Hypofractionated Accelerated Radiotherapy, Cytoprotection and Capecitabine in the Treatment of Rectal Cancer: A Feasibility Study

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Abstract. *Background: This is a report on the feasibility and efficacy of hypofractionated accelerated radiotherapy combined with amifostine cytoprotection (hypoARC) and capecitabine in the treatment of rectal adenocarcinoma. Patients and Methods: Twenty-seven patients (pts) received pre- (14 pts) or postoperative (13 pts) conformal radiotherapy with 10 consecutive fractions of 3.4 Gy in 12 days, supported with subcutaneously administered high-dose amifostine (up to 1000 mg) and capecitabine (daily dose of 600 mg/m^2 twice a day, 5 days per week for 4 weeks). Ten additional patients with inoperable tumors received a higher dose (15 fractions of 3.4 Gy) as a radical intervention and 5 received a lower dose for palliation. Results: Chemotherapy-related toxicity was minimal and radiation grade 2 diarrhoea and proctitis was noted in 3/42 and 4/42 cases, respectively. No peri- or postoperative complications were noted in patients receiving pre-operative radiochemotherapy. Significant tumor regression was confirmed in post- RT CT-imaging and major histological responses were noted in 85% of cases treated before surgery. Late toxicity (median follow-up 26 months) was negligible. The 2-year local relapse-free survival was 85-90% in patients treated with pre- or postoperative radiotherapy and 35% in patients with inoperable tumors. Conclusion: Capecitabine-based hypoARC is feasible with only minimal early and late toxicity and encouraging efficacy.*

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Rectal adenocarcinoma is a common human malignancy with high postoperative cure rates in early local stages. Extramural invasion and lymph node involvement, however, are associated with 40-60% local and distant relapse rates, and for these patients pre- or postoperative radiotherapy and chemotherapy has become a standard treatment option worldwide (1). Indeed, a 10-20% increased local control and survival rate is expected following radiochemotherapy with 5-fluorouracil and leucovorin, whether these are added before or after surgery (2, 3).

Recently, a *per os* pro-drug of 5-fluorouracil, namely capecitabine (Xeloda®), became available for clinical use (4). This is metabolised to active 5-fluoruracil by the enzyme thymidine phosphorylase, which is overexpressed in the tumor environment (cancer cells and stroma) compared to normal tissues (5). Indeed, overexpression of this enzyme relates to colorectal cancer response to capecitabine (6). The efficacy of capecitabine, its better tolerance profile and favourable pharmacoeconomics has resulted in the gradual replacement of 5-fluorouracil/leucovorin regimen by capecitabine in the adjuvant treatment of colorectal cancer (7, 8).

Concurrent administration of capecitabine with radiation has been reported in seven previous studies applying conventionally fractionated radiotherapy (9-15). In this study, we evaluated the feasibility and efficacy of the combination of capecitabine with preoperative, postoperative or radical hypofractionated and accelerated radiotherapy in patients with rectal adenocarcinoma. Using a dose individualization protocol, high-dose amifostine was used daily in order to eventually reduce acute and late sequelae.

Patients and Methods

Forty-two patients with histologically confirmed rectal adenocarcinoma were treated with hypofractionated accelerated radiotherapy supported with amifostine cytoprotection (hypoARC), in combination with capecitabine *per os* chemotherapy. Patients and disease characteristics

are reported in Table I. The protocol was approved by the local Ethics and Scientific Committee and all patients gave written informed consent before therapy. The follow-up of patients alive at the time of analysis ranges from 8-38 months (median 26).

Radiotherapy details. Radiotherapy was based on CT-imaging simulation and 3D-conformal panning (Plato, Nucletron). It was delivered with an 18 MV linear accelerator (Electa) endowed with a multileaf collimator. A four-field technique was used to encompass the lower pelvis and the pelvic nodes up to the sacroiliac joint. Lateral borders of the anteroposterior fields and upper/lower borders of the lateral fields were designed to encompass the regional node areas, rectum and tumor as well as the pre-sacral region. A daily fraction of 3.4 Gy was delivered for 10 consecutive fractions (5 fractions per week) to a total of 34 Gy. This dose corresponds to a biological dose of 42 Gy (normalized total dose, NTD, calculated for α/β=4 Gy, (16, 17)) delivered within 12 days instead of 29. Assuming a λ-value (16) of 0.4-0.8 Gy, the time-corrected biological dose to the tumor was higher by 4-8 Gy (total biological dose to the tumor 46-50 Gy). This radiotherapy scheme was given to 27 patients treated with pre- or postoperative radiotherapy and to 5 patients treated for palliation.

For 10 additional inoperable patients treated with radical intent, a second radiotherapy phase followed after 1-2 weeks. A new radiotherapy conformal planning, based on new CT scan data, was performed focusing on the radiologically detectable tumor mass and nodes. Using these fields, an additional 5 fractions of 3.4 Gy were delivered, increasing the dose to the tumor to 51 Gy, equivalent to an NTD of 63 Gy (for α/β=4 Gy) within 28-35 days (instead of 44 days of a conventional scheme that would deliver the same NTD). Assuming a λ-value (16) of 0.4-0.8 Gy, the time-corrected biological dose to the tumor was increased by 4-12 Gy (total biological dose to the tumor 67-75 Gy).

Cytoprotection. Before each radiotherapy fraction, the patients received amifostine subcutaneously at a dose of 500-1000 mg, depending on their individual tolerance. Details on the individualization of the amifostine dose have been reported previously (18). Amifostine-related fever and/or rash attributed to amifostine (or to any other drug) was followed by immediate interruption of amifostine and oral administration of cortisone and antihistamines for 3 days (19). Local rash at the site of injection was treated with steroid cream application.

Chemotherapy. Chemotherapy with capecitabine at a dose of 600 mg/m^2 twice a day *per os* for 5 days per week (RT days) started together with the first radiotherapy fraction. Patients treated with preoperative radiochemotherapy received capecitabine for 4 weeks and, after a 2-week interval, then underwent surgery. For postsurgical or postradiotherapy chemotherapy, the dose of capecitabine was increased to 800 mg/m^2 twice daily, 5 days per week. Chemotherapy continued for 4 months after surgery or radical radiotherapy.

Pathology scoring or response. Two pathologists scored the efficacy of preoperative radiotherapy independently, using both macroscopic and microscopic criteria. Absence of a viable tumor in the surgical specimen was recorded as a complete pathological response (pCR). Considerable tumor shrinkage, microscopic necrosis but with identification of viable cancer cell foci was scored as partial pathological response (pPR) and all other cases were grouped into a category of minimal or no pathological response (pMR/NR).

Table I. *Patient and disease characteristics*.

No. of patients	42
Age (years)	
Range	22-84
Median	69
Gender	
Male	25
Female	17
Histological grade	
1	8
2	21
3	13
RT setting / Stage	
Preoperative*	14
Stage *C2g*	11
Stage *D1*	3
Postoperative	13
Stage *B2g*	5
Stage *C2g*	6
Stage *D1*	2
Radical*	10
Stage *D1*	5
Recurrent	3
*C***	2
Palliative*	5
Stage *D1, 2*	5

*Staging by CT-scan; **inoperable for medical or personal reasons.

CT scan scoring of response. The response of cases treated with radical radiotherapy was recorded with CT imaging. CR was defined as 95-100% reduction of the measurable lesion within 3 months after treatment completion. Partial and minimal response refer to 50-95% and 25-49% reduction of tumor dimensions respectively. Small reduction of tumor dimensions between 0-24% that lasted at least 2 months after response documentation were considered as stable disease (SD). All other cases were considered as progressive disease (PD), regardless of the initial response.

Follow-up of patients. Radiation toxicity was recorded daily during the radiotherapy phase and weekly thereafter for the first month. Hematological variables and clinical status were recorded every two weeks during the chemotherapy period. Patients were followed up thereafter every three months with clinical examination. CT scan of the chest, abdomen and pelvis was performed every 6 months. Patients treated with radical radiotherapy were evaluated with CT scan and/or endoscopy every 3 months.

Statistical analysis. The statistical analysis and graphical presentation of survival curves was performed using the GraphPad Prism 4.0 version package (GraphPad, San Diego CA, USA; www.graphpad.com). The chi-square two-tailed *t*-test was used for testing differences between categorical variables. Survival curves were plotted using the method of Kaplan and Meier. A *p*-value of <0.05 is considered significant.

Results

Tolerance to amifostine. Dose escalation of amifostine to 1000 mg daily was feasible in 26/42 (61.9%) cases. Nine (21.4%) patients received 750 mg daily, 5 (11.9%) 500 mg and 2 (4.8%) interrupted amifostine due to poor tolerance (vomiting, fatigue) even at the dose level of 500 mg. At the established dose levels, side-effects ranged from none to tolerable nausea and mild fatigue.

Fever / rash appeared in 1/5 (20%), 1/9 (11.1%) and 5/26 (19.2%) patients treated at the 500 mg, 750 mg and 1000 mg dose levels, respectively. This occurred between the 5th and 10th (last) day of therapy. Amifostine was interrupted and oral methylprednisolone and antihistamine treatment for 3 days resulted in complete resolution of the symptomatology. No necrolytic skin syndrome was noted.

Tolerance of capecitabine. Capecitabine, at a dose of 600 mg/m^2 twice a day was well tolerated and no hematological toxicity was noted. One patient refused capecitabine due to intolerable nausea and hemesis that, indeed, regressed after capecitabine cessation. Three patients complained of mild, radiotherapy-irrelevant, diarrhea that started immediately after commencing capecitabine. The dose of 800 mg/m^2 twice a day, used after radiotherapy completion or post-RT surgery, was similarly well tolerated with no hematological or other toxicity.

Acute radiation toxicity. Acute toxicity appeared during the 3rd week after the delivery of the 10 radiotherapy fractions. Grade 1 diarrhea was frequently noted but regressed within 3-5 days. Grade 2 diarrhea demanding oral medication was noted in 3/42 patients (7.1%), but in none of patients receiving 750-1000 mg of amifostine (p=0.06). None of the patients complained of bladder toxicity. Grade 2 proctitis with pain was noted in 4/42 patients (9.5%), all of whom were receiving low amifostine dose (p=0.01). Similarly, skin toxicity grade 2 in the perineal area was noted in only 2/42 (4.8%) patients.

Surgical post-RT experience. Surgeons did not report any technical difficulties during operation that could be attributed to radiation. On the contrary, surgery was facilitated by the evident tumor responses noted which allowed preservation of the sphincter. Out of 14 patients treated with preoperative radiotherapy, 4 (28.6%) underwent abdomino-perineal resection, while 9/13 (69.2%) patients referred for postoperative radiotherapy had a permanent colostomy (p=0.05). It was noted (Table I) that the overall local stage of patients in the preoperative RT group was more advanced than that of the postoperative group.

Tumor response. CT scan performed two weeks after preoperative radiotherapy confirmed significant tumor shrinkage in 10/14 cases (Figure 1). Postoperative histological assessment of response revealed 3/14 (21.4%) PCR, 9/14 (64.3%) PR and 2/14 (14.3%) PMR (Figure 2).

Out of 10 patients receiving radical radiotherapy (15 fractions), 4 (40%) had CR, 4 (40%) had PR and 2 (20%) had stable disease at CT scan performed two months after radiotherapy completion.

Good control of symptomatology (pain, haemorrhage, obstruction) with a duration of at least 6 months was obtained in 4/5 patients treated with a palliative intent.

Late radiation toxicity. At the time of last follow-up (median 26 months) there was only one case (2.4%) with grade 2 bowel radiation toxicity (intermittent urgency with occasional bleeding but no endoscopic findings). There was no case with bladder or other toxicity.

Survival analysis. Figure 3 shows the local relapse-free survival (LRFS) of patients. The 2-year LRFS was 85% and 90% in patients treated with pre- or postoperative radiotherapy, respectively (p=0.46). Patients with inoperable tumors had a 2-year LRFS of 35% (44% in patients treated with radical intent). This was significantly lower compared to the preoperative (p=0.02) and the postoperative (p=0.01) groups. All patients treated with pre- or postoperative radiotherapy were alive at the time of analysis. Distant metastasis appeared in 2/14 (4.3%) patients treated with preoperative RT and in 5/13 (38.5%) patients treated with postoperative RT (p=0.13). The median survival for patients with inoperable tumors treated with radical intent was 18 months.

Discussion

Postoperatve radiotherapy has been established as an important adjuvant treatment following surgery for rectal cancer since the early 980's (20, 21). The addition of chemotherapy was subsequently found to improve the radiotherapy results (22), establishing adjuvant radio-chemotherapy in the clinical practice of rectal oncology. A Swedish trial in the 990's brought forward the important role of pre-operative radiotherapy showing a survival advantage in a large series of patients with rectal cancer treated with an accelerated hypofractionated regimen (5 consecutive fractions of 5 Gy) (23). More recent studies from the German Rectal Study Group and the EORTC confirmed the superiority of preoperative 5-fluorouracil radiochemotherapy (2, 24).

In the present study we investigated the combination of capecitabine, an orally available 5-fluorouracil pro-drug, with radiotherapy as a pre- or postoperative or radical regimen for patients with rectal cancer. Similarly to previously reported studies on such combinations (9-15), capecitabine chemotherapy showed an excellent tolerance

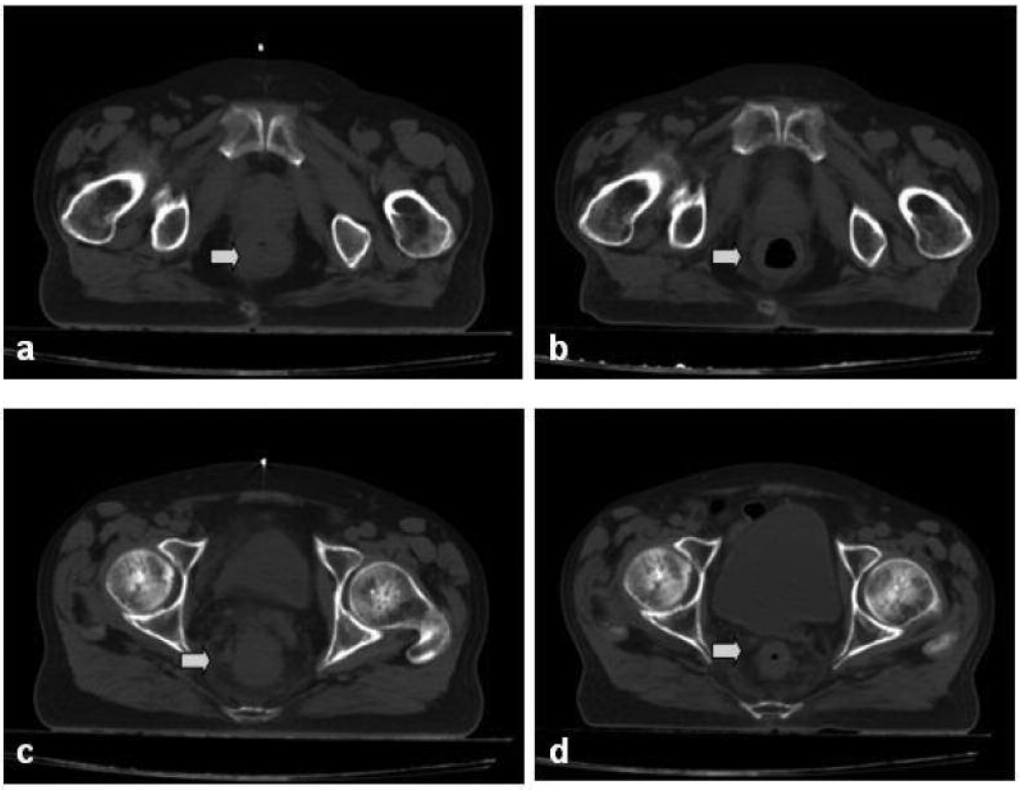

Figure 1. *CT-imaging of two rectal adenocarcinomas (a and c) before starting concurrent accelerated capecitabine radiochemotherapy. Marked response with opening of the obstructed lumen (b) and normalization of the perirectal tissue (d) one month after the completion of the preoperative regimen.*

profile with minimal hematological and intestinal toxicity. This was confirmed in the phase of concurrent radiochemotherapy and in the subsequent adjuvant chemotherapy phase of the current protocol.

In contrast to previous studies applying standard fractionation of radiotherapy that delivers a dose of 45-50 Gy within 5 weeks, our study considered an accelerated hypofractionated regimen, following a similar concept to the Swedish trial (23), delivering 10 fractions of 3.4 Gy in 2 weeks. Acceleration of radiotherapy may be important for counteracting the adverse effect of rapid tumor repopulation and, furthermore, larger radiotherapy fractions may be more effective in cancer cells with low intrinsic radiosensitivity, such as colorectal adenocarcinoma (25, 26). As this regimen was expected to be more toxic for normal tissues, patients were supported with high daily dose of amifostine, a potent cytoprotective agent reducing the radiotherapy sequelae on intestinal and bladder tissues (27, 28).

Indeed, the rather aggressive radiochemotherapy schedule applied had an excellent tolerance with minimal early colitis, impressively low perineal toxicity and proctitis and lack of bladder toxicity. De Paoli *et al*. reported 40% moderate diarrhea, 34% proctitis and 20% perineal toxicity (10). In the study by Souglakos *et al*. grade 3 diarrhea was in the range of 35% (9). The far lower incidence of severe radiation sequelae should be attributed to the conformal radiotherapy techniques applied together with the high amifostine daily doses supporting the regimen. In terms of late toxicity, whether the scheme was applied on a preoperative or postoperative basis, the radiation sequelae were negligible within a median follow-up of 26 months. Similarly, in patients treated with radical intent and very high local radiation dose (15 fractions of 3.4 Gy), no late sequelae were noted.

In terms of efficacy, the 85% rate of major histological responses in patients treated with preoperative radiochemotherapy and the 80% complete and partial response rates obtained for patients treated with radical intent underlie the excellent antitumor activity of the regimen. The 21.4% complete pathologic response noted is similar to the 12-30% reported in previous studies (10, 12, 15). The 85-90% 2-year survival in operable cases and the 44% 2-year survival in inoperable patients treated with radical intent are certainly encouraging.

It is concluded that accelerated hypofractionation of radiotherapy supported with amifostine cytoprotection is a feasible regimen in the pre- and postoperative and radical setting. HypoARC delivers an effective radiation dose within less than half of the time demanded for standard radiotherapy.

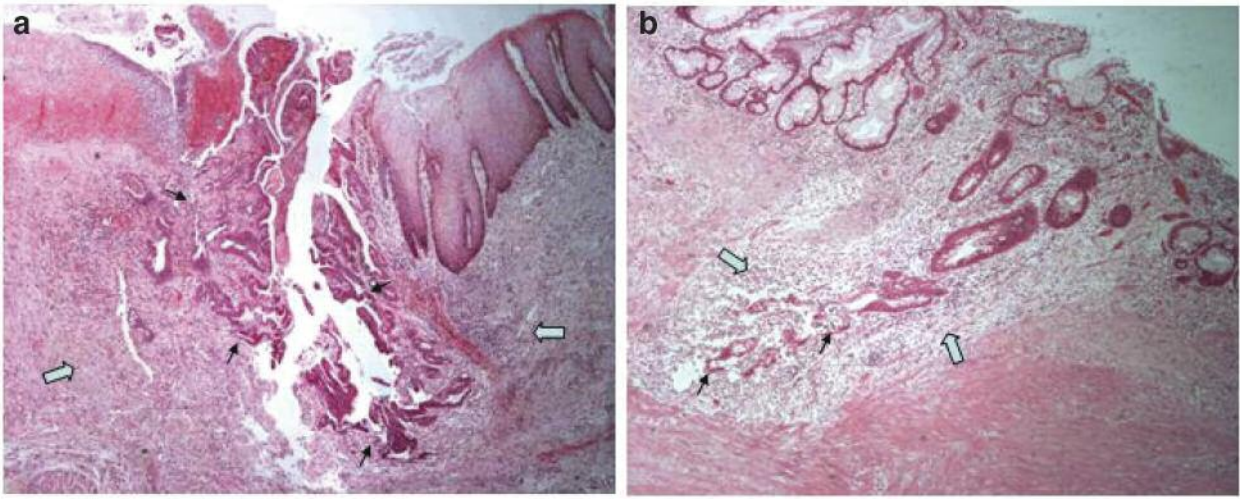

Figure 2. *Hematoxylin-eosin-stained sections one month following accelerated capecitabine radiochemotherapy: (a) tissue area of a pre-existing large T4-stage rectal adenocarcinoma infiltrating the anal region and residual adenocarcinoma foci (thin arrows) with extensive necrosis (large arrows); (b) tissue of a pre-existing rectal adenocarcinoma exhibiting areas of necrosis and fibrosis (large arrows) with residual groups of adenocarcinoma cells (thin arrows).*

This is certainly convenient for the patients and busy radiotherapy departments. Capecitabine daily administration at the doses applied does not include systemic toxicity and nor does it increase radiation sequelae. The toxicity produced by HypoARC radiochemotherapy was lower than the one expected from standard radiochemotherapy and late toxicity appears negligible within the 26 months of median follow-up time available.

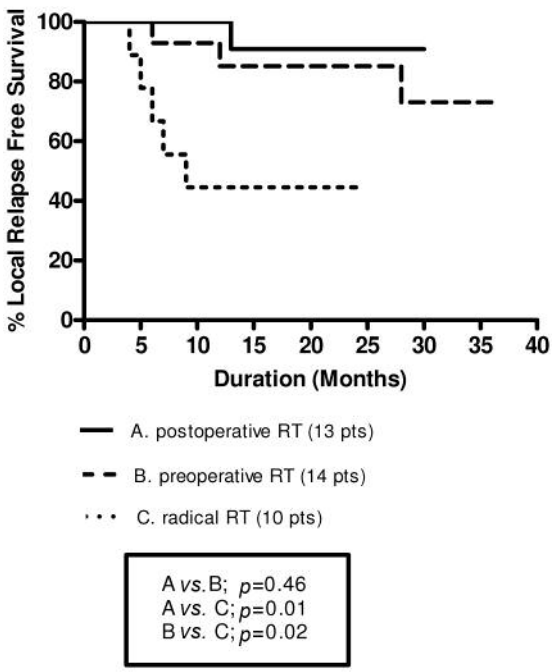

Figure 3. *Kaplan-Meier curves of the local relapse-free survival in patients treated with preoperative, post-operative and radical accelerated capecitabine radiochemotherapy.*

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