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CLINICAL INVESTIGATION **Rectum**

BEVACIZUMAB, CAPECITABINE, AMIFOSTINE, AND PREOPERATIVE HYPOFRACTIONATED ACCELERATED RADIOTHERAPY (HYPOARC) FOR RECTAL CANCER: A PHASE II STUDY

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Purpose: **Bevacizumab has established therapeutic activity in patients with metastatic colorectal cancer, and anti–vascular endothelial growth factor therapy enhances the activity of radiotherapy in experimental models. We assessed the feasibility and efficacy of preoperative radiochemotherapy combined with bevacizumab in patients with rectal cancer.**

Methods and Materials: **Nineteen patients with radiologic T3 and/or N+ rectal carcinoma were treated with preoperative conformal hypofractionated accelerated radiotherapy (3.4 Gy in 10 consecutive fractions) supported with amifostine (500–1,000 mg daily), capecitabine (600 mg/m^2 twice daily, 5 days per week), and bevacizumab (5 mg/kg every 2 weeks for 2 cycles). Surgery followed 6 weeks after the end of radiotherapy. A cohort of 14 sequential patients treated with the same regimen without bevacizumab was available for comparison.**

Results: **Grade 2 or 3 diarrhea was noted in 7 of 19 patients (36.8%), which was statistically worse than patients receiving the same regimen without bevacizumab ($p = 0.01$). A higher incidence of Grade 2 or 3 proctalgia was also noted (21.1%) ($p = 0.03$). Bladder and skin toxicity was negligible. All toxicities regressed completely within 2 weeks after the end of therapy. Pathologic complete and partial response was noted in 7 of 19 cases (36.8%) and 8 of 19 cases (42.1%). Within a median follow-up of 21 months, none of the patients has had late complications develop and only 1 of 18 evaluable cases (5.5%) has had locoregional relapse.**

Conclusions: **Bevacizumab can be safely combined with hypofractionated radiotherapy and capecitabine as a preoperative radiochemotherapy regimen for patients with rectal cancer. The high pathologic complete response rates urges the testing of bevacizumab in randomized studies.** **© 2011 Elsevier Inc.**

Radiotherapy, Capecitabine, Bevacizumab, Amifostine, Rectal cancer.

INTRODUCTION

Colorectal cancer is a common malignant disease, accounting for approximately 10% of all human cancers (1). Pelvic radiochemotherapy based on 5-fluorouracil significantly improves survival of patients with extramural infiltration and/or node involvement (2). A major advance in the treatment of operable rectal cancer is the use of radiotherapy or radiochemotherapy at a preoperative setting. A short preoperative regimen used in a Swedish trial provided 16% and 10% increases in the 5-year local control and survival rates, respectively, compared with surgery alone (3). The German Rectal Cancer Study Group trial showed that preoperative radiochemotherapy improves the 5-year local control rate by 7% and, moreover, early and late sequelae of therapy are significantly fewer compared with postoperative radiochemotherapy (4). Especially in low rectal cancer, preoperative radiotherapy seems to be important in terms of local control but also in terms of preservation of the sphincter and avoidance of permanent colostomy (5).

The addition of 5-fluorouracil to preoperative radiotherapy is important for local control, as shown in the European Organisation for Research and Treatment of Cancer trial (6). In this study continuation of chemotherapy after surgery showed only a marginal, not significant, benefit of a 4% increase in overall survival rate. It is therefore evident that the inclusion of more effective drugs in the preoperative radiochemotherapy phase and postoperative adjuvant chemotherapy phase of therapy would improve control and survival rates of the disease and, eventually, would increase the percentage of candidates for sphincter preservation.

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Tumor angiogenesis is a major process defining tumor growth, invasion, and metastasis, and the prognostic and predictive relevance of high tumor angiogenic activity is well established in colorectal cancer [as previously reviewed (7)]. Vascular endothelial growth factor (VEGF) is a main angiogenic factor, and anti-VEGF monoclonal antibodies, such as bevacizumab, have an established role in the treatment of metastatic colorectal cancer (8). The blockage of angiogenesis during radiotherapy and/or chemotherapy has significantly improved the efficacy of the regimens in experimental models (9, 10). The role of anti-VEGF therapy in an adjuvant or preoperative setting remains, however, obscure.

In this study we examined the feasibility of a combination of preoperative hypofractionated radiochemotherapy with bevacizumab in patients with rectal carcinoma. A control group treated with the same radiochemotherapy regimen without bevacizumab was available for comparison.

METHODS AND MATERIALS

From September 2006 to September 2009, 19 patients with rectal cancer were recruited into a prospective study aiming to investigate the feasibility and efficacy of the combination of the anti-VEGF monoclonal antibody bevacizumab (Avastin, Roche, Basel Switzerland) with a previously established accelerated preoperative chemoradiotherapy scheme (11). In this latter study a cohort of 14 patients with rectal cancer received the same radiochemotherapy regimen without bevacizumab, and this is used as a historical control to compare with the current trial. The control and current groups represent sequential cohorts of patients. The study had been approved by the local scientific and ethics committees, and written informed consent was obtained from all patients.

The patient and disease characteristics are shown in Table 1. All patients underwent a detailed preoperative examination including standard blood and biochemical tests; computed tomography (CT) scan of the chest, abdomen, and pelvis; magnetic resonance imaging of the pelvis; endorectal ultrasound; and bone scan. Inclusion criteria comprised patients with histologically confirmed adenocarcinoma of the rectum, with fixation at rectal examination, radiologic evidence of extramural tumor infiltration, and/or evidence of perirectal lymphadenopathy. Overall, the radiologic stages (American Joint Committee on Cancer/International Union Against Cancer, http://www.cancerstaging.org/staging/index.html) included in the study were either T3 and/or N1/2. Cases with evidence of infiltration to adjacent organs or patients with iliac/para-aortic lymphadenopathy or distant metastasis were excluded. Other exclusion criteria comprised previous pelvic radiotherapy, white blood cell count lower than 2,500/μL, and platelet count lower than 120.000/μL. Patients with a hemoglobin (Hb) level of less than 8.5 g/mL underwent transfusion, whereas patients with an Hb level of 8.5 to 10.5 g/mL received recombinant human erythropoietin, a policy that continued also during therapy so that Hb levels were greater than 10.5 g/dL before entering the study and throughout the radiotherapy period. Pregnant women or patients with major heart, liver, renal, or psychiatric disease or hematologic malignancies were also excluded. The follow-up of patients ranged from 3 to 40 months (median, 20 months), and the follow-up for those patients remaining alive was 12 to 40 months (median, 21 months).

Table 1. Patient, disease, and pre-radiotherapy treatment characteristics

	Bevacizumab	Historical control
No. of patients	19	14
Gender		
F	4	2
M	15	12
Age (y)		
Median	68	62
Range	49–82	22–78
Performance Status		
0	19	14
Location from sphincter		
≤5 cm	7	6
>5 cm	12	8
Histology		
Adenocarcinoma	19	14
Differentiation		
Good	8	7
Moderate/poor	11	7
Stage*		
T3	19	11
T4	0	3
N1	12	11
Surgery before radiotherapy		
Palliative colostomy	0	0
Previous chemotherapy		
No	19	14

* Based on computed tomography/magnetic resonance imaging (American Joint Committee on Cancer system).

Radiotherapy details

An 18-MV linear accelerator endowed with a multileaf collimator was used for the irradiation of patients. Radiotherapy was given to the whole pelvic region including the tumoral mass and the common and external/internal iliac node area with the lower margin reaching the outer margin of the anus. A four-field conformal technique based on CT simulation was used (anteroposterior and lateral fields) to deliver a daily fraction of 3.4 Gy (5 fractions per week) for 9 consecutive fractions, followed by a tenth fraction of 3.4 Gy delivered to the radiologically detectable disease through multiple conformal fields (overall treatment time, 12 days). Our experience with this radiotherapy regimen (without bevacizumab) has been previously published (11).

The normalized total dose (NTD) corrected for overall treatment time was calculated by use of a previously proposed formula (12, 13): for overall treatment time (T), = D [(α/β + d)/(a/b + 2)] + λ(Tc − To), where *Tc* is the number of days required for the delivery of the NTD by use of a conventionally fractionated scheme, *To* is the number of days required for the delivery of the current scheme, and λ is the estimated daily dose consumed to compensate for rapid tumor repopulation. Although the α/β ratio for colorectal cancer is not known, Suwinski *et al.* (14) recently suggested a 5-Gy value. Here, we assumed a value of 4 Gy for normal and 5 Gy for cancer tissues. For cancer cells, a λ value of 0.4 Gy was considered, although higher values may apply for large tumors. For normal tissues, a λ value of 0.2 Gy was adopted in radiobiological calculations. It was therefore estimated that the time-corrected NTD to the normal pelvic tissues is 42 Gy and that for the tumor is 46 Gy. The preoperative regimen used in the Swedish trial (5 Gy in 5 fractions) (3) delivers a time-corrected NTD to the tumor of 45 Gy, which is similar to the dose used in our study.

Cytoprotection

Ondansetron, 8 mg, was administered by mouth, 30 to 60 minutes before amifostine injection, as antiemetic policy. Amifostine, 1,000 mg, was diluted in 5 mL of water for injection and was injected in two sites (usually at the right and left shoulders), with the patient in a sitting position. The higher dose of amifostine (1,000 mg instead of 350–500 mg used in other studies) applied in the protocol was chosen to better protect tissues against the large fractions of radiotherapy in the hypofractionated accelerated radiotherapy scheme.

The dose of 1,000 mg was reached gradually (first day, 500 mg; second day, 750 mg; and third day, 1,000 mg) by use of a previously published algorithm (15). The tolerance of amifostine was recorded daily with a scoring system (15). Fever/rash attributed to amifostine (or to any other drug) was followed by immediate and permanent interruption of amifostine and by oral administration of corticosteroids and antihistamines for 2 to 3 days.

Chemotherapy

Chemotherapy with capecitabine at a dose of 600 mg/m^2 twice a day by mouth, for 5 days per week, started together with the first radiotherapy fraction (11). Capecitabine continued for 4 consecutive weeks. Bevacizumab was given intravenously at a dose of 5 mg/kg every 2 weeks for 2 consecutive cycles, starting on the first day of radiotherapy.

Three weeks after surgery, the dose of capecitabine was increased to 800 mg/m^2 twice daily, 5 days per week. Chemotherapy with capecitabine alone continued for 4 months.

Surgery

Patients underwent surgery (abdominoperineal resection or low abdominal resection with sphincter preservation) 6 weeks after the completion of radiochemotherapy.

Follow-up of patients

Radiation toxicity was recorded daily during the radiotherapy phase and weekly thereafter for the first month. Hematologic variables and clinical status were recorded every 2 weeks during the chemotherapy period. Computed tomography scan of the chest, abdomen, and pelvis was performed at 2 months and every 6 months thereafter.

Pathology scoring of 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 pathologic complete response. Considerable tumor shrinkage with microscopic necrosis but with identification of viable cancer cell foci was scored as partial pathologic response, and all other cases were grouped into a category of minimal or no pathologic response.

Statistical analysis

The statistical analysis and graphical presentation of survival curves were performed with the GraphPad Prism package version 5.0 (GraphPad, San Diego, CA; www.graphpad.com). The chi-square two-tailed t test was used for testing differences between categorical variables. Survival curves were plotted by use of the method of Kaplan and Meier. A p value of <0.05 is considered for significance.

RESULTS

Cytoprotection

By use of the reported individualization algorithm, 16 of 19 patients (84.2%) received 1,000 mg of amifostine before each radiotherapy fraction, 1 of 19 (5.3%) received 750 mg, and 2 of 19 (10.5%) received 500 mg. At this individualized dose level, all patients completed therapy either

Table 2. Early toxicity assessed with National Cancer Institute Common Toxicity Criteria Version 2 scale

	Bevacizumab (n =19) [No. of patients (%)]	Historical control (n =14) [No. of patients (%)]	p Value
Radiation dermatitis			
None	14 (73.7)	10 (71.4)	0.99
Faint erythema/dry desquamation	5 (26.3)	4 (28.6)	
Brisk erythema/ patchy moist desquamation	0 (0)	0 (0)	
Confluent moist desquamation	0 (0)	0 (0)	
Skin necrosis	0 (0)	0 (0)	
Perineal toxicity			
None	13 (78.9)	10 (71.4)	0.99
Dry desquamation	6 (21.1)	4 (28.6)	
Patchy moist desquamation	0 (0)	0 (0)	
Confluent moist desquamation	0 (0)	0 (0)	
Necrosis	0 (0)	0 (0)	
Diarrhea			
None	5 (26.3)	9 (64.3)	0.01
<4 stools/d	7 (36.9)	5 (35.7)	
4–6 stools/d	5 (26.3)	0 (0)	
>6 stools/d or dehydration	2 (10.5)	0 (0)	
Intensive care needed	0 (0)	0 (0)	
Abdominal pain			
None	6 (31.5)	9 (64.3)	0.07
Mild	9 (47.4)	5 (35.7)	
Moderate	4 (21.1)	0 (0)	
Severe	0 (0)	0 (0)	
Proctalgia			
None	9 (47.4)	7 (50)	0.03
Mild pain	5 (26.3)	7 (50)	
Moderate pain	4 (21.0)	0 (0)	
Severe pain	1 (5.3)	0 (0)	
Disabling	0 (0)	0 (0)	
Bladder toxicity			
None	18 (94.7)	14 (100)	0.38
Increased frequency by 2-fold	1 (5.3)	0 (0)	
Increased frequency by >2-fold but less than hourly	0 (0)	0 (0)	
Requirement of catheter	0 (0)	0 (0)	

without symptoms or with mild nausea and/or fatigue. In 2 patients fever/rash developed after the sixth and eighth injection, respectively, and amifostine was interrupted.

Chemotherapy tolerance

Administration of bevacizumab was not followed by hypersensitivity reactions. All patients received 2 cycles of bevacizumab and capecitabine without any chemotherapy-related hematologic or nonhematologic toxicity. Similarly, capecitabine at the dose of 800 mg/m^2 twice a day administered after surgery showed an excellent tolerance without any hematologic or other toxicity.

Pelvic toxicity

Table 2 shows acute toxicity in patients treated in this study compared with 14 patients treated with the same radiotherapy/capecitabine regimen without bevacizumab (11). Moist (Grade 2) skin or perineal desquamation was not noted. Diarrhea was a frequent complication but was severe (Grade 3) in only 2 of 19 patients (10.5%). Moderate or severe proctalgia requiring narcotics appeared in 4 of 19 patients (21.1%). Bladder toxicity was negligible. There was no case of colorectal bleeding.

When we compared the acute toxicity of this cohort with the historical cohort, a significantly increased incidence of Grade 2 to 3 diarrhea ($p = 0.01$) and proctalgia ($p = 0.03$) and a marginally higher incidence of abdominal pain were noted in patients receiving bevacizumab. All toxicities regressed completely within 2 weeks after the end of therapy.

Perioperative complications were minimal. There was no case of delayed would healing or wound infection in either group. There was, however, 1 case of fatal postoperative pulmonary embolism in the group receiving bevacizumab.

In terms of late radiation sequelae, within a median follow-up of 21 months, none of the patients had radiation bladder or intestinal/anal complications develop.

Response

Although endoscopy or CT imaging before surgery was not a routine procedure demanded in the protocol, 9 of 19 patients underwent endoscopy 1 to 3 weeks after radiotherapy. Disappearance of the intraluminal tumor was noted in 3 of 9 cases (33.3%) and significant remission in 5 of 9 (55.5%) (Fig. 1).

Response to preoperative therapy was assessed histologically at the department of pathology (A.G. and E.S.).

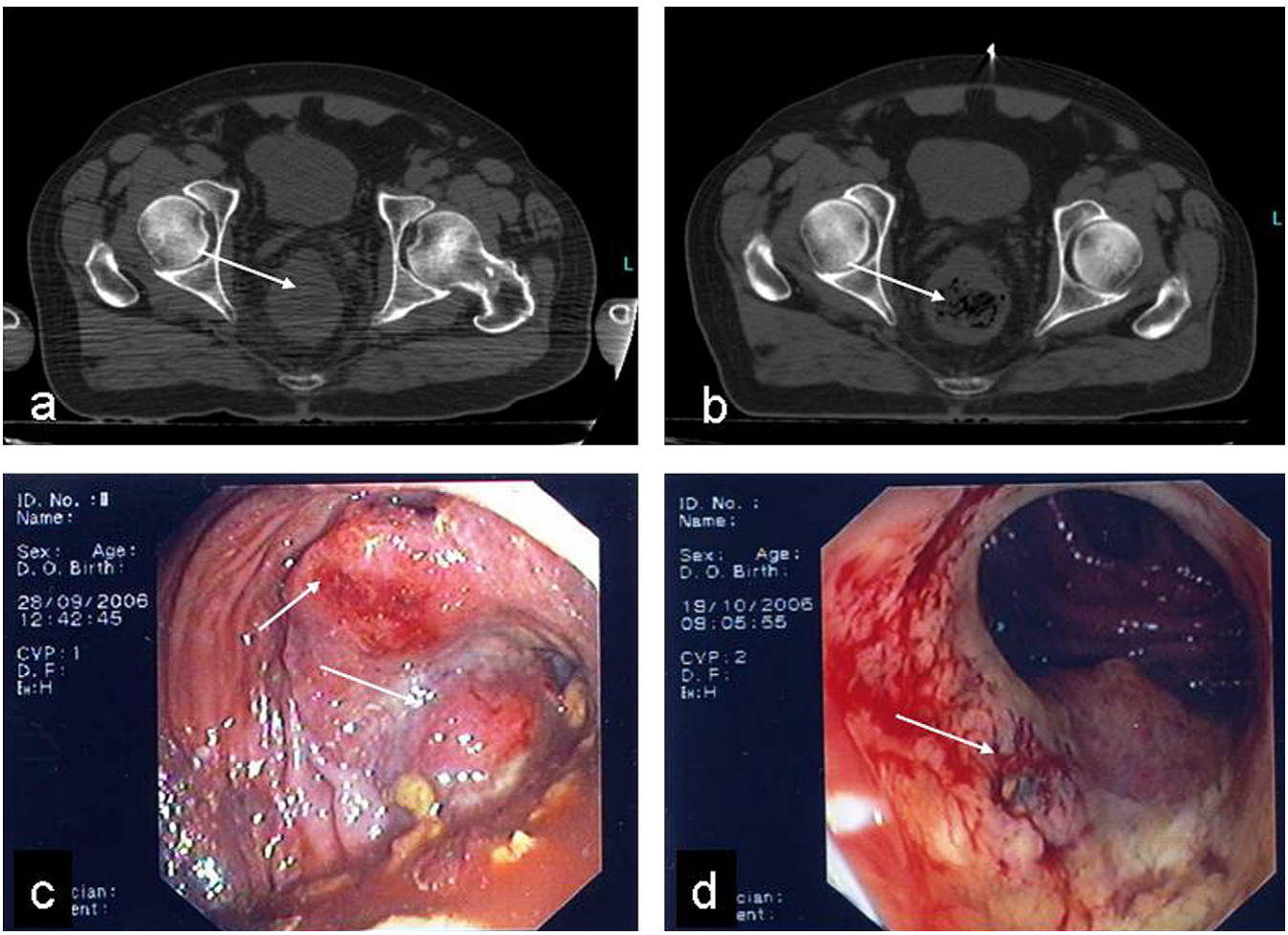

Fig. 1. Tumor obstructing the rectal lumen (arrows in a and c) and tumor regression (arrows in b and d) 1 week after bevacizumab-based preoperative radiochemotherapy as confirmed by (a, b) computed tomography scan and (c, d) endoscopy.

Microscopic complete disappearance of any viable tumor was noted in 7 of 19 cases (36.8%). Pathologic partial response was noted in 8 of 19 cases (42.1%), and minimal or no response in 4 of 19 cases (21.1%).

In the historical control group, the pathologic complete response rate was 21.4% (3/14); the partial response, 64.3% (9 of 14); and the minimal response rate, 14.3% (2 of 14). Statistical analysis showed no significant difference between groups ($p = 0.34$).

Local control and survival

Of 19 patients recruited, 2 died within a median follow-up of 21 months. One patient died of postoperative pulmonary embolism, and one died 14 months after surgery because of recurrent local and metastatic disease. Two additional patients are alive with metastasis but no evidence of locoregional recurrence. All 15 remaining patients are alive with no evidence of locoregional or distant relapse.

Figure 2 shows the Kaplan-Meier curves for local and distant relapse interval and overall survival. There was no significant differences between the current and the historical control groups (data not shown).

DISCUSSION

Preoperative radiotherapy with 5-fluorouracil or its novel prodrug form capecitabine is considered a standard practice for the treatment of rectal adenocarcinoma, especially when extramural infiltration, node enlargement, or lower rectum position is documented with radiology and endoscopy tests. Improved locoregional control, overall survival, and sphincter preservation have been reported in large randomized trials (3–6). Nevertheless, about half of the cases with American Joint Committee on Cancer Stage T3 and/or N+ will die of disease, stressing the importance of clinical research for more effective locoregional and systemic therapy.

The recent establishment of anti-VEGF monoclonal antibody therapy as a valuable addition to chemotherapy for the treatment of metastatic colorectal cancer (8) confirmed the importance of the angiogenic machinery in the biological behavior and resistance of colorectal carcinoma to cytotoxic therapy. If we take into account the experimental evidence of a VEGF rebound after radiotherapy and of the radiosensitization conferred by the blockage of VEGF (9, 10), it is suggested that anti-VEGF policies may prove of importance if administered together with radiochemotherapy in a preoperative or postoperative setting in patients with rectal cancer. Elimination of the immature nonfunctional tumor vessels and vascular normalization leading to improvement of tumor oxygenation have been suggested as mechanisms underlying radiosensitization by bevacizumab (16, 17). Moreover, in a previous Phase I study using gene array analysis, we suggested that radiosensitization may occur through a direct effect of bevacizumab on colorectal tumor cells followed by a wide-scale suppression of transcription factors and genes involved in deoxyribonucleic acid repair and proliferation (18).

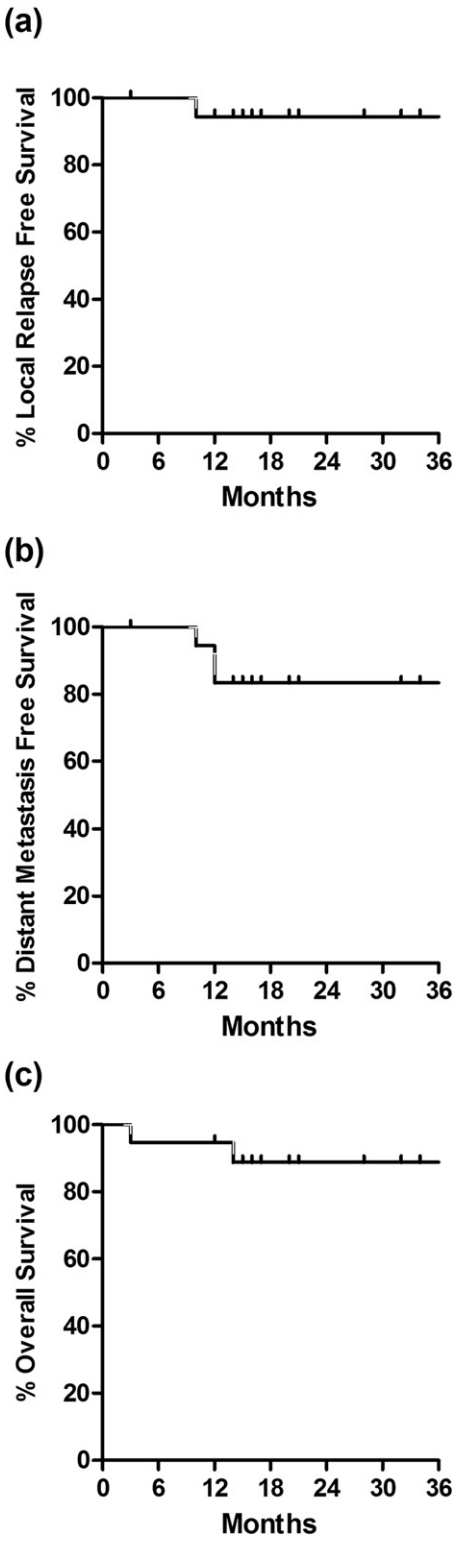

Fig. 2. Kaplan-Meier curves : (a) local relapse-free survival, (b) distant metastasis–free survival, (c) overall disease-specific survival.

In this Phase I/II study we investigated the feasibility of a combination of bevacizumab, at the standard biweekly dose level, with a previously tested hypofractionated radiochemotherapy scheme based on capecitabine (11). Hypofractionation is the standard practice of preoperative radiotherapy

in rectal cancer, and the 10 consecutive fractions of 3.4 Gy used herein are radiobiologically equivalent to the Swedish scheme of 5 fractions of 5 Gy (3). In brief, our previous experience with this scheme (without bevacizumab) showed low acute toxicity, no perioperative complications, and lack of late sequelae (11). We, therefore, had a historical control group of 14 patients to compare with a similar group of patients who would receive the same regimen plus the addition of bevacizumab.

Overall, the regimen showed an acceptable tolerance. When, however, acute toxicities were compared with those of the historical control group, a significantly higher incidence of Grade 2 to 3 diarrhea was noted (35% vs. 0%). Abdominal pain and Grade 2 to 3 proctalgia were also more frequent. Acute toxicities regressed, however, completely within 2 weeks, and surgeons did not report any treatment-related operation difficulties. Moreover, perioperative complications including delayed wound healing or wound infection were not noted, with the exception of one fatal case of pulmonary embolism. Our clinical experience comprises patients who were treated with primary surgery scheduled for postoperative radiochemotherapy who died of postoperative pulmonary embolism. The rate of pulmonary embolism during prolonged bevacizumab-based chemotherapy is estimated to 4% (19), but our case occurred as a postoperative complication, 6 weeks away from a short course of bevacizumab. The relation of embolism to bevacizumab cannot be documented from the current data because large randomized studies are needed to detect any significant increase in this complication. Within a median follow-up of 21 months, late toxicities are negligible.

In terms of efficacy, the pathologic complete response rate in patients treated with bevacizumab was 36.8%, which—though higher than the 21.4% rate documented in the non-bevacizumab cohort—was not significantly different. Within a median follow-up of 21 months, only 1 of 19 patients (5.2%) relapsed locally. Longer follow-up is probably needed to better assess the impact of bevacizumab on survival. Whether this higher, still not statistically significant, pathologic complete response rate documented simply reflects differences in local tumor stage or radio-responsiveness between groups or consists of a promise for a significant survival benefit should be sought in randomized trials. In a study by Crane *et al.* (20), combining capecitabine and bevacizumab radiochemotherapy for Stage T3 rectal cancer, the pathologic complete response rate was 31% and the 2-year local relapse rate 6.2%, which is the same as that noted in our study. In a recent study by Willett *et al.* (21), preoperative 5-fluorouracil and bevacizumab radiochemotherapy resulted in a significant shrinkage of the primary tumor from a mean size of 5 to 2.4 cm. The actuarial 5-year local control rate was 100%.

Bevacizumab can be safely combined with hypofractionated radiotherapy and capecitabine as a preoperative radiochemotherapy regimen for patients with rectal cancer. The acceptable tolerance and the high pathologic complete response rates noted in this study and two previously published studies are encouraging and urge the testing of bevacizumab in randomized studies.

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