the year 2000 another prospective randomized phase-III study became known which failed to prove the significant superiority of simultaneous cisplatin chemoradiation over radiotherapy alone with regard to recurrence-free and total survival of patients with locally advanced cervical cancer [16]. In this study, of which only an abstract has so far been available, cisplatin doses were administered according to the same treatment plan as in our present study. Overall, a number of questions still need to be addressed for this form of therapy to be established as a global standard in the treatment of cervical cancer: For instance, radiation in our center as well as in most other German centers is performed in conformity with a different therapeutic schedule than in the above-cited randomized studies. Brachytherapy is applied according to the HDR afterloading principle. There has been no prospective randomized study to date comparing the various methods of brachytherapy in the context of a combined radiotherapy for cervical cancer with regard to efficacy and toxicity. But there is a strong recommendation to initiate such a study [1].

Moreover, the results of a phase-I/II study in 1993 suggested that a simultaneous course of cisplatin chemoradiation and high-dose rate brachytherapy appears to be associated with a high rate of G3 or G4 late toxicities [24]. 13 of 50 patients (26%) in this study showed such severe late sequelae of therapy, most of which were bowel complications. It must be said, though, that the radiation plan used in this phase-II study deviated from our investigation: Radiation was performed percutaneously with fractions of 2 Gy while brachytherapy consisted in single fractions of 10 Gy up to a total dose of 30 Gy in point A. The weekly cisplatin dose was 30 mg/m^2. The acute toxicity in the study of Souhami et al [24] was only low in one patient given the occurrence of a G3 leukocytopenia. The median onset of severe late sequelae in the cited study appeared already 11 months after therapy. In the present phase-II study, patients have so far been followed up for a median of 19.0 months (range: 10–27 months). Out of 27 patients, we only found two severe late therapeutic sequelae G3/G4 according to the RTOG/EORTC score (7.4%) which in one patient involved the urinary tract and in the other case only manifested itself as an obstruction of the small intestines. One of these two patients did not undergo brachytherapy and the other received a high-dose rate brachytherapy with 2×5 Gy. The high rate of severe gastrointestinal late complications, which was reported by Souhami et al. [24] in their phase-I/II study using a HDR brachytherapy, has not yet been observed in the course of our study. All of the patients enrolled in our phase-II study continue to be followed up at our center especially with regard to any late complications of chemoradiation.

The acute toxicity (see Table 3) in our study was also low. At a relevant frequency, a G3-leukocytopenia occurred in eight of 27 patients (29.6%), making an interruption of cisplatin administration necessary. There was only a non-hematologic toxicity NCI-CTC grade 3: In one patient under an adjuvant chemoradiation who was treated for an anemia with erythropoietin, we found an asymptomatic thrombosis of the renal vein (left) in a computer tomography of the abdomen performed after therapy which had been undetectable in the preoperative computer tomography and required therapeutic anticoagulation. The most common non-hematologic G2 acute toxicity was diarrhea in seven of 27 patients (25.9%).

The relatively low frequencies of acute and chronic side effects of cisplatin chemoradiation in our study were also observed in other phase-II studies and in the cisplatin chemoradiation arms of the randomized GOG studies 120 and 123, in which brachytherapy was always delivered by means of LDR applications as is shown in Table 4 [4, 12, 13, 17, 23, 24]. In no case during our phase-II study did a course of radiation therapy have to be interrupted or discontinued for acute side effects, a factor which is a prerequisite for an optimal therapeutic effect. In the group A of advanced cervical cancer receiving primary therapy in our study, treatment was completed after a median 42.8 days; by contrast, the median duration of therapy in the GOG 120 study was 63 days, with a delay of radiotherapy by 8 days on average [23]. Experimental studies and prospective randomized clinical trials have demonstrated a detrimental effect of prolongation of overall treatment time on local tumor control [20]. We were able to administer all six cisplatin infusions in 18 of 27 women (66.7%); 26 women (96.3%) received four and more courses of cisplatin. This is an even slightly higher frequency than in the randomized GOG 120 and GOG 123 studies with larger sample sizes than in the above-cited phase-I/II study by Souhami et al in 1993 [12, 23, 24]. It was in fact possible in the cisplatin arm of the randomized GOG 120 study to deliver all six courses of the chemotherapeutic agent in 87 of 176 cases (49.4%) [23].

Table 4. Comparison of treatment plans and toxicities: published cisplatin chemoradiation studies in cervical cancer ([a]number of patients in cisplatin chemoradiation arm; [b]adjuvant patients only received brachytherapy with 2 × 5 Gy ED when the resection margins were not tumor-free or the vagina was affected. Patients in FIGO-stage IVA were not given brachytherapy.

Tabelle 4. Vergleich der Therapiepläne und Toxizitäten der publizierten Studien zur simultanen Cisplatin-Radiochemotherapie beim Zervixkarzinom.

Author/Study	No. of patients (n)	FIGO stages	Type of brachytherapy	Cisplatin scheme	Most common acute toxicity (NCI-CTC) G3/G4 hematologic toxicity G2–G4 non-hematologic toxicity n = no. of patients (%)	Most common late toxicity G3/G4 (RTOG/EORTC score) n = no. of patients (%)
Rose 1999 GOG 120	176[a]	IIB–IVA	LDR	40 mg/m² weekly × 6	Leukopenia G3: 21/176 (11.9%) Gastrointestinal effects G2: 28/176 (15.9%)	No data
Keys 1999 GOG 123	183[a]	IB2 neoadjuvant	LDR	40 mg/m² weekly × 6	Hematologic toxicity G3: 33/183 (18.0%) Gastrointestinal effects G2: 49/183 (26.8%)	No data
Malfetano 1997 Phase-II study	67	IIB–IIIB	LDR	1 mg/kg weekly × 6	No G4 hematologic toxicity 2 treatment-related deaths: pulmonary emboli	Gastrointestinal tract G3/G4: 2/67 (3.0%)
Fields 1996 Phase-II study	59	IB–IVA	LDR	20 mg/m², d1–5, q3 wks × 4	No data	Gastrointestinal tract G3/G4: 4/59 (6.8%)
Pearcey 1995 NCIC Clinical Trials Group	60	IB2 (> 5 cm) IVA	LDR	50 mg/m², d1, 11, 21, 31	Granulocytopenia G3: 6/60 (10%) Nausea/vomiting G2: 17/60 (28.3%)	Gastrointestinal tract G3/G4: 2/60 (3.3%)
Souhami 1993 Phase-I/II study	50	IIA–IVA	HDR-AL	30 mg/m² weekly × 6	Leukopenia G3: 1/50 (2%) Nausea/vomiting G2: 25/50 (50%)	Gastrointestinal tract G3/G4: 13/50 (26%)
Author's Phase-II study	27	IB1–IIB adjuvant IIB–IVA	HDR-AL[b]	40 mg/m² weekly × 6	Leukopenia G3: 8/27 (29.6%) Diarrhea G2: 7/27 (25.9%)	Urinary tract G3/G4: 1/27 (3.7%) Gastrointestinal tract G3/G4: 1/27 (3.7%)

Although the therapeutic response in our study, with twelve of 13 cases (92.3%) of a complete clinical remission in locally advanced cancers, including ten patients in stages IIIB–IVA, is excellent, no comparison with our results of radiotherapy alone can yet be drawn on account of the rather small sample size and the short median follow-up period of 18.8 months.

It may be recommended to wait for the results of the ongoing and recently completed phase-I/II and randomized phase-III studies on simultaneous chemoradiation for cervical cancer to be better able to answer the question as to the most effective and least toxic scheme of chemotherapy and to further optimize this form of treatment. Available therapeutic agents for use in the chemoradiation of cervical cancer, in addition to cisplatin, include 5-fluorouracil, paclitaxel, carboplatin, mitomycin C, combinations platin/paclitaxel or platin/mitomycin C, or such novel substances as capecitabine, which may be delivered concurrently with radiation [21].

Furthermore, the role of deep regional hyperthermia and prevention of anemia to optimize chemoradiation of cervical cancer should be investigated [8, 9].

The combination of cisplatin 50 mg/m² d 1 and 29, 5-fluorouracil 4 g/m² (96 hr) d 1 and 29 delivered simultaneously with radiotherapy, when combined with hydroxyurea according to the above dosage plan, has proven to be equally effective, but more toxic, as compared to a simultaneous course of cisplatin 40 mg/m² weekly [23]. Even though different dosages of the combination cisplatin/5-fluorouracil were used in the chemoradiation of cervical cancer, a superiority of that combination over a cisplatin chemoradiation alone is unlikely [6, 7, 11, 14, 25, 27].

Recently, the interim results of a prospective randomized phase-III study were published which suggest that a simultaneous chemoradiation with mitomycin C 15 mg/m² i.v., weeks 1 and 6, may be superior to a course of radiotherapy alone both in regard to total and progression-free survival, especially in the locally advanced stages IIIB of cervical cancer [22].

Two further prospective randomized studies on chemoradiation have meanwhile been terminated the results of which are not yet available: a Dutch study which compared a simultaneous course of chemoradiation with carboplatin and 5-fluorouracil to radiotherapy alone in stages IB2–IVA, and the three-arm GOG-165 study, which compared a chemoradiation with cisplatin to a chemoradiation with 5-fluorouracil and radiotherapy alone in stages IIB–IVA.

Other ongoing phase-I/II studies examine a concurrent chemoradiation with cisplatin/paclitaxel (GOG 9803/ GOG

9804) and a simultaneous chemoradiation with carboplatin (GOG phase-I trial).

It may be summarized that a concurrent chemoradiation with cisplatin 40 mg/m^2 weekly, in combination with a HDR brachytherapy beside a percutaneous high-voltage radiation, also constitutes a safe and effective therapeutic method.

From our point of view, a further prospective and randomized study in locally advanced cervical cancer would be useful to prove the superiority of simultaneous chemoradiation over radiotherapy alone also according to a radiation plan with a HDR brachytherapy like the one used in our phase-II study.

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