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A Pilot Study of a New Therapeutic Approach in the Treatment of Locally Advanced Stages of Rectal Cancer: Neoadjuvant Radiation, Chemotherapy and Regional Hyperthermia

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The synergistic effects of hyperthermia (temperatures ≥41°C) when combined with radiotherapy or cytotoxic drugs, as well as a modulation of tumour-related immunological phenomena have been demonstrated preclinically. Local or regional hyperthermia in combination with radiation or chemotherapy has been studied in patients during recent years, and has convincingly demonstrated that hyperthermia is feasible and tolerated by patients. Furthermore, there is strong evidence that hyperthermia may provide an improvement in local control as compared with radiotherapy or chemotherapy alone. Systems based on radiowave irradiation allow sufficiently tolerable and effective regional hyperthermic therapy in patients with rectal carcinomas. Used as part of curative pre-operative and postoperative multimodal therapeutic strategies in high-risk patients with locally advanced rectal carcinomas, hyperthermia may result in improved local control and a higher rate of sphincter-sparing procedures. 20 patients with non-resectable, locally advanced primary or recurring rectal carcinoma T3/4 entered a phase I/II study of pre-operative radiochemothermotherapy with folinic acid and 5-fluorouracil, radiation (45 Gy HD), as well as regional hyperthermia once a week followed by chemotherapy after surgery. The regimen proved to be sufficiently tolerable. Acute grade III or IV toxicities did not occur after hyperthermia. Tumour resections were performed on 14 of the 20 patients, with 13 being complete. In 9 of the carcinomas, downstaging compared with the pretherapeutic stage was achieved. In 3 of 6 patients with persistent non-resectable tumours, local control has now been maintained for more than 12 months. One patient progressed locally during neoadjuvant combination therapy. These results prompted the initiation of a prospective randomised study to evaluate the relative importance of regional hyperthermia in this setting.

Key words: rectal carcinoma, hyperthermia, neoadjuvant therapy, radiochemotherapy, thermotherapy, 5-fluorouracil, radiation

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INTRODUCTION

IN ADVANCED rectal carcinomas, local control is a major problem for many patients [1, 2]. Postoperative 5-fluorouracil (5-FU)-based radiochemotherapy takes advantage of the sensitising effect of radiation and the adjuvant systemic effect of 5-FU. It is used after precise histopathological staging in patients with Dukes stages B and C rectal cancer to improve local tumour control and overall survival [3–5]. Because prognosis for patients with unresectable, locally advanced or recurrent rectal carcinomas is still unsatisfactory, new treatment strategies need to be evaluated. In this context, the problems of determining tumour stage pre-operatively and defining non-resectability must be emphasised. Endosonography is currently recognised as the most accurate method for pre-operative staging (uT) of rectal carcinomas [6]. For patients with stages uT3/4 and N+ or recurrent tumours, data are emerging which indicate that pre-operative radiotherapy with or without chemotherapy is of some benefit [4, 7]. Studies on pre-operative radiotherapy for non-resectable rectal carcinomas show resectability rates of 40–64% and low rates of complete remission (<10%). In comparison with historical controls, the addition of chemotherapy appears to increase resectability to 80–90%, and the number of complete remissions to as much as 20% [8, 9]. For certain risk groups, the local recurrence rate can still be a major problem, for example, in clinical stage IV, local failure of 50% is still evident, despite pre-operative radiotherapy [2]. In patients with clinical stages II/III and for those with distal rectal carcinomas (<6 cm anorectal line), Ahmad and associates found that local control after pre-operative radiotherapy and potential curative surgical interventions was strongly dependent on radiation dose [1]. In addition to T and N stage, the histological characteristics, especially lymphangiosis carcinomatosa (L+) or vessel invasion (V+) proved to be prognostic determinants for locoregional

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recurrence [5]. Therefore, patients with uT3/T4 and at least one of these risk factors (N+, L+, V+) can be considered at high risk.

In vitro and *in vivo* investigations have provided clear evidence that increasing temperature can result in a supra-additive amplification of the effects of radiation and certain cytotoxic drugs [10–14]. Additionally, hyperthermia has been found to affect effector cells of the immune system (natural killer cells) and biological response modifiers [15, 16]. Alternatively, *in vivo*, tumour microcirculation may be a target for the effects of hyperthermia [17]. When given consecutively (ideally simultaneously), even moderate temperatures of 40.5–41°C can enhance the effect of radio and chemotherapeutics [18–20]. The biochemical mechanisms of this amplifying effect are still being studied. Radiation sensitisation is believed to be mainly due to the influence of hyperthermia on repair enzymes (recovery from sublethal or potentially lethal radiation damage) [10, 11, 21, 22], whereas the interaction with cytotoxic drugs has other causes, such as an increase in cellular uptake, modification of intracellular distribution, metabolism of the drug and an increase in reaction rate at specific DNA sites of action [11, 12, 23].

Clinical studies using different types of heating devices for local and regional hyperthermia (RHT) have resulted in data suggestive of improved response rates by the combination of hyperthermia and radiation or chemotherapy as compared to radiation or chemotherapy alone [13, 24–33]. Indeed, several phase III studies, evaluating the role of hyperthermia in bimodal treatment strategies, have been initiated [34]. Multimodal treatment strategies may take advantage of local synergisms of radiation and RHT, and cytotoxic drugs and RHT, as well as cytotoxic drugs and radiation [14, 35].

To evaluate feasability, toxicity and antitumour effects of RHT, added to a neoadjuvant protocol of simultaneous radiochemotherapy in high-risk patients with locally advanced rectal cancer, we performed a prospective open phase I/II pilot study.

PATIENTS AND METHODS

After informed consent had been obtained, 20 patients (Table 1) with non-resectable, locally advanced (uT3/T4) or recurrent (without prior radiation or chemotherapy) rectal carcinomas underwent multimodality pre-operative therapy (Figure 1) consisting of radiotherapy (planning target volume dose 45 Gy), chemotherapy (5-FU and low doses of folinic acid), and thermotherapy (RHT using the BSD 2000 system). The pretherapeutic staging included computed tomography (CT) and endosonography and in some patients MRT scans and/or staging laparotomy. UICC stages, which were ascertained using endosonography, visualising processes and clinically, are shown in Table 1.

Regional hyperthermia was performed once a week throughout the entire 5 (–6) week pre-operative treatment phase, using the BSD 2000's Sigma ring applicator. RHT was administered using a standard setting at 90 MHz with a 20–40°C phase delay

Table 1. Patients' characteristics (n = 20)

Male/female	14/6
Age (years)	62 (range 30–75)
uT3/uT4	8/12
uN0/uN+	0/20
Primary/relapse	15/5
Karnofsky status	80 (range 70–100)

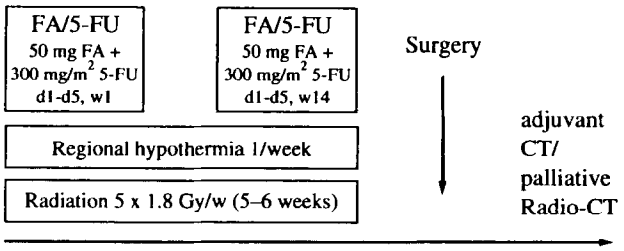

Figure 1. Neoadjuvant radiochemothermotherapy in non-resectable, locally advanced rectal cancer: treatment schedule. FA, folinic acid; 5-FU, 5-fluorouracil; CT, chemotherapy.

in the pair of antennas at bottom and a 5–20° delay in the side pairs (supine position of patient). Two-dimensionally, this phase delay shifts the focus caudally into the presacral space.

Thermometry was performed by inserting a Teflon catheter with an external diameter of 1.8 mm (Angiomed™) non-invasively into the rectum, into the tumour region and beyond, while the patient was lying on his left side. The catheter's tumour contact path was reconstructed with the help of CT documentation and parameters determined endoscopically. Only for presacral recurrent tumours after abdomino-perineal rectum extirpation was a catheter implanted invasively under CT guidance.

Temperatures were measured continuously using a high-frequency, inert, temperature-dependent resistance via a high-resistance lead (Bowman thermistor), and temperature/position curves were regularly plotted using a scanning system driven by a stepping motor. The data collected were later analysed to obtain the time-based index temperatures T_{20}, T_{50}, T_{90} and the minimum and maximum contact temperatures in the tumour. The data transfer and evaluation programme was developed by Basu and Bierbass [36, 37]. T_X is the temperature above which x% of the time-averaged temperatures assigned to tumour contact measurement points climbed during the actual therapeutic period. The 60-min therapeutic period started when at least one tumour contact measurement point had reached 41°C, or at the latest after 30 min.

Radiotherapy was performed as soon as possible (within 45 min) after RHT using an open table-top device, and the patient in the prone position [38]. A planning CT was carried out on each patient in this particular position. All were irradiated using the three-field technique and lateral wedge filters. Standard shields were used to protect lateral field corners, dorsal soft tissues (skin, rima ani) and, when necessary, cranial ventral sections of the small intestine. The upper field border was positioned at S1 (lower edge), occasionally at L5 (lower edge) if the rectal carcinoma was proximally located. The ventral border was determined by the position of the primary tumour and the infiltration into the surroundings (especially prostate). Images of the small intestine were obtained using gastrografine in order to document the sections of the small intestine situated in the field of radiation. Fractionation was 5 × 1.8 Gy in the reference point (isocentre) with a maximum of less than 2 Gy. This resulted in a target volume dose of 45 Gy and a maximum dose of less than 50 Gy.

Chemotherapy using short infusions of folinic acid (50 mg) followed by 5-FU (300 mg/m²) was given on days 1–5 and 22–26 30 min before irradiation or during the initial phase of regional hyperthermia. Postoperatively, another four courses of folinic acid (50 mg) followed by 5-FU (dose adjustment according to

Table 2. Acute toxicities of regional hyperthermia (% of regional hyperthermia sessions)

Hot spots (temporarily)	54%
Pain (tumour site)	16%
Heat sensation (tumour site)	14%
Musculoskeletal syndrome	30%
Burns (grade II)	12%
Systemic stress	3%

individual toxicities: 300–450 mg/m^2) were administered on days 1–5 every fourth week, starting 2–4 weeks after surgery.

Surgery was performed after restaging procedures 4–5 weeks after the last radiation dose had been applied. When the restaging procedures demonstrated persisting non-operability, a radiation boost up to a dose of 60 Gy was considered as soon as possible.

Side-effects were documented using the WHO score system at weekly intervals and during hyperthermia treatment. Routine CT examinations were performed before and after the multimodal therapy. Some of the patients were given pre- and post-therapeutic MRT examinations, both with and without contrasting agent (T1- and T2-weighted sequences).

RESULTS

There was no treatment-related or -unrelated mortality during or within 9 weeks after the treatment phase. In 90% of the patients, pre-operative radiochemotherapy could be given as planned or with a short delay of less than 5 days. The calculated number of RHT sessions was reached in 80% of the patients, with only 1 of the patients refusing RHT after the second session. 2 patients received one and 1 patient received two RHTs less than calculated, due to skin toxicity or technical problems.

There was no grade III or IV acute toxicity of intestine, bladder or skin during RHT (Table 2). In 30% of patients, tenderness or aching (musculoskeletal syndrome) was reported at predilection sites (suprapubic region, inguinal region, thigh, lateral gluteal region) after RHT. Diarrhoea (grade III–IV) occurred in 35% of patients, required therapy, causing radiotherapy to be temporarily interrupted in 6 patients. In 20% of patients, serious skin reactions (WHO III) with moist epitheliolysis occurred around the rima ani. In 1 patient, therapy had to be interrupted because of this skin reaction.

The tumour contact temperatures were 0.2–0.6°C lower than the temperatures measured intratumorally (data from more than 50 patients with pelvic tumours). Thermal parameters are indicated in Table 3. Potentially effective hyperthermia was possible in most patients, with contact temperatures ≥42°C reached in 55% and ≥41°C reached in 95% of the sessions. None of the thermal parameters could be correlated with response.

Multimodality therapy led to a significant reduction in discomfort in all 5 patients who had presented with pain in the presacral or anal regions. From CT or MRT scans, 6 patients demonstrated objectively verifiable decreases in tumour size or reduction in wall thickness. The surgical procedure resulted in primary uneventful wound healing in 14 patients. Perioperative morbidity occurred in 6 patients (30%), an incidence similar to that observed after neoadjuvant radiochemotherapy.

Observation time is currently 6–15 months. Tumours were considered resectable following neoadjuvant therapy in 14 patients (Figure 2). One patient had residual disease (R2) following surgery, and progressed. 13 (65%) patients had complete resections (R0), and pathological downstaging was possible in nine tumours. Of the 13 patients who received complete resections, 2 had histologically confirmed complete response of the primary tumour. 12 patients are currently free of disease, and 1 relapsed locally and in the liver 4 months after the end of adjuvant chemotherapy.

Of the 6 patients with non-resectable tumours, 2 progressed 2 and 4 months after completion of radiotherapy. One is now stable on intensified palliative chemotherapy, and the other died 6.5 months after entering the study. The other 4 patients received a radiation boost up to a total volume dose of 60 Gy, as soon as possible following re-evaluation, and further RHT was performed on 2 of these patients. 3 of these 4 patients achieved a progression-free clinical remission for more than 12 months, and the other patient progressed.

DISCUSSION

For a high-risk group of patients with rectal carcinomas, intensive therapy seems necessary in order to improve local tumour control and overall prognosis [4, 5]. Hyperthermia is a potential candidate for inclusion in multimodality treatment of these patients [39].

We believe that performing regional hyperthermia with intraluminal temperature monitoring without intratumoral temperature measurement, is justifiable because we have extensive experience of hyperthermia on pelvic tumours using invasive as well as intraluminal temperature measurements. Research (simulation studies, phantom measurements) and clinical experience have demonstrated the standard setting described here to be the optimal use of the equipment available [37, 40, 41]. However, it is not yet clear whether temperature-related parameters can be considered as indicators of the effectiveness of thermotherapy in the patients studied—exisiting data on uniform patient groups (e.g. primary advanced stages uT4) and

Table 3. Thermal parameters (°C)

	Mean (range)
RHT sessions/patient	5.3 (2–10)
T_{min}	39.5 (38.5–41.7)
T_{90}	39.8 (38.8–41.7)
T_{50}	40.7 (39.8–42.0)
T_{20}	41.1 (40.2–42.5)
T_{max}	41.4 (40.5–43.0)

T_{min}, Minimum contact temperature; T_{max}, maximum contact temperature; T_{20-90}, time-based index temperatures.

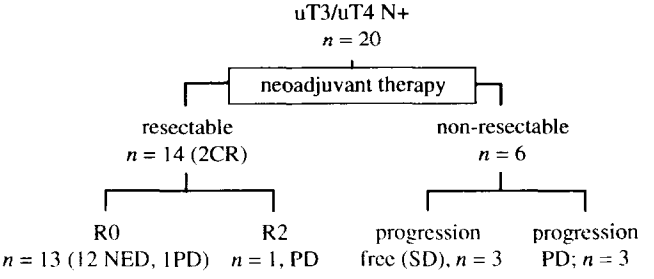

Figure 2. Clinical outcome in 20 patients with non-resectable, locally advanced rectal cancer undergoing neoadjuvant radiochemothermotherapy. PD, progressive disease; NED, no evidence of disease; SD, stable disease; CR, complete remission.

observation periods are not yet sufficient. A correlation of intratumoral-registered thermal parameters and treatment results has been demonstrated in patients with superficial and deep-seated tumours by some groups [27, 33, 42–44]. The maximum tumour contact temperatures achieved and the corresponding index temperatures, as well as the frequency of the musculoskeletal syndrome resulting from hot-spot formation, all underline the importance of continuing to improve the technology and methods used in hyperthermia.

These preliminary results clearly prove the acute toxicity of pre-operative radiochemothermotherapy to be acceptable and tolerated by most of these elderly patients. With regard to the whole treatment strategy, there are, nevertheless, some ways of increasing the level of tolerance. It is well known that the combination of radiotherapy and 5-FU/leucovorin chemotherapy increases the toxicity in the intestine (colitis), particularly in the small intestine (diarrhoea, enteritis), as compared with either modality alone. Alternative modes to apply chemotherapy, such as prolonged continuous infusions may be considered. Furthermore, we must strive for more carefully conforming adaptation of the isodose distribution to the target volume, while omitting the relevant areas of the small intestine. This can be done using conformative irradiation techniques and CT-supported planning (with small intestine contrasting). Irradiation planning involving rectal carcinomas is currently performed using the quasi-3D planning system together with individual screens. As temperatures of 42–43°C were often measured in the rima ani during RHT in the patients studied here, hyperthermic sensitisation may be important for the observed rate of radiogenic skin reactions. For this reason, a special cooling pipe has been developed, and our preliminary experience with this device is suggestive of reduced skin reactions.

We believe that the preliminary tumour responses observed by this multimodality approach warrant further studies. For meaningful conclusions on the duration of local control and overall survival, the patient number must be increased and the observation period prolonged. To address the relative clinical impact of RHT in this setting, a prospective, randomised, multicentre study was initiated.

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