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Preoperative Hyperthermia Combined with Radiochemotherapy in Locally Advanced Rectal Cancer

A Phase II Clinical Trial

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Objective

A prospective phase II study was performed to determine the feasibility and efficacy in terms of response rate, resectability, and morbidity in patients with locally advanced rectal cancer who received preoperative regional hyperthermia combined with radiochemotherapy (HRCT).

Summary Background Data

Recent studies suggest that preoperative radiochemotherapy in locally advanced rectal cancer can induce downstaging, but after resection the incidence of local recurrences remains high. Hyperthermia (HT) may add tumoricidal effects and improve the efficacy of radiochemotherapy in a trimodal approach.

Patients and Methods

Thirty-seven patients with histologically proven rectal cancer and T3 or T4 lesions, as determined by endorectal ultrasound and computed tomography, entered the trial. 5-Fluorouracil (300–350 mg/m^2) and leucovorin (50 mg) were administered on days 1 to 5 and 22 to 26. Regional HT using the SIGMA 60 applicator (BSD-2000) was given once a week before radiotherapy (45 Gy with 1.8-Gy fractions for 5 weeks). Surgery followed 4 to 6 weeks after completion of HRCT.

Results

Preoperative treatment was generally well tolerated, with 16% of patients developing grade III toxicity. No grade IV complications were observed. The overall resectability rate was 32 of 36 patients (89%), and 31 resection specimens had negative margins (R0). One patient refused surgery. In 5 patients (14%), the histopathologic report confirmed no evidence of residual tumor (pCR). A partial remission (PR) was observed in 17 patients (46%). The survival rate after 38 months was 86%. In none of the patients was local recurrence detected after R0(L), but five patients developed distant metastases.

Conclusion

Preoperative HRCT is feasible and effective and may contribute to locoregional tumor control of advanced rectal cancer, which is to be proven in an ongoing phase III trial.

In rectal cancer, resection with negative margins is the major tool for achieving long-term survival. However, in locally advanced tumors (UICC stages II and III), local recurrences after surgery alone have been reported in up to 58% of patients.[1,2] For recurrent rectal cancer, the prognosis is poor.[3,4]

Because there is no serosal layer covering the rectal tumors extending beyond the rectal wall (T3), they might easily spread within the pelvis. Consequently, circumferential margin involvement within the pelvis plays a major role in the development of local recurrences.[5] As a consequence of randomized trials comparing postoperative radiochemotherapy with surgery alone, in 1990 the consensus conference of the U.S. National Institutes of Health recommended combined adjuvant postoperative pelvic irradiation and chemotherapy as the standard therapy for stage II and III primary rectal cancer.[6]

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Efforts to improve the treatment results of stage III tumors further focus on preoperative radiotherapy or combined radiochemotherapy. The rationale is: 1) to irradiate the tumor in a well-oxygenated status[7,8]; 2) to prevent tumor cell seeding during surgery; 3) to reduce radiotherapy-related small-bowel toxicity[9]; and 4) to downstage the tumor volume, which might facilitate resection.[10]

Tumor fixation[11,12] is a particularly unfavorable prognostic factor and may indicate nonresectability. Preoperative radiotherapy for initially nonresectable rectal carcinomas resulted in a resectability rate of 40% to 64% and a complete remission rate of approximately 10%.[10,13,14] Even after complete resection, local failure rates of up to 65% have been reported, depending on the degree of tumor fixation.[10,13,14] Chemotherapy added to radiation increases the resectability rate to 71% to 90% and the rate of complete remissions to 20%.[15,16]

To intensify preoperative radiotherapy further in locally advanced rectal cancer, several approaches have been evaluated, such as different schemes of combined chemotherapy[17–19] and hyperthermia.[20–25] *In vitro* temperatures of 40° to 43°C enhance the effect of radio- and chemotherapy.[26] Interference with the repair of radiation-induced DNA damage[27] and a synergistic interaction with cytotoxic drugs have been reported as modes of action.[26,28] Various clinical phase II and III trials using different heating devices for local and regional hyperthermia (HT) have shown encouraging results when compared with radiation or chemotherapy alone.

Experience with rectal cancer is limited to the application of endocavitary HT in addition to radiotherapy.[22,24,29] The different stages of tumors treated, the use of 5-fluorouracil (5-FU) as suppositories,[22] and the lack of thermometry data may interfere with the assessment of its true clinical value.

We therefore were interested in adding thermotherapy to preoperative radiotherapy in combination with systemic chemotherapy of primary, locally advanced rectal cancer. In a pilot study, the feasibility of the approach was verified.[30] This report analyzes the data of the phase II trial with regard to toxicity and response as well as surgical treatment and morbidity.

PATIENTS AND METHODS

Study Design

Thirty-seven patients with locally advanced primary rectal cancer and a biopsy-proven adenocarcinoma were entered into the study (Table 1). They all presented with tumor infiltration beyond the rectal wall at endorectal ultrasound (ERUS) and computed tomography (CT) scan and were subjected to combined modality therapy (Fig. 1). Four to six weeks after completion of preoperative treatment, restaging was accomplished, and all patients were scheduled for laparotomy. If an R0 resection could be achieved, four cycles of adjuvant chemotherapy were administered postoperatively. Patients with incomplete resections (positive resection margins or macroscopically residual tumor) underwent further radiotherapy of up to 60 Gy, combined with HT, chemotherapy, or both. If the tumor was still not resectable at surgical exploration, further therapy was determined on an individual basis. All patients were required to give written informed consent. The study was approved by the ethics committee of the Humboldt University of Berlin.

Table 1. CHARACTERISTICS OF PATIENTS* AND TUMORS

	Depth of Infiltration by Endorectal Ultrasound		
	uT3 (n = 23)	uT4 (n = 14)	Total (n = 37)
Infiltration of adjacent organs			
Rectovaginal septum (uterine, cervix, vagina)		2	2
Prostate, ovary		6	6
Urogenital tract (bladder, ureter, spermatic gland)		6	6
Tumor level from the anal verge			
0–5 cm	11	7	18 (48.6%)
6–10 cm	8	6	14 (37.8%)
11–16 cm	4	1	5 (13.5%)
Clinical stage (Mason)			
2 (tethered, partially fixed)	5		5 (13.5%)
3 (fixed in two directions)	9	3	12 (32.4%)
4 (advanced fixation)	8	11	19 (51.4%)
Unknown	1		1 (2.7%)
Lymph nodes			
Suspicious	13	8	21 (56.8%)
Not suspicious	10	6	16 (43.2%)
Distant tumor spread			
Liver	1	1	2
Lung		1	1
Surgeon's estimation of resectability			
Potentially resectable	15	1	16 (43.2%)
Not resectable (after clinical staging)	6	8	14 (37.8%)
Not resectable (after explorative laparotomy)	2	5	7 (18.9%)

* Sex (male/female): 31/6; median age and range (yr): 59.1 (31–74).

Eligibility Criteria

Eligibility criteria were as follows: Karnofsky performance status > 70; white blood cell count ≥ 4.0 cells/mm^3; hemoglobin ≥ 10 mg/dL; platelets (PLT) ≥ 150,000/mm^3; creatinine ≥ 1.5 mg/dL; and total serum bilirubin ≥ 1.5 mg/dL. At rectoscopy with a rigid rectoscope, the distal margin of the tumor had to be located up to 16 cm from above the anal verge.

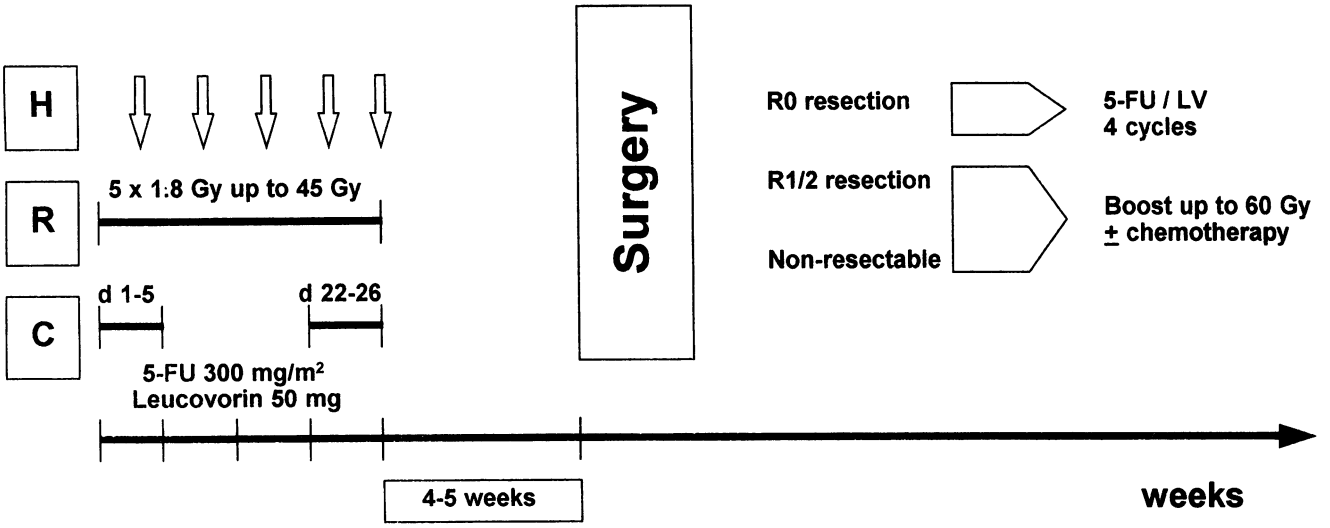

Figure 1. Scheme of the trial. H, hyperthermia; R, radiotherapy; C, chemotherapy.

Exclusion Criteria

Excluded were patients with prior malignancies (except for nonmelanoma skin cancer), prior pelvic irradiation, or prior chemotherapy, and patients with metallic implants, such as hip reconstruction or pacemakers, because of the interaction between HT and radiowaves.

Investigations

The pre- and posttreatment evaluation included a complete history and physical examination, rectoscopy and colonoscopy, barium enema study, ERUS, CT scan of the whole abdomen and pelvis, ultrasound of the abdomen, and a chest x-ray, as well as complete blood count, platelet count, SMA-20, carcinoembryonic antigen (CEA), and CA 19-9. At clinical examination, fixation of the tumor within the pelvis was evaluated according to Mason.[11] Immobility in two orthogonal directions was considered as resectable (Mason grade 3). Tumors with advanced fixation or "frozen pelvis" (Mason grade 4) were regarded as nonresectable. Seven patients underwent exploratory laparotomy and were judged to have nonresectable lesions. Patients with solitary metastases (liver, lung) were included in the study if their lesions were assessed as resectable.

Treatment

Regional Hyperthermia

Regional HT was administered at weekly intervals, and the BSD-2000's (BSD Medical Corp., Salt Lake City, UT) SIGMA 60 ring applicator was used. This system functions via radiofrequency at 90 MHz with a 20° to 40° phase delay on the pair of antennas at the dorsum and a 5° to 20° delay on the lateral pairs (supine position of the patient). This phase shift delays the power deposition pattern dorsally into the presacral space, and it proved to be the most practical in clinical use.[31,32]

Endoluminal thermometry catheters were placed in the rectum, bladder, and vagina. The therapeutic period of HT began when one tumor-related measurement point reached 42°C or 30 minutes after the power was turned on, whichever was earlier. Continuous heat treatment over a period of 60 minutes was attempted. Temperature position curves were recorded along the catheters at intervals of 5 to 10 minutes.

Index temperatures (T_X) in contact with the tumor were determined for every temperature/position curve recorded.[33] During the therapeutic period, the mean T_X values in the temperature/position curves were calculated with respect to time. The time during which the index temperature of T_{90} (when 90% of the measurement points in contact with the tumor reached the same temperature) remained above the reference temperature (T_{ref}) of 40.5°C[34] was determined and expressed as cumulative minutes ($T_{90} > T_{ref}$).

Radiotherapy

Radiotherapy was performed using an open tabletop device with the patient in a prone position 15 to 20 minutes after HT. A computer plan was based on the CT scan in the same position. A three-field technique with lateral wedge filters was employed. Individualized blockings were used to protect lateral field corners, dorsal soft tissues (skin, rima ani), and, if necessary, cranial ventral parts of the small intestine. The upper field border was positioned at level L5–S1, depending on the location of the primary tumor. The ventral border depended on the location of the tumor and its degree of infiltration into the surrounding structures. In most cases, the ventral field edge passed through the central third of the head of the femur. Images of the small intestine were obtained using barium sulfate contrast media to doc-

Table 2. TOXICITY SCORE FOR REGIONAL HYPERTHERMIA

Grade	Criteria
0	General discomfort (bolus pressure, systemic stress); no limitation of heat treatment
I	Local discomfort (hot-spot phenomenon, positioning), which requires rearrangement of treatment set-up; heat treatment can be accomplished with some restrictions in total power and power distribution
II	More severe local discomfort or systemic stress, which persists after the end of treatment and evidently limits the efficiency
III	Every kind of toxicity, which causes the patient to refuse further heat treatments (hot-spots, musculoskeletal syndrome, claustrophobia, etc.)
IV	Burns or tissue damage or any other complication related to the heat treatment

ument and minimize the parts of small intestine in the radiation fields.

Radiation was delivered 5 days a week with a fractionation of 1.8 Gy to the reference point (isocenter). Total dose in the reference point was 45 Gy, with a maximum dose of less than 50 Gy.

Chemotherapy

Chemotherapy was administered in two cycles on days 1 to 5 and 22 to 26 before irradiation or during HT. Fifty milligrams of leucovorin (LV) was given by intravenous infusion over 30 minutes, followed by a 5-fluorouracil (5-FU) bolus (300 mg/m^2 per day in the first course and 350 mg/m^2 in the second). This regimen was also used postoperatively.

Toxicity attributed to chemotherapy was recorded according to the World Health Organization,[35] and adverse reactions from radiotherapy were graded according to the LENT SOMA tables.[36] To assess toxicity caused by HT, we inaugurated a scoring system (Table 2). If the toxicity was grade III, treatment modalities were interrupted. The patients were re-evaluated at weekly intervals before continuing the protocol, and the dose of 5-FU was reduced by 25%.

Surgery

Surgery followed 4 to 6 weeks after completion of preoperative treatment. Any attempt was made to do an anterior resection if at least a 2-cm distal margin of safety could be obtained. The anastomosis usually was created with the "double-stapling" technique.[37] If this could not be achieved, an abdominoperineal excision was performed. Tumors invading or extending to surrounding structures (urinary bladder, prostate, small bowel, or ovary) underwent monobloc extended resection to obtain safe margins. However, evisceration procedures or those requiring resection of the sacrum were not thought adequate to resect primary tumors. Lymph node dissection up to the stem of the inferior mesenteric artery and including the total mesorectum was generally performed.

Assessment of Response

At preoperative re-evaluation, a complete response (CR) was presumed if no evidence of tumor could be proven by endoscopy, ERUS, or biopsy. A partial response (PR) was presumed if the maximum tumor diameter (transverse or longitudinal) measured by endoscopy or CT showed a decrease of at least 50%.

Histopathologic examination of the resected specimen followed the guidelines of the TNM system.[38] Patients with no evidence of the primary cancer were reported as CR. A PR was noted if the tumor depth infiltration at the resection specimen (ypT) decreased with respect to the pretherapeutic endosonographic staging.

Follow-Up and Statistical Analysis

All patients were followed up carefully with a clinical examination, abdominal and endorectal ultrasound, chest x-ray, and measurement of CEA serum levels every 3 months in the first 2 years after treatment. Colonoscopy was performed at yearly intervals.

To evaluate predictors of response, temperature distributions during HT (T_{90}), depth of infiltration (uT3 *vs.* uT4), nodal status (uN+ *vs.* uN0), and tumor height above the anal verge were subjected to variance analysis using the ANOVA program (SPSS, Chicago, IL). Survival was calculated from the first day of treatment using the Kaplan-Meier method. Failures, both local and distant, were verified by clinical examination, radiographic studies, and biopsy. Local failure was defined as any failure within the pelvis, distant failure as any failure outside the pelvis.

RESULTS

Toxicity During Preoperative Treatment

Thirty patients completed preoperative hyperthermia combined with radiochemotherapy (HRCT) according to the protocol. There were no deaths (related or unrelated to treatment preoperatively) during the first 3 months after the start of treatment. Therapy had to be stopped in 1 patient who developed diarrhea after receiving 41.5 Gy of radiotherapy; 32 of 37 patients received all scheduled HT sessions. One patient refused further HT after the first session because of general discomfort, another two patients because of claustrophobia. HT was abandoned in another patient after three sessions due to local complaints and in one patient for cardiac rhythm disorders.

Adverse reactions were observed starting during week 3 of therapy. They were mostly related to the small bowel and rectum (diarrhea, cramping, proctitis). A second aspect of complaints arose from the skin, particularly the rima ani (ery-

Table 3. ACUTE TOXICITY OF TRIMODAL THERAPY ACCORDING TO LENT SOMA (1995) AND HT SCORE

	Grade	Number (%)
Nausea	0	35 (94.6)
	I	2 (5.4)
Skin	0	12 (32.4)
	I	7 (18.9)
	II	12 (32.4)
	III	6 (16.2)
Diarrhea	0	11 (29.7)
	I	10 (27.0)
	II	11 (29.7)
	III	5 (13.5)
Bladder	0	25 (67.6)
	I	7 (18.9)
	II	4 (10.8)
	III	1 (2.7)
Regional hyperthermia	0	9 (24.3)
	I	10 (27.0)
	II	15 (40.5)
	III	3 (8.1)

thema and epitheliolysis). Grade III toxicities to the intestine and the skin occurred particularly during the initial period of the study. Skin reactions could be reduced by a specially designed circulatory cooling system for the rima ani. In summary, 15 patients experienced grade III toxicities.

Regional HT applied in a ring system with a balloon of water positioned on the abdomen for 60 to 90 minutes induced nonspecific circulatory stress and general arduousness in the majority of patients. As shown in Table 3, the toxicity of HT was within the same range as that of chemo- or radiotherapy.

Late toxicity, such as chronic bowel dysfunction, ulcerations of the rectum or bladder, or obstruction or stricture of the ureter, has not yet been observed. Sexual dysfunction was documented in 2 of the 31 male patients (erectility, ejaculation) and 1 of the 6 female patients (dyspareunia).

One adverse event that might be associated with late toxicity occurred in a 60-year-old patient who presented with a uT4 tumor invading the prostate with progression after preoperative treatment. Laparotomy confirmed that it was nonresectable, and radiochemotherapy was completed up to 61 Gy. Five months later, he presented with septicemia because of perforation of the rectum. We could not differentiate exactly between tumor-related necrosis or treatment-induced tissue damage.

Surgery and Perioperative Morbidity

Thirty-six patients underwent laparotomy. One patient refused surgery after completion of HRTC. In this patient the tumor distance from the anal verge was 2 cm, and the tumor size did not change by ERUS and CT. In 32 patients (86.5%), the primary tumor was resected. In 4 patients (10.8%), the tumor was found to be nonresectable due to fixation to the lateral pelvis or the prostate, and a colostomy was performed. Thirty-one resection specimens (96.9%) had negative histologic margins. Another two patients (in addition to those with already known liver metastases) were found to have liver lesions at laparotomy; one of them subsequently underwent a liver resection.

Surgical treatment resulted in a sphincter-preserving procedure in 19 of 37 patients (51%). Besides anterior resection, in three patients a colonic pouch with a pouch-anal anastomosis was performed. Another two patients had a sphincter-saving procedure by transanal full-layer resection (Table 4).

The median blood loss was 860 mL per patient (range 200–2000 mL per patient). Homologous blood transfusions were necessary in 9 patients, with a median of 2.2 units per patient (range 1–4 units per patient). There was no mortality within 90 days postoperatively. Complications included two patients with anastomotic leakages. One patient required reintervention and a colostomy had to be performed; the other one could be treated conservatively. Seven patients had delayed wound healing, one relating to the abdomen and six to the perineal wound after an abdominoperineal excision, which responded to local wound care. Two patients developed pneumonia and required antibiotic treatment. Cardiac abnormalities were recorded in one patient with a heart rhythm disorder, with complete resuscitation after medical therapy.

Table 4. SURGICAL PROCEDURES AFTER PREOPERATIVE TRIMODAL THERAPY

	Preoperative Clinical Assessment of Resectability		
	Resectable (n = 16)	Nonresectable (n = 21)	Total (n = 37)
Nonresectable		5	5 (14%)
Denying surgery		1	
Explorative laparotomy		4	
R0 resection (≤5 cm from anal verge)	7	5	12 (32%)
APR	5	4	9
AR	1	1	2
Transanal full-layer resection	1		1
R0 resection (>5 cm from anal verge)	7	8	15 (41%)
APR	1	1	2
AR	5	7	12
Transanal full-layer resection	1		1
R1/R2 resection*	2	3	5 (14%)
APR		2	2
AR	2	1	3

APR = abdominoperineal resection; AR = anterior resection.
* Resection with concomitant distant metastases in four patients (R2) and in one patient with positive margin (R1).

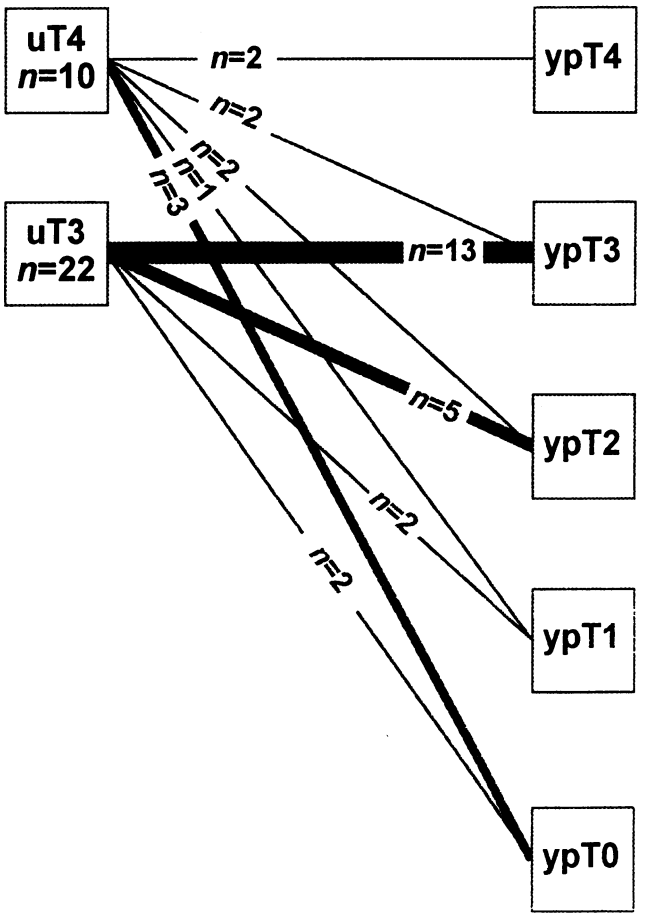

Figure 2. Comparison of the depth of tumor infiltration into the rectal wall between pretherapeutic assessment and pathohistologic report at the resection specimen (downstaging).

Evaluation of Response

In Figure 2, the depth of tumor infiltration into the rectal wall, as measured by pretherapeutic ERUS, is compared to the histologic findings in the 32 patients who underwent resection. We found downstaging in 17 of 32 patients (53%); in particular, organ infiltration of uT4 tumors was present before HRCT in 10 patients and could be detected after treatment in only 2 patients. Less infiltration was observed in 9 of the 23 patients with uT3 tumors.

However, after preoperative treatment, ERUS (yuT at restaging) classified the T category correctly as compared with the histopathologic reappraisal in only 50% (16/32) of the cases. In 14 patients, ERUS suggested a higher T category than found at histopathology; in 2 patients, tumor infiltration at histology was deeper than predicted by ERUS.

Before HRCT, 21 patients were classified as having tumor in the lymph nodes, and 18 of them underwent resection. Of those, the histopathologic report revealed 8 specimens with node-negative tumors (ypN0, response rate 44%).

In five resection specimens, no residual tumor could be detected at histology, resulting in a pCR rate of 13.5%.

Table 5. RESPONSE OF THE PRIMARY TUMORS (N = 37)

	Initial Classification of Tumor Depth		
	uT3 (n = 23)	uT4 (n = 14)	Total (n = 37)
CR	2	3	5 (14%)
PR	11	6	17 (46%)
NC	10*	3	13 (35%)
PD		2	2 (5%)

CR = complete tumor remission; PR = partial remission (50% diminution of tumor volume) or downstaging of T-classification; NC = no change in tumor volume (*i.e.*, <50%) and stage; PD = progressive disease.
* In one patient who denied surgery response was evaluated from clinical staging.

Another 17 specimens showed downstaging of uT *versus* ypT or a 50% decrease in tumor size, as documented by CT or ERUS, resulting in a PR rate of 45.9%. Thus, the overall response rate was 59.4% (Table 5).

Response Analysis

As shown in Table 6, the response was found to be significantly dependent on the index temperature (T_{90}), as well as the time during which T_{90} was effective (above the reference temperature). Cut-off values were found to be T_{90} at 40.3° to 40.5°C and the sum of cumulative minutes at $T_{90} \geq 40.5$°C for 120 to 150 minutes for all heat treatments in an individual patient. Patients whose thermal parameters were above that threshold had a significantly better response rate than those with a cumulative T_{90} of less than 2 hours ($p = 0.005$). The groups thus generated had response rates that differed by almost a factor of 2—40% to 50% as opposed to 80% to 90%. The maximum mean contact temperature of the tumor (T_{max}) had no significant influence on the response rate.

Follow-Up and Survival

The overall survival rate of 37 patients was 56%. After a median observation period of 21 months, 27 patients with

Table 6. ANALYSIS OF VARIANCE OF THE RESPONSE IN 37 PATIENTS WITH RESPECT TO THERMAL PARAMETERS T_{90} AND CUM MIN $T_{90} \geq 40.5$ C

	Factor	Response (%)	Significance
T_{90}	<40.5°C	33	0.015
	≥40.5°C	75	
cum min $T_{90} \geq 40.5$°C	<120 min	43	0.007
	8≥120 min	87	

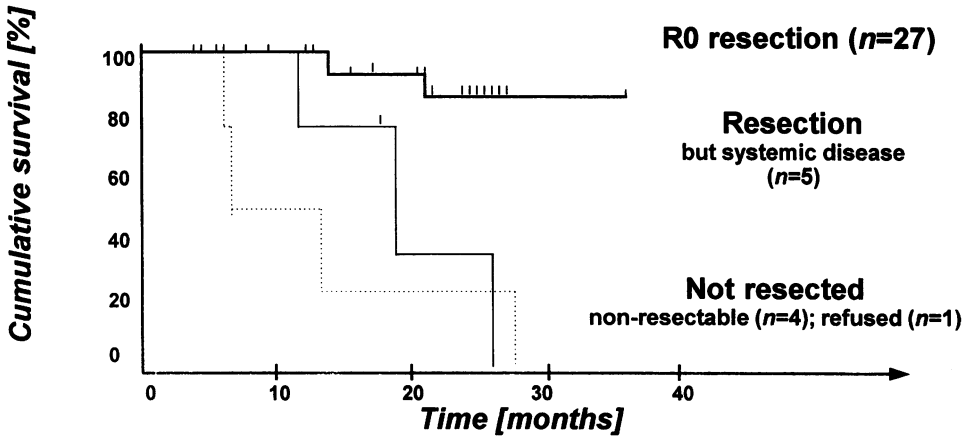

Figure 3. Kaplan-Meier estimated survival distribution, according to curative resection, palliative resection, or nonresectability.

R0 tumor resection showed an actuarial survival of 86% at 38 months (Fig. 3). The median survival time has not yet been reached. In patients who were resected with positive margins or distant metastases, the median survival was 18.8 months. Patients with nonresectable tumors had a median survival time of 6.2 months (6–27 months).

No local recurrence was detected after resection with negative margins. One patient (with N3 nodes) suffered from progressive para-aortal node disease. Metastases were identified in 4 of the 32 patients (12.5%); 2 of them died after 14 and 19 months.

All patients with nonresectable cancer died of progressive disease with survival times from 6 to 27 months. Three of them died as a result of local progression, and in two patients simultaneous progression of lung and liver metastases was observed. One patient died of distant metastases with his tumor locally controlled.

DISCUSSION

There is a strong rationale to add thermotherapy to the preoperative combined modality treatment of rectal cancer. The antitumor effects of HT exceeding 42°C have clearly been demonstrated.[20–25] HT may improve the oxygenation status of tumors and thus support radiotherapeutic effects.[27] Additional HT improved response rates and local control in malignant melanoma, head and neck, breast, or esophageal cancer.[39–41]

Studies of HT in rectal cancer with endocavitary heating methods show that it seems to improve the effect of radiotherapy.[24,29,42] A randomized trial using endocavitary HT (microwaves, 915 MHz) in addition to radiotherapy (3 × 4 Gy up to 40 Gy) studied patients with locally advanced T4 tumors. The radical resection rate was significantly increased in the combined treatment group (55.4% *vs.* 27.1% with radiotherapy alone).[29] This was reflected in a significantly improved 5-year survival rate (36% *vs.* 7%). Using similar equipment, Mori et al.[42] treated 11 patients with deep-seated rectal cancer (Dukes' A–C) and reported a beneficial response in 6 of the 11 cases.

Another phase III trial treated 146 patients with rectal cancer (Dukes' A–C) either by preoperative radiothermotherapy (endoluminal, 30–40 Gy) or preoperative radiotherapy alone.[24] Patients in the control arm underwent surgery with no preoperative treatment. The combined treatment group achieved a significantly increased complete response rate (22.7% *vs.* 5.3%), resulting in the best 5-year survival rate of 66.7% *versus* 50% after radiotherapy and 40.5% in the control group.

Primary nonresectable and recurrent rectal tumors, some of which had already been irradiated, were subjected to HT using a capacity system (Thermotron, Yamamoto Vinyter Co., Osaka, Japan) or microwave applicators (433-MHz lens applicator).[23] The response rate of 54% determined by CT and the local control rate of 28% after 12 months were higher than in the group treated with radiation alone (36% and 22%, respectively) but failed to reach significance.

In the phase II study presented here, regional radiowave HT with a phased-array system was used in addition to radiochemotherapy, which is the standard preoperative treatment for advanced rectal cancer. The antenna system allows heat distribution to be influenced so that maximal heat can be focused on the tumor. Our results were obtained in a group of patients with clinically advanced tumors invading beyond the rectal wall to surrounding structures or adjacent organs. The prognostic significance of tumor fixation of rectal carcinoma has been reported by the Medical Research Council.[43] Preoperative radiotherapy is recommended for fixed or advanced fixed tumors and has been shown to decrease local recurrence rates.[44,45] In contrast, less advanced tumors that are clinically mobile or tethered may also be effectively treated by surgery and postoperative radiochemotherapy.[6,45]

ERUS provides accurate staging of primary rectal cancer.[46,47] Clinical assessment of tumor fixation does not

discriminate between tumor invasion and attachment because of inflammatory reaction. ERUS confirms with high diagnostic accuracy the extent of tumor invasion beyond the rectal wall. In untreated rectal cancer, the diagnostic accuracy of ERUS for the T categories is 87%[47]; therefore, ERUS was used to assess the eligibility of patients. Consequently, the downstaging rate of 59% achieved in our study might be even more valuable compared to trials omitting pretherapeutic endosonography as a basis for entering patients in the study. However, the accuracy of ERUS is lowered after HRCT: only 50% of the specimens were correctly staged for depth of wall penetration and 59% tumor-occupied lymph nodes. The underlying reasons may be edema formation and the difficulty in differentiating between intratumoral fibrosis and infiltration of the rectal wall. This phenomenon has also been described after radiochemotherapy.[48]

In our series, the response rate was 59.4%, with 14% complete remissions. A further 37% of the resection specimens had residual disease as small remnants and were staged as ypT2 or less. Our results seem to show improved effects of HRCT compared to radiotherapy alone or radiochemotherapy (Table 7). The high proportion of fixed and advanced fixed tumors in our study group should be taken into consideration.

Even after a full course of preoperative radiotherapy for fixed or tethered rectal cancer, the local recurrence rates remain high, ranging from 16% to 43%.[13,14,44] The incidence of local recurrences after resection of fixed tumors was still 38% after combined preoperative radiochemotherapy.[18] Minsky et al.[16] added leucovorin to 5-FU in combination with 50.4 Gy in 20 patients with fixed tumors and found a 29% actuarial local failure rate at 3 years. When fixation was advanced, this rose to 50%.[49] To improve local control, intensified preoperative therapy may be the most promising way to treat these patients.

Table 7 summarizes the data of different preoperative treatment regimens for advanced rectal cancer. Except for the study by Chan et al.[18] using mitomycin during systemic chemotherapy, the rate of pathologic CR ranges from 10% to 15%. Radiotherapy alone achieved a pCR rate of only 8%. The overall response rate (pCR and PR) reaches 60% if HT is added to standard radiochemotherapy. Most promising, however, the local control rate is still 100% for patients who have had a curative operation. It does not seem too early to evaluate this, because 80% of local recurrences in rectal cancer are detected within 24 months after resection of the primary tumor, with a peak at 6 to 12 months.[3]

One major finding of our study is that temperature measurement points in contact with the tumor (T_{90}, cumulative minutes at T_{90} (cum min T_{90}) $\geq$ 40.5 C) correlate with the response to HRCT. Up to now, this phenomenon has been reported only for superficial malignancies.[34] The thermal parameters are influenced by the power densities achieved in the tumor and by the perfusion. Power deposition patterns might be improved by certain system parameters (*e.g.*, phases/amplitudes of chan-

Table 7. SUMMARY OF PREOPERATIVE TREATMENT REGIMENS

Reference	n	Mason (%)		Treatment		pCR (ypT0) (%)	Response Rate (CR + PR) (%)	Pathological Results	Resectability (%)	Recurrence Rate (%)	
		2–3	4	RT (Gy)	CT					Local*	Distant
Mohiuddin et al.[53]	147	51	49	45	—	8	NA	†ypA: 4%, ypB1: 21%, ypB2: 34%, ypC1/2: 33% ypT1: 5%, ypT2: 49%	100	13	17
Chan et al.[18]	46	65	35	45	5-FU, MMC	4	45	ypT3: 34%, ypT4: 7% ypT1: 0%, ypT2: 32%,	89	20	41
Chen et al.[19]	31	100	—	56	5FU†	10	29	ypT3: 42%, ypT4: 16%	100	16	10
Minsky et al.[54]	24	21	75	50.4	5-FU, LV	13	NA	NA	100	NA	NA
Chari et al.[55]	43	100	—	45	5-FU, cisplatin	27	49	NA	100	5	15
Current study	37	46	54	45 + HT	5-FU, LV	14	60	ypT1: 8%, ypT2: 19%, ypT3: 41%, ypT4: 5%	89	0	19

RT = radiation therapy; CT = chemotherapy, HT = regional hyperthermia; 5-FU = 5-fluorouracil; MMC = mitomycin C; LV = Leucovorin; NA = not available.
* Local recurrence as well as a component with distant metastases.
† Astler-Coller stages.
‡ Continuous infusion.

nels). Perfusion might depend on systemic parameters such as heart rate or blood pressure. The complex relations between these parameters and strategies for further improvement of RT/HT will be discussed in a later paper.

Patient anxiety, general discomfort, and pain during treatment because of the "hot-spot phenomenon" (specific acute to subacute side effects caused by the electrical interface)[32] are problems in the regional HT of deep-seated tumors and are reported to be present in up to 60% of cases.[20,31] Acute side effects due to regional HT seem to be acceptable regarding grade II/III toxicity, yielding rates comparable to the toxicity induced by the other modalities. However, the local increase in electrical field intensity causes an increase in temperature during HT application, resulting in discomfort. Hot spots have been analyzed using model calculations, but they remain very difficult to predict individually.[50] The morbidity of combined radiochemotherapy treatment-related toxicity (grade III) was reported to affect 19% to 69% of the patients.[16,19,51] Some of these patients were treated with large daily fractions (2.5 Gy) without routine use of small-bowel exclusion, and patients with recurrent rectal cancers after abdominoperineal excision were included in the study. Within our group of patients, adding HT did not induce increased grade III toxicity (14%), and none of the patients experienced grade IV side effects.

The preclinical rationale for HT has been known for a long time. In addition to its cytotoxic and sensitizing effects, other reasons for its effectiveness have recently been discussed. In particular, HT might improve reoxygenation (possibly by raising perfusion), which enhances the effects of radiotherapy.[8] This might explain why benefits have been obtained at low temperatures (T_{90} 40–40.5 C) unlikely to damage cells under *in vivo* conditions. It also gives a rationale to apply radiotherapy after heat treatment, as in our study. Vascular breakdown in experimental tumors under HT supported the common practice of applying HT after radiotherapy, because hypoxia might be increased. However, our experience with this group of patients gives evidence of increased perfusion in or at the tumor under HT. Therefore, the optimal sequence of radiotherapy and HT is still an open question.

In conclusion, this phase II study demonstrates that a trimodal therapy regimen with acceptable toxicity can be applied safely in patients with advanced rectal carcinomas. HT was used as part of this regimen and did not increase the side effects of radiotherapy and chemotherapy once the rima ani cooling system was introduced. The resectability rate was good and, except for one patient, all could be resected with curative intent and low perioperative morbidity. The next step in developing thermotherapy might be to reach 120 minutes of cumulative HT at 40.5°C or higher in all patients.

Similar to the treatment results in soft-tissue sarcoma,[52] HT added to radiochemotherapy in advanced rectal cancer yielded an excellent response of 60%, with 14% histologically proven complete remissions. The true value of HT in this setting, however, will be assessed in a randomized phase III trial that is underway.

References

1. Rich T, Gunderson LL, Lew R, et al. Patterns of recurrence of rectal cancer after potentially curative surgery. Cancer 1983; 52:1317–1329.
2. Duncan W, Smith AN, Freedman LF, et al. Clinico-pathological features of prognostic significance in operable rectal cancer in 17 centres in the U.K. Br J Surg 1984; 50:435–442.
3. Herfarth C, Schlag P, Hohenberger P. Surgical strategies in locoregional recurrences of gastrointestinal carcinoma. World J Surg 1987; 11:504–510.
4. Maetani S, Nishikawa T, Iijima Y, et al. Extensive en bloc resection of regionally recurrent carcinoma of the rectum. Cancer 1992; 69:2876–2883.
5. Adam IJ, Mohamdee MO, Martin IG, et al. Role of circumferential margin involvement in the local recurrence of rectal cancer. Lancet 1994; 344:707–711.
6. NIH consensus conference. Adjuvant therapy for patients with colon and rectal cancer. JAMA 1990; 264:1444–1450.
7. Tannock IF. Oxygen diffusion and the distribution of cellular radiosensitivity in tumours. Br J Radiol 1972; 45:515–524.
8. Oleson JR. Hyperthermia from the clinic to the laboratory: A hypothesis. Int J Hyperthermia 1995; 11:315–322.
9. Minsky BD, Cohen AM, Kemeny N, et al. Combined modality therapy of rectal cancer: Decreased acute toxicity with the preoperative approach. J Clin Oncol 1992; 10:1218–1224.
10. Mohiuddin M, Marks G, Bannon J. High-dose preoperative radiation and full thickness local excision: A new option for selected T3 distal rectal cancers. Int J Radiat Oncol Biol Phys 1994; 30:845–849.
11. Mason AY. Malignant tumors of the rectum: Local excision. Clin Gastroenterol 1975; 4:582–593.
12. Pearlman NW, Stiegmann GV, Donohue RE. Extended resection of fixed rectal cancer. Cancer 1989; 63:2438–2441.
13. Dosoretz DE, Gunderson LL, Hedberg S, et al. Preoperative irradiation for unresectable rectal and rectosigmoid carcinomas. Cancer 1983; 52:814–818.
14. Whiting JF, Howes A, Osteen RT. Preoperative irradiation for unresectable carcinoma of the rectum. Surg Gynecol Obstet 1993; 176: 203–207.
15. Frykholm G, Glimelius B, Pahlman L. Preoperative irradiation with or without chemotherapy (MFL) in the treatment of primarily nonresectable adenocarcinoma of the rectum. Results from two consecutive studies. Eur J Cancer Clin Oncol 1989; 25:1535–1541.
16. Minsky BD, Cohen AM, Kemeny N, et al. Pre-operative combined 5-FU, low-dose leucovorin, and sequential radiation therapy for unresectable rectal cancer. Int J Radiat Oncol Biol Phys 1993; 25:821–827.
17. Minsky BD, Cohen AM, Kemeny N, et al. The efficacy of preoperative 5-fluorouracil, high-dose leucovorin, and sequential radiation therapy for unresectable rectal cancer. Cancer 1993; 71:3486–3492.
18. Chan A, Wong A, Langevin J, Khoo R. Preoperative concurrent 5-fluorouracil infusion, mitomycin C and pelvic radiation therapy in tethered and fixed rectal carcinoma. Int J Radiat Oncol Biol Phys 1993; 25:791–799.
19. Chen E, Mohiuddin M, Brodovsky H, et al. Downstaging of advanced rectal cancer following combined preoperative chemotherapy and high-dose radiation. Int J Radiat Oncol Biol Phys 1994; 30:169–175.
20. Petrovich Z, Langholz B, Gibbs Fa, et al. Regional hyperthermia for advanced tumors: A clinical study of 353 patients. Int J Radiat Oncol Biol Phys 1989; 16:601–607.
21. Kakehi M, Ueda K, Mukojima T, et al. Multi-institutional clinical studies on hyperthermia combined with radiotherapy or chemotherapy in advanced cancer of deep-seated organs. Int J Hyperthermia 1990; 6:719–740.
22. Takahashi T, Horie H, Kojima O, Itoh M. Preoperative combined treatment with radiation, intraluminal hyperthermia, and 5-fluorouracil suppositories for patients with rectal cancer. Jpn J Surg 1993; 23: 1043–1048.

23. Nishimura Y, Hiraoka M, Akuta K, et al. Hyperthermia combined with radiation therapy for primarily unresectable and recurrent colorectal cancer. Int J Radiat Oncol Biol Phys 1992; 23:759–768.
24. You QS, Wang RZ, Suen GQ, et al. Combination preoperative radiation and endocavitary hyperthermia for rectal cancer: Long-term results of 44 patients. Int J Hyperthermia 1993; 9:19–24.
25. Colacchio TA, Coughlin C, Taylor J, et al. Intraoperative radiation therapy and hyperthermia. Morbidity and mortality from this combined treatment modality for unresectable intra-abdominal carcinomas. Arch Surg 1990; 125:370–375.
26. Bull JMC. An update on the anticancer effect of combination of chemotherapy and hyperthermia. Cancer Res 1984; 44:4853–4856.
27. Herman TS, Teicher BA, Jochelson M, et al. Rationale for use of local hyperthermia with radiation therapy and selected anticancer drugs in locally advanced human malignancies. Int J Hyperthermia 1988; 4:143–158.
28. Dewey WC, Hopwood LE, Sapareto SA, Gerweck LE. Cellular responses to combinations of hyperthermia and radiation. Radiology 1977; 123:463–474.
29. Berdov BA, Menteshashvili GZ. Thermoradiotherapy of patients with locally advanced carcinoma of the rectum. Int J Hyperthermia 1990; 6:881–890.
30. Riess H, Loeffel J, Wust P, et al. A pilot study of a new therapeutic approach in the treatment of locally advanced stages of rectal cancer: Neoadjuvant radiation, chemotherapy and regional hyperthermia. Eur J Cancer 1995; 31A:1356–1360.
31. Feldmann HJ, Molls M, Adler S, et al. Hyperthermia in eccentrically located pelvic tumors: Excessive heating of the perineal fat and normal tissue temperatures. Int J Radiat Oncol Biol Phys 1991; 20:1017–1022.
32. Wust P, Stahl H, Loeffel J, et al. Clinical, physiological and anatomical determinants for temperature elevations in radiofrequency hyperthermia. Int J Hyperthermia 1995; 11:151–167.
33. Oleson JR, Dewhirst MW, Harrelson JM, et al. Tumor temperature distributions predict hyperthermia effect. Int J Radiat Oncol Biol Phys 1989; 16:559–570.
34. Leopold KA, Dewhirst MW, Samulski TV, et al. Cumulative minutes with T_{90} greater than $Temp_{index}$ is predictive of response of superficial malignancies to hyperthermia and radiation. Int J Radiat Oncol Biol Phys 1993; 25:841–847.
35. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. Cancer 1981; 47:207–214.
36. RTOG, EORTC. LENT SOMA Tables. Radiother Oncol 1995; 35:17–60.
37. Knight CD, Griffen FD. An improved technique for low anterior resection of the rectum using the EEA stapler. Surgery 1980; 88:710–714.
38. Hermanek P, Wittekind C. The pathologist and the residual tumor (R) classification. Pathol Res Pract 1994; 190:115–123.
39. Overgaard J, Gonzalez Gonzalez D, Hulshof MC, et al. Randomized trial of hyperthermia as adjuvant to radiotherapy for recurrent or metastatic malignant melanoma. Lancet 1995; 345:540–543.
40. Valdagni R, Amichetti M. Report of long-term follow-up in a randomized trial comparing radiation therapy and radiation plus hyperthermia to metastatic lymph nodes in stage IV head and neck patients. Int J Radiat Oncol Biol Phys 1993; 28:163–169.
41. Sugimachi K, Kitamura K, Baba K, et al. Hyperthermia combined with chemotherapy and irradiation for patients with carcinoma of the oesophagus: A prospective randomized trial. Int J Hyperthermia 1992; 8:289–295.
42. Mori M, Sugimachi K, Matsuda H, et al. Preoperative hyperthermochemoradiotherapy for patients with rectal cancer. Dis Colon Rectum 1989; 32:316–322.
43. Clinico-pathological features of prognostic significance in operable rectal cancer in 17 centres in the U.K. (Third report of the M.R.C. Trial, on behalf of the Working Party). Br J Cancer 1984; 50:435–442.
44. Tobin RL, Mohiuddin M, Marks G. Preoperative irradiation for cancer of the rectum with extrarectal fixation. Int J Radiat Oncol Biol Phys 1991; 21:1127–1132.
45. Mohiuddin M, Regine WF, Marks G. Prognostic significance of tumor fixation of rectal carcinoma. Cancer 1996; 78:717–722.
46. Cohen JL, Grotz RL, Welch JP, Deckers PJ. Intrarectal sonography. A new technique for the assessment of rectal tumors. Am Surg 1991; 57:459–462.
47. Beynon J, Mortensen NJ, Channer JL, Rigby H. Rectal endosonography accurately predicts depth of penetration in rectal cancer. Int J Colorectal Dis 1992,7:4–7.
48. Glaser F, Kuntz C, Schlag P, Herfarth C. Endorectal ultrasound for control of preoperative radiotherapy of rectal cancer. Ann Surg 1993; 217:64–71.
49. Mohiuddin M, Ahmad NR, Marks G. A selective approach to adjunctive therapy for cancer of the rectum. Int J Radiat Oncol Biol Phys 1993; 27:765–772.
50. Wust P, Meier T, Seebass M, et al. Noninvasive prediction of SAR distributions with an electro-optical E field sensor. Int J Hyperthermia 1995; 11:295–310.
51. Danjoux CE, Gelber RD, Catton GE, Klaassen DJ. Combination chemo-radiotherapy for residual, recurrent or inoperable carcinoma of the rectum: E.C.O.G. study (EST 3276). Int J Radiat Oncol Biol Phys 1985; 11:765–771.
52. Issels RD, Prenninger SW, Nagele A, et al. Ifosfamide plus etoposide combined with regional hyperthermia in patients with locally advanced sarcomas: a phase II study. J Clin Oncol 1990; 8:1818–1829.
53. Mohiuddin M, Marks G. Patterns of recurrence following high-dose preoperative radiation and sphincter-preserving surgery for cancer of the rectum. Dis Colon Rectum 1993; 36:117–126.
54. Minsky BD, Cohen A, Enker W, et al. Preoperative 5- fluorouracil, low-dose leucovorin, and concurrent radiation therapy for rectal cancer. Cancer 1994; 73:273–280.
55. Chari RS, Tyler DS, Anscher MS, et al. Preoperative radiation and chemotherapy in the treatment of adenocarcinoma of the rectum. Ann Surg 1995; 221:778–787.