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REGIONAL RADIOFREQUENCY HYPERTHERMIA INCREASES LOCAL EFFICACY OF PREOPERATIVE CHEMO-RADIATION IN LOCALLY ADVANCED OR RECURRENT RECTAL CANCER - INTERIM ANALYSIS OF A PHASE III CLINICAL TRIAL

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Purpose: Local control of rectal cancer is still a relevant clinical problem, especially for certain risk factors such as complete fixation, infiltration of neighboring structures (uT4) or recurrencies. Regional hyperthermia (RHT) based on annular phased array (APA) technology has already been shown to improve local control and survival in cervical carcinomas (v. d. Zee et al 1997, IORBP 39,2,Suppl,207). A phase II clinical trial gave favorable results applying hyperthermic radio-chemotherapy (HRCT) preoperatively upon uT3/4 rectal carcinomas (Rau et al 1998, Ann.Surg. 228). Therefore, a phase III trial has been conducted in Germany to evaluate regional hyperthermia in the same preoperative regimen for rectal cancer.

Materials & Methods: From 1995 to 1997 75 patients were recruited by the participating German centers (Berlin, Essen, Tübingen, Lübeck) and evaluated in an interim analysis. Six patients dropped out after randomisation because of protocol violations (2 with HRCT, 4 with RCT), while 37 evaluable patients remained in arm A (HRCT) and 32 patients in arm B (RCT). Both groups were statistically balanced with respect to endosonographic T-classification (uT3: 65%, uT4: 16%, rT3/4: 19%), N-classification (uN0: 36%, uN+: 64%), age (59±10 y), sex (46 male, 23 female), degree of stenosis (45% stenosing), and localisation (0-7 cm ab ano: 65%, >7 cm: 35%). Radiotherapy was administered in standard technique (5x1,8 Gy up to 45 Gy, prone position in a belly-board, three conformal fields based on 3D CT planning), together with 5-FU (300-350 mg/m^2) and folinic acid (50 mg) on day 1-5 and day 29-33. Regional hyperthermia was performed in the APA system BSD-2000 (SIGMA-60 applicator) once a week just before radiotherapy. Temperatures were if ever possible endoluminally registered, i.e. in contact to the tumor, and statistically analysed with respect to position and time yielding thermal parameter like index temperatures and cumulative minutes as well as specific absorption rates and perfusion information. Surgery followed 4-6 weeks after completion of the preoperative course.

Results: Preoperative treatment was generally well tolerated with one breaking off and three interruptions in every arm; two grade IV toxicities, 15 grade III in 37 pts (overall 46%) with HRCT; two grade IV, 11 grade III in 32 pts (overall 41%) with RCT. In four further pts in the HRCT-arm RHT remained incomplete because of unspecific toxicity related to the heating procedure. Resectability rate was 55/56 (98%) for primary tumors (with 51/56 RØ-resections, i.e. 91%), and 5/13 (38%, RØ-resections) for recurrencies with statistically equal distribution in both treatment arms (resectability 89% arm A, 91% arm B). Severe postoperative complications demanding intensive-care or re-operation occured in 4/33 pts of arm A (12%) and 7/29 pts of arm B (24%), i.e. no perioperative morbidity was added by RHT. In 56 evaluable resected carcinomas we found response (pT<uT or PR according WHO) in 22/30 (73%) pts (arm A) vs 13/26 (50%) pts (arm B) which is marginally significant ($p<0.1$). The significance level of $p=0.05$ was achieved for the subgroup of primary carcinomas (75 vs 48%). The response rate was significantly higher in the patient group with T90≥ 40.5 °C (83%, $p=0.01$) or cum min (T90≥40.5 °C) ≥ 120 min (84%, $p=0.005$). Overall survival was ~90%, disease-free survival ~80%, and local control 100% for a median observation time of 14 months (1-32 months), with no difference of statistical relevance between both arms.

Conclusions: The interim analysis of our phase III study shows that available RHT-technology already increases response rates of RCT against locally advanced rectal cancer without adding relevant toxicity. Survival, disease-free survival, and local control are excellent, but still statistically undistinguishable for both arms due to the short observation time. Completion of the study is planned in the year 2000 with 180 pts. Furthermore, large potentials to develop and refine the technological level of radiofrequency RHT must be utilized to full advantage in the next years.

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OUTCOME AND TREATMENT TOLERANCE FOR HIV-POSITIVE PATIENTS WITH ANAL CANCER BASED ON PRETREATMENT CD4 COUNT

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Purpose/Objective: To assess the outcome and tolerance of HIV-positive patients with anal cancer to standard therapy based on their pretreatment CD4 count.

Materials & Methods: Between 1991 and 1997, 17 HIV-positive patients with documented pretreatment CD4 counts were treated at the University of California, San Francisco or its affiliated hospitals with either concurrent chemotherapy and radiation or radiation alone. The outcome and complications of treatment were correlated with the patients' pretreatment CD4 count. Complications reported were ANC < 500, platelet count < 50,000, and treatment break +/- hospitalization for severe moist desquamation or gastrointestinal toxicity. Median follow-up was 17 months.

Results: Of the 9 patients with pretreatment CD4 counts ≥ 200, all were controlled with chemoradiation. With regards to toxicity, 1 had a drop in ANC to 260, while 2 others required a break of at least 2 weeks; however, none were hospitalized due to these complications. Patients were controlled regardless of whether Mitomycin-C was given for 1 or both cycles of 5FU. Of the 8 patients with pretreatment CD4 counts < 200, 6 who received concurrent chemotherapy and radiation were controlled. 4 maintained anal function while 2 required colostomies for complications of therapy. Overall 5/8 of these patients had severe complications of decreased counts, intractable diarrhea or moist desquamation requiring hospitalization. The 2 patients treated with radiation alone failed therapy and required colostomies for salvage.

Conclusion: Patients who present with pretreatment CD4 counts ≥ 200 should be treated with standard concurrent chemotherapy 5FU/Mitomycin-C and radiation. It may be possible to omit Mitomycin-C with the second cycle of 5FU. Patients with pretreatment CD4 < 200 have a markedly decreased tolerance to therapy and in this series half of these patients ultimately required a colostomy either for therapy-related complications or treatment failure. Nevertheless, 6/8 patients in this poor prognosis group were ultimately controlled with a combination of concurrent chemotherapy and radiation plus surgical salvage.