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Feasibility and Morbidity of Combined Hyperthermia and Radiochemotherapy in Recurrent Rectal Cancer – Preliminary Results

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Key Words
Recurrence · Colorectal cancer · Hyperthermia · Irradiation · Chemotherapy

Summary
Background: The local recurrence rate of colorectal cancer has been significantly reduced due to the use of combined radiochemotherapy. Despite this improvement regarding locally advanced tumour recurrences, the treatment strategy for pre-treated patients remains difficult and unresolved. **Patients and Methods:** We analysed treatment and follow-up data of 14 patients with local recurrence of rectal cancer who were treated with radiation therapy (RT), chemotherapy (CT) and regional hyperthermia (RHT) from November 1997 to December 2001. Nine of these patients had received irradiation and CT (= pre-treated patients) in the past. For this group, 30.6–39.6 Gy RT, 5-fluorouracil (5-FU) as a continuous infusion over 5 days per week (350 mg/m^2/24 h) combined with RHT twice a week was given. The 5 remaining patients (= not pre-treated) received conformal irradiation of 45 Gy with a boost between 9 and 14.4 Gy, combined with continuous infusion of 5-FU on days 1–4, and 29–33 (500 mg/m^2/ 24 h), and RHT twice a week. Response to therapy was evaluated by means of computed tomography (CT) or magnetic resonance imaging (MRI) and by clinical follow-up. **Results:** Among 13 evaluated cases, the overall objective response rate was 54% (5 complete responses, 2 partial responses). At mean follow-up of 13.9 months (range 5–32 months) 7 patients were alive. **Conclusion:** The therapeutic regimen appears to be active in the treatment of local recurrences of rectal cancer. Larger-scaled studies are needed to evaluate the potency of hyperthermia in this therapeutic strategy.

Schlüsselwörter
Rezidiv · Kolorektale Karzinome · Hyperthermie · Bestrahlung · Chemotherapie

Zusammenfassung
Hintergrund: Die Rate lokaler Rezidive von kolorektalen Karzinomen wurde durch die Einführung der kombinierten Radiochemotherapie gesenkt. Trotz dieser Fortschritte ist die Strategie bei der Therapie von lokal fortgeschrittenen Rezidiven vorbehandelter Patienten problematisch und ungelöst. **Patienten und Methoden:** Wir analysierten retrospektiv die Daten zu Behandlung und Follow-up von 14 Patienten, die zwischen November 1997 und Dezember 2001 wegen Lokalrezidiven eines Rektumkarzinoms mit Bestrahlung (RT), Chemotherapie (CT) und Hyperthermie (RHT) behandelt wurden. Hiervon waren 9 Patienten mit Radiochemotherapie vorbehandelt worden (vorbehandelte Patienten). Diese Gruppe der vorbehandelten Patienten erhielt jeweils 30,6–39,6 Gy RT und 5-Fluorouracil (5-FU) als kontinuierliche Infusion 5 Tage pro Woche (350 mg/m^2/24 h) in Kombination mit RHT zweimal wöchentlich. Die 5 übrigen Patienten (nicht vorbehandelt) erhielten eine konformale RT mit 45,0 Gy mit einer zusätzlichen Boost-RT zwischen 9,0 und 14,4 Gy in Kombination mit einer kontinuierlichen Infusion von 5-FU an den Tagen 1–4 und 29–33 (500 mg/m^2/ 24 h) und RHT zweimal wöchentlich. Das Ansprechen auf die Therapie wurde mittels Computertomographie (CT) oder Magnetresonanztomographie (MRI) sowie klinischem Follow-up evaluiert. **Ergebnisse:** Unter 13 auswertbaren Fällen betrug die Ansprechrate 54% (5 vollständige Remissionen, 2 partielle Remissionen). Nach einer mittleren Nachbeobachtungszeit von 13,9 Monaten (Bereich 5–32 Monate), waren noch 7 Patienten am Leben. **Schlussfolgerung:** Das beschriebene Therapieregime scheint bei Lokalrezidiven von Rektumkarzinomen wirksam zu sein. Der wirksame Anteil der Hyperthermie muss anhand von Studien mit größeren Patietenzahlen überprüft werden.

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Introduction

Colorectal cancer is one of the main cancer-related causes of death. In Germany, the incidence of colorectal carcinoma amounts to 55,000–60,000 cases per year, with a portion of one third with localisation primarily in the rectum. Over the past decades, significant progress has been made in developing effective adjuvant treatment regimens. Combined pre-operative or post-operative therapy has significantly contributed to improvement of local control and to survival of these patients [1–3]. The local recurrence rate has been dramatically lowered through the use of radiotherapy (RT), especially in combination with chemotherapy (CT). Modern radiation techniques, such as conformal radiation, and new chemotherapeutic regimens may have the potential to further increase the therapeutic benefit. However, the treatment of inoperable, advanced local tumour recurrences in patients who were treated with surgery and radiochemotherapy (RCT) before, remains a challenge to both the medical and the radiation oncologist. The aim of any treatment strategy for this cohort is to increase local tumour control. At the same time, therapy-related side-effects should be kept to a minimum as they can dramatically reduce the patient's quality of life. All effort's goal still remains to enable a curative resection of the tumour, hence optimistic long-term perspectives can only be achieved if a resection can be performed.

Regional hyperthermia therapy (RHT) in combination with RT or CT, yielded impressive results in phase-III studies [4–6]. Profound research has produced a scientific basis for the simultaneous application of hyperthermia in combination with ionising irradiation and/or systemic CT [7]. Hyperthermia (HT) has become more widely accepted in the clinical setting since substantial technical improvements have been made to achieve selective temperature increases in both superficial and more remote tumour locations [7]. The rationale for the use of HT is based on the observations of (a) augmentation of the potency of the used antineoplastic drugs, (b) enhancement of perfusion and oxygenation in the treated area, and (c) direct cytotoxic effects of heat when tissue temperatures are increased up to 44 °C. Synergistic effects of RHT and RCT are well known [8]. In general, toxicity of HT is low. HT is a useful adjunct to RT to enhance local control of advanced malignancies. The measured temperature distribution in the tumour and in the immediately adjacent tissue is an important prognostic factor for the outcome [8].

A combined therapeutic regimen of HT and RT has been reported to yield a higher clinical response rate and local control rate than RT alone [4–6]. Nevertheless, HT is still not viewed as an established standard treatment modality in cases of locally recurrent rectal cancer. The majority of patients with local tumour recurrences were treated with both surgery and RCT. Therefore, the options of local tumour treatment are limited due to the cumulative effects of high dose irradiation. Based on the published literature [4–6] and on our own experience with RHT [7], we decided to combine the treatment modalities of RHT and RCT with a limited irradiation dose in order to enhance the local tumour control in patients who had been irradiated in the past. In this article, we report upon 14 patients treated with this regime and evaluated in retrospective to determine the feasibility and morbidity of combined external beam RT, continuous infusion of 5-fluorouracil (5-FU), and external microwave HT.

Patients and Methods

This report is based on retrospective observation and evaluation of two groups of patients affected by a locally recurrent rectal cancer:

a. pre-treated patients who had already been treated with surgery and RCT in the past (previously irradiated, PI-group);
b. pre-treated patients with surgery alone (first-time irradiation, FI-group).

All patients had evidence of tumour recurrence as demonstrated by computed tomography (CT) or magnetic resonance imaging (MRI), and all were considered inoperable.

From November 1997 to December 2001, 14 patients with locally recurrent rectal cancer were treated with a combination of RCT and RHT. All patients had undergone attempts of curative surgical resections in the past. Surgical resection had been followed by irradiation in 9 cases (PI-group) with a total dose of 40–59.4 Gy and a fractionation of 1.8 Gy. Eight of 9 patients had received a continuous infusion of 5-FU in the first and the fifth week of irradiation. The 9th patient had been treated with 40 Gy at the initial time of diagnosis at another hospital. All local recurrences in the PI-group were considered inoperable at evaluation for feasibility.

Patients of the PI-group were treated with external beam irradiation (conformal irradiation with a 4-fields technique) again, with 30.6 Gy (4 patients), 36 Gy (4 patients), and 39.6 Gy (1 patient), respectively. A fractionation of 5×1.8 Gy was applied. The total cumulative doses ranged from 84 Gy to 95.4 Gy. CT regimen consisted of a continuous infusion of 5-FU at a dose of 350 mg/m^2/24 h for 5 days per week. This treatment regimen was combined with HT twice a week.

Dose finding in the PI-group was based on the following criteria:

a. pre-irradiation dose, including time passed since the last irradiation;
b. acute reaction during the current combined treatment.

Of the 5 patients who had not been irradiated in the past (FI-group) 3 were treated with 54 Gy (45 Gy plus a 9 Gy boost), 1 patient was treated with 59.4 Gy (45 Gy plus a 14.4 Gy boost), and 1 patient was treated with 45 Gy. Again, conformal irradiation was applied with a 4-fields technique. Dose finding was based on the dose of post-operative irradiation applied in this group. All patients were irradiated with 5×1.8 Gy/week with a photon irradiation of 15 MV. CT regimen also included a continuous 5-FU infusion at a dose of 500 mg/m^2/24 h on days 1–4 and 29–33.

HT was applied twice a week during the period of RT for all patients one hour after RT. HT was performed by using the annular phased array system BSD-2000/3D (BSD Medical Corporation, Salt Lake City, UT) with two types of applicators (Sigma-60 and Sigma-Eye, BSD Medical Corporation, Salt Lake City, UT). The Sigma-60 applicator is a 2D annular phased array with a single ring of 8 dipole antennas. The Sigma Eye applicator is an enhanced version of the Sigma-60 which provides 3D steering using a triple ring of 24 dipole elliptical phased arrays with free phase selection for every antenna pair.

Therapy consisted of a plateau of 1-h HT-treatment after a temperature of at least 42 °C had been achieved, or 30 min after initiation of the heating process.

81 HT treatments were performed in 14 patients (mean 5.8 RHT per patient). In 11 of the 14 patients tumour-related temperature near the tumour was measured via an endoluminally inserted catheter (rectal or

Table 1. Patient characteristics

Patient	Sex	Month and year of initial diagnosis	Stage at the time of initial diagnosis	Previous treatments	Previous radiation dose (total), Gy	Month and year of local tumour recurrence
1	female	08/98	pT3+pT2M0G2Nx	OP, RCT	54.0	09/00
2	female	01/94	pT2pN1M0G2	OP,RCT,HT,CT	40.0	10/00
3	female	06/95	pT2N0M0G2	OP, RCT	59.4	02/01
4	male	12/92	PT2N3G2M0	OP, RCT	50.0	03/01
5	female	04/91	pT3pN2M0G2–3	OP, RCT	50.0	07/00
6	male	01/96	pT3pN0M0G1–2	OP, RCT	50.4	07/01
7	female	07/96	pT1pN1M0G2	OP, RCT, CT	50.6	11/00
8	male	09/93	pT2pN0M0G2	OP, RCT, CT	54.0	08/00
9	female	01/00	pT3pN2M0G3R1	OP, RCT	45.0	11/00
10	male	03/89	pT3pN0M0G2	OP	no	06/97
11	female	05/99	pT4pN0M0G2	OP	no	09/99
12	male	05/00	pT3pN2M1(Liver)G2–3	OP, CT	no	02/01
13	male	11/95	pT3pN3M1G2–3	OP	no	08/01
14	male	01/96	pT3N0M0G2	OP	no	12/98

OP = Surgery; RCT = radiation combined with chemotherapy; CT = chemotherapy.

vaginal). Endoluminal temperature measurement was not possible in the remaining 3 male patients due to iatrogenic closure of the anal canal. Temperature measuring catheters (Cook, Moenchengladbach, Germany) with a measuring tract of 10–15 cm were routinely placed in the patient's rectum or vagina before initiation of HT and were subsequently removed after each treatment session.

Response to the treatment was evaluated by CT or MRI and by clinical follow-up at the end of therapy and every 3 months thereafter. The response was rated complete, if there was no evidence of recurrent tumour on CT or MRI, and partial, if there was a tumour reduction of more than 50%. If a tumour volume reduction of less than 50% was observed, the patient was rated to have no change. Morbidity and side-effects were evaluated according to the common toxicity criteria (CTC) [9–10].

Results

From November 1997 to December 2001, 14 patients with recurrent rectal cancer were enrolled. Patient characteristics are summarised in table 1. One patient from the FI-group had to be excluded from the evaluation, since an R1 resection had been performed before initiation of RCT and HT. Thus, response was not possible.

Of the PI-group patients, 2 showed a complete remission, while 1 had a partial remission. No change was observed in 5 patients, whereas 1 patient had progressive disease. In the FI-group of patients with first-time RT, 3 showed a complete remission, and one a partial remission.

For all observed patients, complete remission was observed in 38.5%, partial remission in 15.3%, no change in 38.5%, and progression in 7.7%. Two patients of the FI-group subsequently underwent surgery with a curative intention – one patient with a radiographic complete remission had an R1 resection 4 weeks after conclusion of therapy, and 1 patient with a radiographic partial remission underwent an R2 resection, also 4 weeks after RCT + HT. Two patients from the PI-group underwent a palliative resection after the treatment.

On the average, 5.8 sessions of HT were performed (range 1 to 10). One patient underwent only one session of HT due to pronounced, uncontrollable pain during the treatment. Fifty-five of 81 treatments were available for temperature analysis of measurements of adjacent tissues by endoluminal catheters (e.g. rectum, bladder, vagina). Average maximum temperature (T_{max}) was 40.3 °C (range 39.6 to 41.1 °C) and the median time-averaged temperatures achieved in 20%, 50% and 90% of all measured tumour sites were 39.7 °C (T_{20}) (range 39.1 to 40.4 °C), 39.3 °C (T_{50}) (range 38.9 to 39.8 °C), and 38.8 °C (T_{90}) (range 38.4 to 39.2 °C), respectively.

Evaluating side-effects, no abscess, no sinus tract formation, no delay of wound healing, no bleeding has been observed. A subileus has been reported during the follow-up of 1 patient as a late toxicity. Five patients suffered from a skin reaction, 1 rated grade I, 2 grade I–II, another was rated grade II–III and yet another grade III. All patients suffering from skin reactions higher than grade I, belonged to the PI-group. Diarrhoea grade II–III was observed in 2 patients (15.4%). During HT, 5 patients complained about pain during the treatment. As mentioned above, 1 patient declined to proceed with HT after the first session. The other 4 patients received i.v. analgesia with opiates and proceeded with HT treatment regimen without further constraints.

During the mean follow-up of 13.9 months (range 5–32 months), 7 patients showed no signs of local progression. Five patients had signs of local progression during the observation period, but were still alive at the time of this writing. Seven patients died from distant metastases or local progression.

Discussion

Local recurrences of colorectal cancer can be understood as manifestations of disseminated disease spreading locoregionally; synchronal distant metastases are often found in patients with the diagnosis of a local recurrence and the probability of cure or long-time survival is low [11]. However, survival varies widely depending on tumour growth rate, which is determined biologically but also influenced by surgery [11].

At present, there is no standard treatment regimen for locally advanced recurrent rectal cancer. Treatment regimens for locally recurrent rectal cancer have significantly changed over the past two decades with treatment goals shifting from palliation to possible cure. Various treatments methods have been applied, such as RT combined with α-interferon [12], intraoperative irradiation [13], re-irradiation by itself [14], or CT [15]. However, if resection of the local tumour recurrence is possible, it remains the most favoured and most promising curative approach. Attempts to find new chemotherapeutic agents or radiosensitisers to enhance the local tumour control are being pursued eagerly [16, 17]. The optimal point in time for using CT in a multimodal regimen currently is under investigation. With modern radiation techniques such as 3D-conformal irradiation, a relatively low rate of morbidity and a low rate of toxicity can be achieved, even if pre-irradiation was performed. The results of combining RCT with RHT have been encouraging for a variety of tumour types [6–8, 18]. Combination of RHT with re-RCT appears to be useful in treatment strategies for local tumour recurrences, and synergistic effects may contribute to a better local control. The mainstay of therapy remains RCT, however. Although it has been shown that a combined treatment of rectal cancer with RCT and RHT improved local control [4–6], the adverse effects of the combined therapy are defined insufficiently.

Our observations show a better local control in the group with higher irradiation doses (3 complete and 1 partial remission), while local control was less efficient in the group of patients receiving a lower dose of (re-)irradiation. Thus, the major effect regarding local control may be connected to the dose of irradiation. This observation goes with the findings of Romano et al. [18] who treated patients with locally advanced rectal cancer with a combination of RT and RHT. In their study the complete response rate was 32.5%, using radiation with a total dose of 64 Gy. Due to the different irradiation doses in our 2 groups, it is difficult to define an optimal dose. Both, irradiation dose given before reoccurrence of tumour and the acute side-effects during therapy, must be taken into account. Based on our preliminary experience, we believe that a radiation dose of 36–39.6 Gy (5 × 1.8 Gy) in previously irradiated patients could be a compromise. In patients not irradiated before, we consider the optimal dose to be 45 Gy plus a 9–14.6 Gy boost.

Survey of the distribution of temperatures achieved by HT is crucial to maintain a constant quality. The rationale for using an endoluminal temperature measurement was the previously demonstrated correlation between the endoluminally measured temperature and the intratumoural temperature rises [19]. Clinical experience shows that endoluminally measured temperatures are generally 1–2 °C lower than the temperature measured within the tumour tissue. This explains the moderately high average of maximum therapeutic temperatures achieved in our patients.

This therapeutic regimen was shown to be moderately toxic in our patient groups in combination with HT and CT and no interruption of therapy was necessary. A dermatitis grade III was observed in 2 patients with re-irradiation who had received a cumulative dose of 84–94.5 Gy. This can be attributed to (a) a high cumulative irradiation dose and (b) the combination of RHT and RCT. Side-effects such as dermatitis and diarrhoea (toxicity grade III) have been mentioned by Anscher et al. [5] in the treatment of recurrent rectal cancer with re-irradiation and hyperthermia.

In this analysis, follow-up time has been relatively short and emphasis lay on feasibility, morbidity and toxicity of a combined implementation of the described methods. The introduction of a multimodal therapeutic regimen has been demonstrated to have a clear-cut advantage over RT alone [4–6, 18]. In concordance with previous data, the addition of HT to the treatment regimen does not seem to enhance toxicity or subacute morbidity [4–6, 18]. This combined therapeutic regimen appears to be active against locally recurrent rectal cancer warranting further consideration as a treatment option for this population of suffering patients.

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