Radiation Therapy and Simultaneous Chemotherapy for Recurrent Cervical Carcinoma

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Purpose: To evaluate the efficacy and toxicity in patients with recurrence of cervical cancer treated with radiotherapy and simultaneous chemotherapy.
Patients and Methods: Between 1987 and 2001, 24 patients with recurrent cervical carcinoma were treated with concurrent chemoradiotherapy. Nine patients had incomplete tumor resection prior to radiation therapy. Irradiation was delivered to a total dose of 60 Gy, in three patients with central recurrences supplemented by brachytherapy. One patient was treated with brachytherapy alone. Simultaneous chemotherapy was done as a combined therapy of 5-fluorouracil-(5-FU, 600 mg/m^2/d1–5, 29–33) and cisplatin (20 mg/m^2/d1–5, 29–33; 16/24 patients) or of 5-FU (1,000 mg/m^2/d1–5, 29–33) and mitomycin C (10 mg/m^2/d2, 30; 1/24 patients). Cisplatin alone (25 mg/m^2/d1–5) and carboplatin alone (800 mg/m^2/d1–5) were administered in 5/24 patients (21%) and 2/24 patients (8%).
Results: The 5-year local recurrence-free survival rate was 37%, disease-free survival 33%, and overall survival 34%. Grade 3 toxicity (NCI-CTC grade 3) occurred mainly as diarrhea (38%), leukopenia (33%), and nausea (21%). Severe toxicity (grade 4) was not seen in any of the patients.
Conclusion: Radiation therapy with simultaneous chemotherapy for recurrences of cervical cancer is an effective treatment with acceptable toxicity.

Key Words: Recurrent cervical carcinoma · Radiochemotherapy

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Radiochemotherapie bei Zervixkarzinomrezidiven

Ziel: Ermittlung der Wirksamkeit und Toxizität einer Radiochemotherapie bei Patientinnen mit Zervixkarzinomrezidiven.
Patienten und Methodik: Von 1987 bis 2001 wurden 24 Patientinnen mit Zervixkarzinomrezidiven mit einer Radiochemotherapie behandelt. Neun Patientinnen hatten vor der Therapie eine unvollständige Tumorresektion. Die Gesamtdosis der Radiotherapie betrug 60 Gy; drei Patientinnen mit zentralen Zervixkarzinomrezidiven wurden zusätzlich einer Brachytherapie unterzogen. Eine Patientin erhielt eine alleinige Brachytherapie. Die simultane Chemotherapie wurde als Zweifachtherapie mit 5-Fluorouracil (5-FU, 600 mg/m^2/d1–5, 29–33) und Cisplatin (20 mg/m^2/d1–5, 29–33; 16/24 Patientinnen) oder 5-FU (1000 mg/m^2/d1–5, 29–33) und Mitomycin C (10 mg/m^2/d2, 30; 1/24 Patientinnen) durchgeführt. Eine Monotherapie mit Cisplatin (25 mg/m^2/d1–5) oder Carboplatin (800 mg/m^2/d1–5) erhielten 5/24 Patientinnen (21%) bzw. 2/24 Patientinnen (8%).
Ergebnisse: Nach 5 Jahren betrugen die lokale Tumorkontrolle 37%, das krankheitsfreie Überleben 33% und das Gesamtüberleben 34%. Grad-3-Toxizitäten (NCI-CTC-Grad 3) traten als Diarrhö (38%), Leukopenie (33%) und Übelkeit (21%) auf. Schwere Toxizitäten (NCI-CTC-Grad 4) wurden bei keiner Patientin beobachtet.
Schlussfolgerung: Die Radiochemotherapie bei Zervixkarzinomrezidiven ist eine wirksame Behandlung mit tolerablen Nebenwirkungen.

Schlüsselwörter: Zervixkarzinomrezidive · Radiochemotherapie

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Introduction

Radiation therapy or chemotherapy is the most frequent treatment modality for recurrences of cervical carcinoma. Unfortunately, the results are mostly disappointing. Prognosis is poor, in particular if repeated radical surgery is not possible.

This retrospective study analyzed the effectiveness and the side effects of simultaneous chemotherapy and radiation therapy and the influence of selected prognostic factors in patients with recurrences of cervical carcinoma.

Patients and Methods

Patient Characteristics

Between 1987 and 2001, 24 patients with recurrent cervical carcinoma were treated with radiation therapy and simultaneous chemotherapy at our institution (Table 1). As prior therapy, 6–158 months earlier (median: 24 months earlier), 22 patients underwent radical hysterectomy, sometimes followed by radiation therapy (n = 8) or chemotherapy (n = 1). Two of the eight patients with postoperative irradiation were treated with external beam alone (total dose: 58.0 and 46.5 Gy), four with brachytherapy alone (total dose: 50.0, 28.0, 42.0, and 28.0 Gy), and two patients with external beam therapy (total dose: 55.8 and 49.2 Gy) in combination with brachytherapy (total dose: 30.0 and 36.0 Gy). Two patients had definitive radiotherapy as first line therapy. Both of them received external beam therapy up to a total dose of 60.0 Gy, one of them in combination with brachytherapy (30.0 Gy). First line therapy is listed in Table 2.

16 patients (67%) had pelvic sidewall recurrences, five (21%) central pelvic recurrences, and three (13%) isolated paraaortic lymph node metastases. Details of patient and tumor characteristics are given in Table 1. Tumor volume was measured with CT scan, based on tumor contours every 3–5 mm slice.

Table 1. Patient and tumor characteristics.

Tabelle 1. Patienten und Tumorcharakteristik.

Patients (n)	24
Median age (years)	48 (range: 26–77)
Location of recurrence	
• Pelvic sidewall recurrence (n)	16
• Central pelvic recurrence (n)	5
• Isolated paraaortic lymph node recurrence (n)	3
Tumor volume	
• < 97 ml (n)	12
• > 97 ml (n)	12
> 1/3 necrosis in the tumor mass (n)	7

Surgery

9/24 (37.5%) patients with large tumor extension to the pelvic sidewall received some kind of incomplete tumor resection prior to radiation therapy.

Radiation Therapy

20/24 (83%) patients underwent external beam therapy (6-MV photon beam) without brachytherapy. The median dose given by external-beam to the pelvis and/or the paraaortic and iliac lymph nodes was 47 Gy (36–50 Gy), the median dose administered to the recurrent tumor site amounted to 59.4 Gy (54–61 Gy). 3/24 patients (12.5%) underwent external beam irradiation (26–54 Gy) in combination with brachytherapy. Low-dose-rate intracavitary implants with ^{191}Ir and a total dose of 19.6 or 25 Gy were used in two patients. One patient received high-dose-rate brachytherapy (36 Gy in six fractions) given by vaginal cylinder. 1/24 patients (4%) underwent pulsed-dose-rate interstitial brachytherapy alone (55.9 Gy).

Chemotherapy

In all patients chemotherapy was performed simultaneously with irradiation. 15/24 patients (62.5%) received chemotherapy (5-fluorouracil [5-FU, 600 mg/m^2] and cisplatin (20 mg/m^2]) on days 1–5 and 29–33 of external beam radiotherapy. Cisplatin alone at a dose of 25 mg/m^2/d1–5 was administered to 5/24 patients (21%) and carboplatin alone (800 mg/m^2/d1–5) to 2/24 patients (8%). 1/24 patients (4%) received two courses of chemotherapy with 5-FU (1,000 mg/m^2/d1–5, 29–33) and mitomycin C (10 mg/m^2/d2, 30), and the patient who underwent brachytherapy alone received 20 mg/m^2 of cisplatin on days 1–5. Current therapy is summarized in Table 3.

Table 2. First-line therapy.

Tabelle 2. Erstlinientherapie.

	Patients (n)
Radical hysterectomy	13/24
Radical hysterectomy + chemotherapy	1/24
Radical hysterectomy + external-beam therapy	2/24
Radical hysterectomy + external-beam therapy + brachytherapy	2/24
Radical hysterectomy + brachytherapy	4/24
External-beam therapy alone	1/24
External-beam therapy + brachytherapy	1/24

Table 3. Current therapy.

Tabelle 3. Aktuelle Therapie.

	Patients (n)
Debulking operation	9/24
External-beam radiation therapy + chemotherapy	20/24
External-beam radiation therapy + brachytherapy	3/24
Brachytherapy + chemotherapy	1/24

Data Analysis

The analysis was accomplished after a mean follow-up of 38 months (4–137 months). No patient was lost to follow-up. The main endpoints evaluated included overall survival, local recurrence-free survival, and disease-free survival according to the Kaplan-Meier method, and the differences were determined by using the log-rank test. Survival was calculated from the time of recurrence to the time of death or, for survivors, the date of last follow-up. The location of recurrence was classified as pelvic sidewall recurrence, if pelvic sidewall fixation was observed in CT scan, or as central pelvic recurrence, if the tumor mass involved pelvic structures without sidewall fixation. The tumor response was documented by CT scan 6 weeks after the end of radiation therapy.

Results

Therapy Efficacy

At the time of evaluation 7/24 patients (29%) were alive without evidence of disease after a mean follow-up of 38 months (4–137 months). The local recurrence-free, disease-free and overall survival rates at 10 years were 37%, 25% and 17%, respectively (Figures 1 to 3).

A complete response 6 weeks after the end of therapy was achieved in 6/24 patients (25%), and in 8/24 (33%) a partial response was seen. 10/24 patients (42%) showed no response or progression of disease. 14/24 patients (58%) developed second locoregional recurrences after a median period of 12 months (4–137 months).

Patients with a small tumor volume (< 97 cm^3) without necrosis showed better results than patients with a large tumor volume with necrosis. The influence of tumor volume and necrosis on initial tumor response is presented in Figures 4 and 5. There was a statistically significant difference between the 5-year survival rates of patients with large tumor volume (> 97 cm^3) and patients with smaller tumor volume: 8% versus 26% for overall survival (p = 0.05; Figure 6), 8% versus 42% for disease-free survival (p = 0.02; Figure 7). The extent of necrosis in the tumor, despite some trends, did not

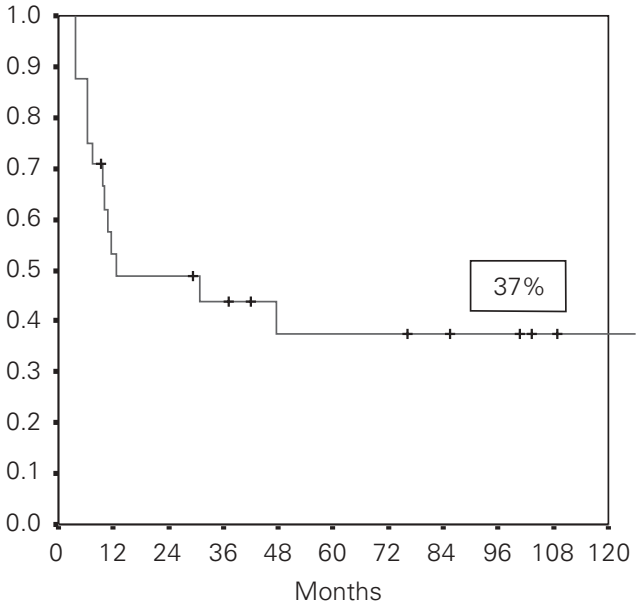

Figure 1. Local recurrence-free survival curve of all 24 patients.

Abbildung 1. Lokale Tumorkontrolle aller 24 Patientinnen.

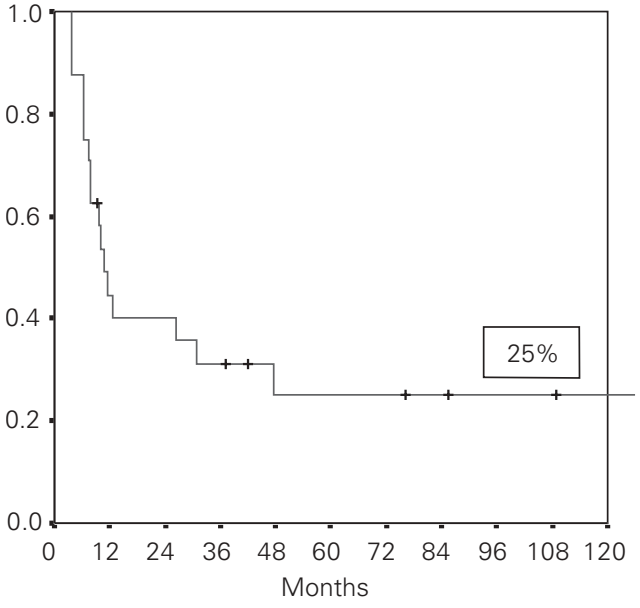

Figure 2. Disease-free survival curve of all 24 patients.

Abbildung 2. Krankheitsfreies Überleben aller 24 Patientinnen.

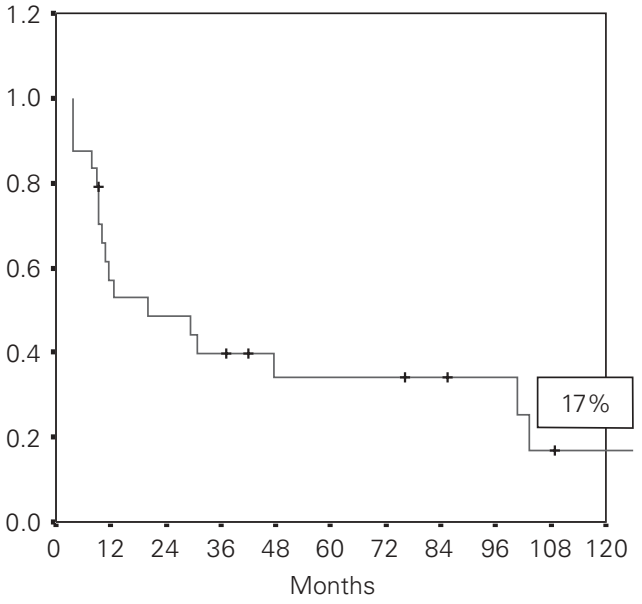

Figure 3. Overall survival curve of all 24 patients.

Abbildung 3. Gesamtüberleben aller 24 Patientinnen.

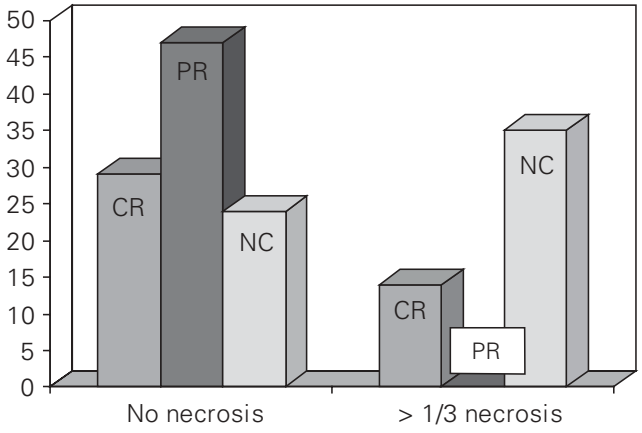

Figure 4. Initial response depending on the influence of necrosis. CR: complete response; PR: partial response; NC: no change.

Abbildung 4. Abhängigkeit des Therapieansprechens vom Nekroseanteil im Tumor. CR: Vollremission; PR: Teilremission; NC: keine Veränderung.

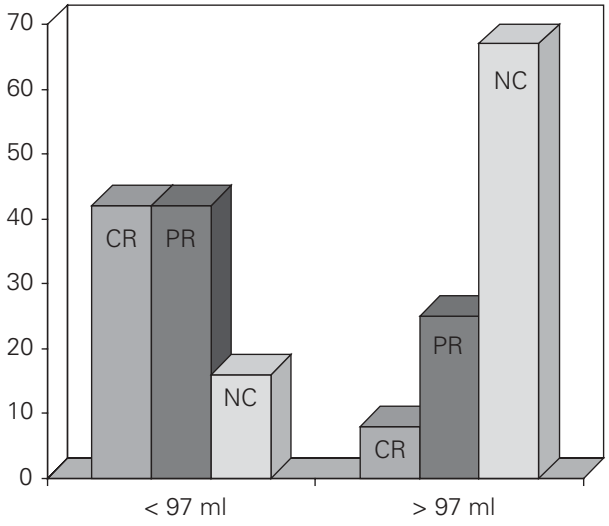

Figure 5. Initial response depending on the influence of tumor volume (median 97 ml). CR: complete response; PR: partial response; NC: no change.

Abbildung 5. Abhängigkeit des Therapieansprechens von der Tumorgröße. CR: Vollremission; PR: Teilremission; NC: keine Veränderung.

significantly influence the rates of overall and disease-free survival (p = 0.09, p = 0.12; Figures 8 and 9). Also, an analysis of the influence of other important treatment- or tumor-related factors such as use of radiation therapy modality and dose, tumor grading, lymphangiosis, histology, and site of recurrence, on the treatment results did not show statistically significant differences.

Toxicity

Treatment-related toxicity following radiochemotherapy is summarized in Table 4. Grade 3 toxicity occurred mainly as diarrhea (38%), leukopenia (33%), and nausea with or without vomiting (21%). Severe grade 4 toxicity was not seen in any of the patients. Due to the toxicity 13 patients (53%) were not able to receive the full dose of chemotherapy as described before. Radiation therapy was aborted in two patients at a dose of 45 Gy because of gastrointestinal toxicity (grade 3).

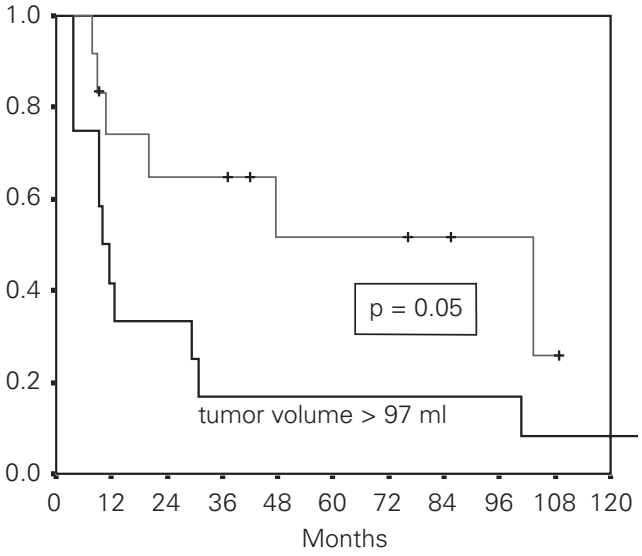

Figure 6. Influence of tumor volume on overall survival.

Abbildung 6. Einfluss der Tumorgröße auf das Gesamtüberleben.

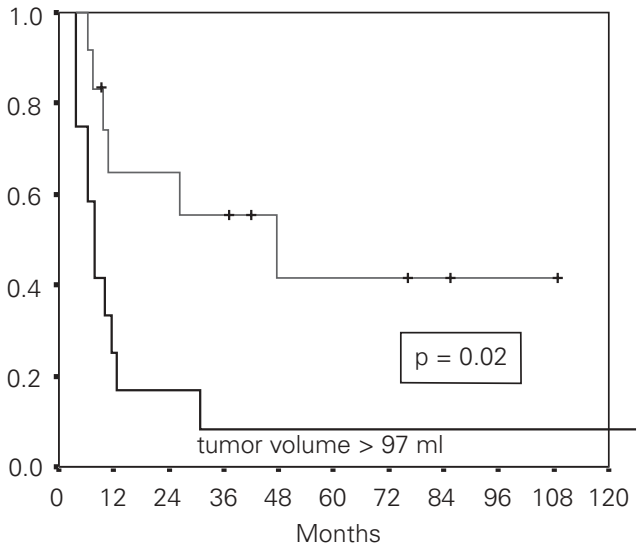

Figure 7. Influence of tumor volume on disease-free survival.

Abbildung 7. Einfluss der Tumorgröße auf das krankheitsfreie Überleben.

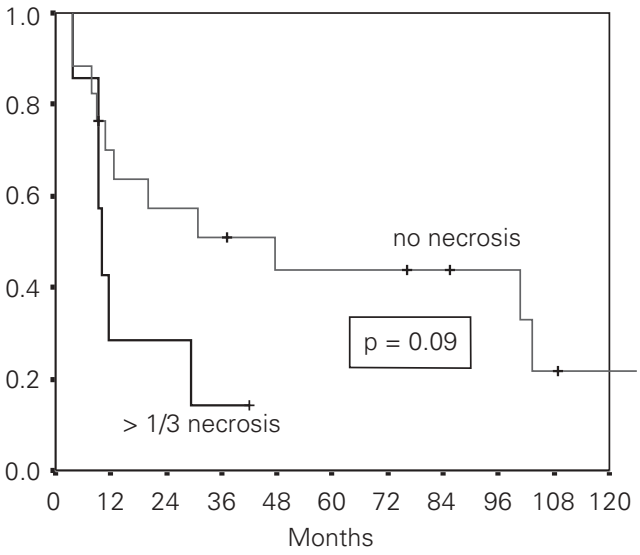

Figure 8. Influence of necrosis on overall survival.

Abbildung 8. Einfluss des Nekroseanteils im Tumor auf das Gesamtüberleben.

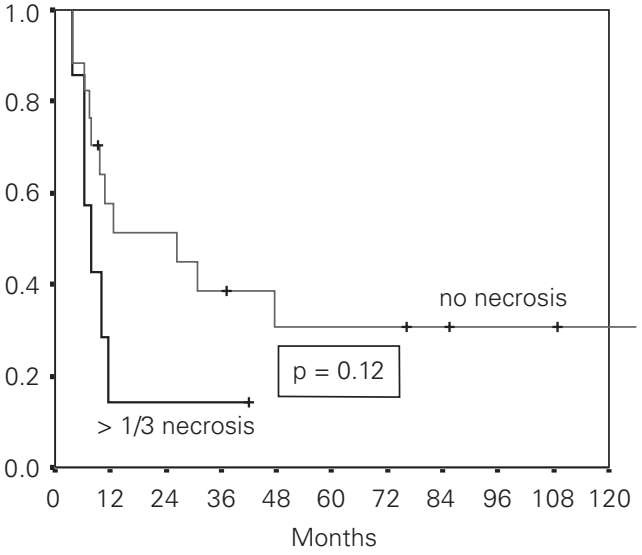

Figure 9. Influence of necrosis on disease free survival.

Abbildung 9. Einfluss des Nekroseanteils im Tumor auf das krankheitsfreie Überleben.

Discussion

10–20% of all patients treated for cervical cancer will develop local recurrent disease without detectable distant metastases [2, 3, 17, 22]. Most recurrences are diagnosed during the first 1–2 years after initial treatment [3, 15, 20, 22]. This fact is in accordance with our experience; we registered recurrences after a median time of 16 months following therapy of primary cancer.

Overall, central pelvic recurrences with small tumor sizes have a better outcome than recurrences infiltrating the pelvic wall or relapses located beyond the pelvis [1, 8, 9, 12–14, 18, 26], for two reasons: First, recurrences limited to the vagina are more easily detected with clinical pelvic examination than are pelvic wall recurrences; and an earlier diagnosis generally allows for detection of cervical relapses with small tumor sizes. Second, central recurrences of cervical cancer offer better aggressive and curative treatment modalities. Encouraging results of external-beam radiation therapy in combination with brachytherapy are reported from other institutions [18, 26]. The current series confirms the findings by others with a 5-year overall survival of 39% for patients with central recurrence of cervical cancer [9, 12, 14, 23, 26].

In the current series we could show a significant influence of tumor volume on survival rates. The fact that the tumor volume determines the treatment results justifies frequent follow-ups to detect locoregional recurrent cervical carcinoma, in particular pelvic sidewall recurrences, in an earlier stage. Frequent physical examinations, CT scan, MRI techniques, cytologic screening and liberal use of biopsy are effective methods [5, 6, 11, 20].

If a recurrence is diagnosed, different curative treatment approaches exist: pelvic exenteration, CORT (combined operative and radiotherapeutic treatment), IORT (intraoperative radiation therapy), or irradiation with simultaneous chemotherapy [10, 16, 21].

An important role to improve survival of patients subjected to nonoperative treatment modalities falls to a combined treatment with pelvic irradiation and systemic chemotherapy [24]. The efficacy of radiotherapy or chemotherapy alone is limited [4, 6, 7, 19, 25, 27].

In our series we could show that the addition of simultaneous chemotherapy to irradiation results in a respectable survival and local control rate not only for patients with central pelvic recurrences but also for patients with pelvic sidewall recurrences and distant recurrences. The benefit of add-

Table 4. Acute toxicity during radiochemotherapy.

Tabelle 4. Akute Toxizitäten während der Radiochemotherapie.

	Grade 1–2 n (%)	Grade 3 n (%)	Grade 4 n (%)
Leukopenia	13 (54)	8 (33)	0
Anemia	17 (71)	0	0
Thrombocytopenia	6 (25)	1 (4)	0
Creatinine	2 (8)	2 (8)	0
Diarrhea/nausea/vomiting	11 (46)	14 (59)	0
Erythema	1 (4)	2 (8)	0

ing chemotherapy to irradiation in the treatment of recurrent cervical carcinoma has been shown in other series [4, 25, 27]. For example, in the study by Thomas et al. [25] the number of 5-FU courses administered had a significant influence on pelvic control and survival. In the study by Cerrotta et al. [4] four of six patients with recurrent squamous cell carcinoma of the uterine cervix showed complete regression after concurrent radiotherapy and weekly paclitaxel as radiosensitizer. Chou et al. [6] have shown that only patients with isolated paraaortic lymph node recurrence who received irradiation and concurrent cisplatin-based chemotherapy enjoyed long-term, disease-free survival.

We suggest the treatment of first local pelvic recurrences or isolated paraaortic lymph node metastases with curative attempt has to be combined radio- and chemotherapy.

For second recurrent disease such as distant metastases no curative therapy is currently available. Chemotherapeutic agents produce transient responses in some patients but do not result in their cure. In our series all patients who developed second recurrences after treatment of the first local recurrence died.

Conclusion

Radiation therapy with simultaneous chemotherapy in patients with recurrences of cervical carcinoma is an effective treatment with acceptable toxicity. For recurrences diagnosed with small tumor size ($< 100\ cm^3$) without necrosis, irradiation and simultaneous chemotherapy can be used in a curative attempt.

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