This is an Open Access article licensed under the terms of the Creative Commons Attribution-NonCommercial 3.0 Unported license (CC BY-NC) (www.karger.com/OA-license), applicable to the online version of the article only. Distribution permitted for non-commercial purposes only.

Clinical Study

Phase II Study of Preoperative Concurrent Chemoradiotherapy with S-1 plus Bevacizumab for Locally Advanced Resectable Rectal Adenocarcinoma

Sotaro Sadahiro^a Toshiyuki Suzuki^a Akira Tanaka^a Kazutake Okada^a
Gota Saito^a Akemi Kamijo^a Takeshi Akiba^b Shuichi Kawada^b

Departments of ^aSurgery and ^bRadiology, Tokai University, Isehara, Japan

Key Words

Rectal cancer · Chemoradiotherapy · Phase II study · S-1 · Bevacizumab

Abstract

Objective: A single-arm phase II clinical trial was conducted to evaluate the safety and efficacy of preoperative chemoradiotherapy (CRT) with concurrent S-1, bevacizumab, and radiation in patients with locally advanced rectal cancer (LARC). **Methods:** Fifty-two patients with LARC were enrolled. A total dose of 45 Gy was delivered in 25 fractions over 5 weeks, S-1 was administered orally twice a day on days 1–14 and 22–35, and bevacizumab was administered on days 1, 15, and 29. Surgical resection was scheduled 8 weeks (6–10 weeks) after completing the CRT. **Results:** All 52 patients underwent R0 radical surgery. Sphincter preservation was possible in 38 (73.1%) patients. A pathologic complete response was obtained in 10 (19.2%) patients, a pathologic downstaging was achieved in 37 (71.2%) patients, and the tumor shrinkage rate was 77.1%. The only grade 3 adverse events were leukopenia and rash in 1 (1.9%) patient. The rate of postoperative complications was 28.8%. Anastomotic leakage occurred in 9 (23.7%) of the 38 patients who underwent sphincter-preserving surgery. Perineal wound dehiscence developed in 2 (14.3%) of the 14 patients who received an abdominoperineal resection. **Conclusions:** Adding bevacizumab to S-1 clearly increased the incidence of wound-related complications, with no distinct enhancement of tumor response.

© 2014 S. Karger AG, Basel

Prof. Sotaro Sadahiro
Department of Surgery, Tokai University
143 Shimokasuya
Isehara-shi, Kanagawa 259-1193 (Japan)
E-Mail sadahiro@is.icc.u-tokai.ac.jp

Introduction

For patients with clinical stage II and III rectal cancer, preoperative treatment with radiotherapy and 5-fluorouracil (5-FU)-based chemotherapy is recommended [1]. Capecitabine, an oral fluoropyrimidine, can be regarded as a convenient alternative to 5-FU in patients who receive preoperative chemoradiotherapy (CRT) for locally advanced rectal cancer (LARC) [2].

S-1 is an oral anticancer drug that combines tegafur, a prodrug of 5-FU, with 5-chloro-2,4-dihydropyrimidine (CDHP) and potassium oxonate (Oxo) in a molar ratio of 1:0.4:1 [3, 4]. We previously performed a phase I/II study of preoperative concurrent CRT with S-1 in patients with LARC and reported that the effectiveness of CRT with S-1 was similar to that of CRT with capecitabine. Moreover, CRT with S-1 was associated with mild adverse events, with no hand-foot syndrome [5].

Bevacizumab is a monoclonal antibody to vascular endothelial growth factor (VEGF) that is used to treat advanced colorectal cancer. Preclinical models have suggested that the induction of VEGF by radiation contributes to tumor radioresistance and that anti-VEGF monoclonal antibody treatment can compensate for resistance to radiation [6, 7]. Preoperative CRT combining bevacizumab with 5-FU or capecitabine is thus considered promising for the management of LARC, but adequate evidence supporting the efficacy and safety of such regimens is lacking [8–10].

The aim of this single-arm phase II clinical trial was to evaluate the safety and efficacy of preoperative CRT with concurrent S-1, bevacizumab, and radiation in patients with LARC. This study was approved by the Institutional Review Board of our university (10R-113), and all patients provided their written informed consent.

Patients and Methods

Study Design

This study was a nonrandomized, single-institution, phase II trial designed to evaluate the feasibility, safety, and efficacy of neoadjuvant radiotherapy with concurrent oral S-1 and bevacizumab in patients with locally advanced resectable rectal adenocarcinoma. The primary endpoint was the pathologic complete response (pCR) rate. We also evaluated acute toxicity, perioperative morbidity, the degree of tumor shrinkage, and the downstaging rate as secondary endpoints.

Eligibility Criteria

Patients with a histologically confirmed diagnosis of adenocarcinoma of the middle or lower rectum (cT3–T4, M0 or Tx, N+, M0) were enrolled. Additional eligibility criteria were as follows: no prior chemotherapy or pelvic radiation; an Eastern Cooperative Oncology Group performance status of ≤ 1 ; age 20–80 years; adequate organ function, as defined by a leukocyte count of $\geq 4,000$ to $\leq 12,000/\text{mm}^3$, a neutrophil count of $\geq 2,000/\text{mm}^3$, a platelet count of $\geq 100,000/\text{mm}^3$, a hemoglobin level of ≥ 9 g/dl, a serum bilirubin level of ≤ 1.5 mg/dl, serum aspartate aminotransferase and alanine aminotransferase levels of ≤ 100 U/l, a serum creatinine level of ≤ 1.1 mg/dl (for men) or ≤ 0.7 mg/dl (for women), and a creatinine clearance of ≥ 50 ml/min; the ability to ingest food and drugs orally; and no high medical risks.

Radiotherapy

A total irradiation dose of 45 Gy was delivered in daily fractions of 1.8 Gy, 5 days per week for 5 weeks, using a four-field box technique. The patients were irradiated using a 15-MV linear accelerator. All patients underwent computed tomography (CT) simulation for three-dimensional conformal radiotherapy. The gross tumor volumes of the primary rectal mural tumor and lymph nodes >1.0 cm in diameter were visualized on CT and magnetic resonance imaging (MRI). The clinical target volume included the gross tumor volume, mesorectum, presacral space, and the entire sacral hollow and regional lymphatics, including the perirectal, internal iliac, and presacral lymphatics. The planning target volume was located 1 cm outside of the clinical target volume. In accordance with these definitions, the treatment fields were set as follows: the lateral

borders of the planning target volume were 1.5 cm lateral to the widest bony margin of the true pelvic wall; the superior border was placed at L5–S1; the inferior border within the anal canal; the anterior border at the most posterior aspect of the symphysis pubis, and the posterior border at the most posterior aspect of the sacrum. All patients underwent three-dimensional treatment planning.

Chemotherapy

S-1 was given orally twice a day (after breakfast and dinner) on days 1–14 and 22–35. The initial dose of S-1 was the standard dose used for monotherapy (80 mg/m²/day). Bevacizumab was administered at 5 mg/kg body weight on days 1, 15, and 29.

Safety Assessment and Dose Modifications

The pretreatment evaluation included a clinical history and physical examination, complete blood cell count, blood chemistry, chest and abdominopelvic CT, colonoscopy with biopsy, contrast barium enema examination, pelvic MRI, and transrectal ultrasonography. Toxic effects were assessed every week during therapy and for 2 weeks after the end of treatment. A physical examination, blood cell count, and blood chemistry were conducted, and the results were recorded. The following recommendations were used for dose modification: if a patient had hematologic toxicity (grade 3 or higher leukopenia or neutropenia or grade 2 or higher thrombocytopenia) or nonhematologic toxicity (grade 3 or higher), S-1 chemotherapy was temporarily discontinued until the toxicity resolved to grade 2 or lower, and treatment was restarted at a lower dose of S-1 (65 mg/m²/day); bevacizumab was withdrawn in the event of thrombosis, perforation of the gastrointestinal tract, or bleeding (grade 3 or higher).

Surgery and Postoperative Adjuvant Chemotherapy

Surgical resection was scheduled to be performed 8 weeks (6–10 weeks) after completing the CRT. The surgical techniques included low anterior resection and abdominoperineal resection, performed using mesorectal resection techniques. Postoperative adjuvant chemotherapy, consisting of 8 courses of S-1 for 2 weeks repeated every 3 weeks, was recommended but was not included in the study protocol.

Evaluation of Tumor Response and Tumor Shrinkage

Tumor response was evaluated on the basis of the histologic findings of resected specimens. The tumor regression grade (TRG) was used to evaluate histologic regression [11]. A pathologic tumor response was determined by the presence of pathologic downstaging or a pCR.

Double-contrast barium enema examination and MRI volumetry were performed before CRT and immediately before surgery. A 1.5-tesla MRI system with a surface coil was used. Before the MRI, colonic irrigation was performed, and then barium was infused. Cross-sectional areas were measured on axial T2-weighted images. The degree of tumor shrinkage on barium enema examination was calculated by measuring the tumor along the major axis (length along the long axis of the bowel) on lateral views. The methods used to measure the degree of tumor shrinkage have been described previously [12–14].

Early Stopping Rule and Statistical Analysis

Since we had no experience using radiotherapy combined with S-1 and bevacizumab, the study was scheduled to be prematurely terminated if the incidence of grade 4 or higher treatment-related adverse events was >8.19%. The incidence of 8.19% was based on the frequency of grade 4 or higher serious adverse reactions in specific use surveillance performed after bevacizumab was approved for the treatment of curatively unresectable advanced or recurrent colon cancer and rectal cancer in Japan (patients enrolled: 2,712; patients included in the analysis: 2,698) [15]. In that study, the numbers of enrolled patients in whom treatment was prematurely terminated and the numbers of events were as follows: 10 patients, 3 events; 20 patients, 5 events; 30 patients, 7 events; 40 patients, 8 events, and 50 patients, 9 events.

Preoperative CRT with regimens combining bevacizumab with 5-FU or capecitabine has been reported to have a pCR rate of 9–32% in patients with LARC [8–10]. We previously obtained a pCR rate of 22% (95% confidence interval 8.6–42.3) in patients who received CRT with S-1 alone [5]. In the present study, we assumed that the pCR rate would be 25%, with a minimum activity level pCR rate of 10%, an α level of 0.05 (two-sided), and a β level of 0.20. We estimated that 49 patients would be required. The target number of patients was therefore set at 52, taking excluded patients and dropouts into account.

Table 1. Patient demographics
(n = 52)

Median age (range), years	59 (32–73)
Gender	
Male/female	39 (75)/13 (25)
Performance status	
0/1	43 (83)/9 (17)
Median distance from the anal verge (mean ± SD), cm	5.5 (5.1±2.3)
Site	
Middle/lower rectum	26 (50)/26 (50)
Histologic type differentiation	
Well/moderate/poor	33 (63)/18 (35)/1 (2)
cStage	
II/III	16 (31)/36 (69)
cT	
2/3/4	2 (4)/49 (94)/1 (2)
cN	
0/1	16 (31)/36 (69)
Values are given as numbers (%) unless indicated otherwise.	

Results

Patients

A total of 52 patients were enrolled from February 2011 through September 2013. The patients' characteristics are shown in table 1. Sixteen patients (31%) had clinical stage II disease, and 36 (69%) had clinical stage III disease.

Toxicity and Compliance with Treatment

The main adverse events are shown in table 2. Dose reduction and transient withdrawal of irradiation were performed because of adverse events in only 1 patient. In this patient, the dose of S-1 was reduced because grade 3 leukopenia occurred on day 7 of treatment, and the lower dose of S-1 was given until day 14. S-1 was not given on days 15–21, as originally scheduled. Treatment with the reduced dose of S-1 was resumed on day 22, but a grade 3 rash developed on day 28, and both S-1 and radiotherapy were discontinued. Only radiotherapy was resumed on day 35 and was completed (the patient received a total dose of 45 Gy in 25 fractions). Bevacizumab was administered 3 times, as scheduled. The other patients had no grade 3 or higher adverse events. Grade 2 anal pain developed in 24 (46.2%) patients.

Surgery

All 52 patients underwent radical surgery. Sphincter-preserving surgery was performed in 38 (73.1%) of the 52 patients. All patients received R0 resection. The median interval between completing the radiotherapy and surgery was 55 days (range 38–70).

Tumor Response and Postoperative Complications

Among the 52 patients, 10 had a pCR. The pCR rate was thus 19.2% (95% confidence interval 9.6–32.5). One patient had complete regression of the primary tumor, but a residual tumor was found in the perirectal lymph nodes. Histologic regression was evaluated to be TRG 1 in 11 (21.2%) patients and TRG 2 in 12 (23.1%) patients; marked tumor regression (TRG 1 or 2) was thus obtained in 23 (44.2%) of the 52 patients (table 3). In addition, 27 (51.9%) patients achieved T downstaging, and 25 (48.1%) patients achieved N downstaging, accounting for a combined pathologic downstaging rate of 71.2% (37 of the 52 patients). The

Table 2. Adverse events in the 52 patients

	All	Grade				
		1	2	3	4	3/4
Hematologic adverse events						
Leukopenia	28 (53.8)	13	14	1	0	1 (1.9)
Neutropenia	17 (32.7)	13	4	0	0	0
Anemia	16 (30.8)	9	7	0	0	0
Thrombocytopenia	1 (1.9)	0	1	0	0	0
Nonhematologic adverse events						
AST/ALT	0	0	0	0	0	0
Anorexia	23 (44.2)	13	10	0	0	0
Vomiting	1 (1.9)	1	0	0	0	0
Diarrhea	30 (57.7)	22	8	0	0	0
Fatigue	35 (67.3)	29	6	–	–	–
Stomatitis	4 (7.7)	3	1	0	0	0
Rash	1 (1.9)	0	0	1	0	1 (1.9)
Hypertension	3 (5.8)	0	3	0	0	0
Anal pain	31 (59.6)	7	24	0	–	0

Values are given as numbers (%).

Table 3. Histologic tumor regression in the 52 patients

TRG 1	(pCR, absence of viable cancer cells in the resected specimen)	11 (21.2)
TRG 2	(presence of residual cancer cells)	12 (23.1)
TRG 3	(fibrosis outgrowing residual cancer cells)	17 (32.7)
TRG 4	(residual cancer cells outgrowing fibrosis)	11 (21.2)
TRG 5	(absence of response)	1 (1.9)

Values are given as numbers (%).

Table 4. Degree of tumor shrinkage in the 52 patients

Method of detection	Mean shrinkage ± SD, %
Barium enema (two-dimensional)	51.8 ± 16.4
MRI (three-dimensional)	77.1 ± 13.0

degree of tumor shrinkage was $51.8 \pm 16.4\%$ as assessed two-dimensionally on barium enema examination and $77.1 \pm 13.0\%$ as assessed three-dimensionally on MRI volumetry (table 4).

The postoperative complication rate was 28.8% (15 of the 52 patients). Anastomotic leakage occurred in 9 (23.7%) of the 38 patients who underwent sphincter-preserving surgery. Perineal wound dehiscence developed in 2 (14.3%) of the 14 patients who underwent abdominoperineal resection. A rectovaginal fistula was found in 1 (1.9%) patient 2 months after surgery.

Discussion

Preoperative radiotherapy with concurrent 5-FU-based chemotherapy decreases the risk of local recurrence and remains a standard of care in patients with LARC. The achievement of a pCR and a negative circumferential resection margin correlate with a good prognosis and

are considered potential early markers of the efficacy of CRT [16]. In recent studies comparing the outcomes of preoperative CRT with 5-FU or capecitabine in patients with LARC, the pCR rate ranged from 11 to 18% for 5-FU and from 16 to 30% for capecitabine, with no significant difference between the drugs [17–20]. In our previous study of preoperative CRT with S-1 alone, the pCR rate was 22%, consistent with the results of previous studies [5].

Antiangiogenic therapy has been an important strategy in cancer treatment since the time that bevacizumab combined with 5-FU-based chemotherapy was shown to significantly improve overall survival in patients with metastatic colorectal cancer [21]. Willett et al. [22] were the first to show that bevacizumab monotherapy has clinically significant antivasculature and vascular-normalizing effects in rectal cancer. They obtained a pCR rate of 16% (5 of 32 patients) in a phase II study of bevacizumab plus preoperative 5-FU and radiation in LARC [9]. Subsequently, Spigel et al. [23] obtained a pCR rate of 29% (10 of 35 patients) in a phase II study of preoperative 5-FU-based CRT plus bevacizumab. Recently, an increasing number of studies have evaluated preoperative CRT with capecitabine plus bevacizumab in patients with LARC. Marijnen et al. [8] obtained a pCR rate of 9% (2 of 23 patients) in an interim analysis of a multicenter clinical trial. In subsequent phase II studies, pCR rates of 32% (8 of 25 patients) were reported by Crane et al. [10], 13% (8 of 61 patients) by Velenik et al. [24], and 14% (6 of 43 patients) by Gasparini et al. [25]. In our study, the pCR rate was 19.2% (10 of 52 patients), which was generally consistent with these values.

In previous studies of preoperative fluoropyrimidine-based CRT, we obtained tumor shrinkage rates of 69% [5] and 71% [14] on MRI. In the present study, the tumor shrinkage rate was 77%, which was in accord with previous results.

As mentioned above, the tumor response in patients with LARC who received preoperative CRT with S-1 plus bevacizumab was comparable to the response previously obtained by combining bevacizumab with 5-FU or capecitabine. However, a clinically significant potentiation of the tumor response was not apparent in those patients who received bevacizumab in addition to S-1, contrary to our expectations.

In our study, adverse events were extremely mild during CRT as well as during the period from completing the CRT to surgery. The only grade 3 or higher adverse events were leukopenia and rash (both grade 3) in 1 (1.9%) patient during CRT. In our previous study, grade 3 diarrhea developed in 3 (11.1%) of 27 patients who received CRT with S-1 [5]. In contrast, no patient who received CRT with S-1 plus bevacizumab had grade 3 or higher diarrhea in the present study. However, grade 1 or 2 anal pain was reported by 31 (59.6%) of the 52 patients, and 24 (46.2%) patients had grade 2 anal pain. Anal pain did not occur in patients with LARC who received CRT with S-1 alone [5]. The incidence of proctitis/proctalgia was reported to be 18.8% (6 of 32 patients) in patients who received CRT with 5-FU plus bevacizumab in a study by Willett et al. [9] and 20.9% (9 of 43 patients) in patients who received CRT with capecitabine plus bevacizumab in a study by Gasparini et al. [25]. However, since many studies did not report the occurrence of proctitis or proctalgia, these complications were apparently not problematic in previous studies of CRT. The mechanism underlying the increase in anal pain associated with the concomitant use of bevacizumab remains unknown.

In the present study, anastomotic leakage developed in 9 (23.7%) of the 38 patients who underwent sphincter-preserving surgery, and perineal wound dehiscence developed in 2 (14.3%) of the 14 patients who underwent abdominoperineal resection, indicating a trend toward a high rate of wound-related complications after surgery. In our previous study of patients who received CRT with S-1 alone, the rates of suture failure and delayed wound healing were 4.3% (1 of 23 patients) and 13.3% (4 of 30 patients), respectively [5]. In another study on CRT with capecitabine plus bevacizumab, Crane et al. [10] reported that 2 (20.0%) of 10 patients had suture failure after low anterior resection, 2 (33.3%) of 6 patients had delayed wound healing, and 2 (33.3%) of 6 patients had perineal wound dehiscence after

abdominoperineal resection. Velenik et al. [24] reported that among 60 patients who received CRT with capecitabine plus bevacizumab, including 42 patients who underwent sphincter-preserving surgery, the rate of delayed wound healing was 30.0% (18 patients), with a suture failure rate of 11.7% (7 patients). Although these studies are not phase III trials, these findings suggest that the concurrent use of bevacizumab might increase the risk of wound-related complications. Caution is therefore required.

Long-term effects of this combination regimen cannot be judged by this trial. Long-term follow-up results on survival and on local control are needed to determine the potential impact of adding bevacizumab to preoperative standard CRT. We also recognize that using pCR as surrogate marker in rectal cancer is problematic.

In conclusion, the major effect associated with adding bevacizumab to CRT for LARC was an increase in the incidence rate of wound-related complications. Although adverse events were extremely mild both during CRT and during the period from completing the CRT to surgery, the concurrent administration of bevacizumab with capecitabine- or S-1-based CRT apparently offers no clinically significant benefit in patients with LARC.

Disclosure Statement

The authors declare that they have no competing interests. None of the authors received any funding support for this work.

References

- 1 Willett CG, Czito BG, Bendell JC: Radiation therapy in stage II and III rectal cancer. *Clin Cancer Res* 2007;13:6903s–6908s.
- 2 Hofheinz R-D, Wenz F, Post S, Matzdorff A, Laechelt S, Hartmann JT, Müller L, Link H, Moehler M, Kettner E, Fritz E, Hieber U, Lindemann HW, Grunewald M, Kremers S, Constantin C, Hipp M, Hartung G, Gencer D, Kienle P, Burkholder I, Hochhaus A: Chemoradiotherapy with capecitabine versus fluorouracil for locally advanced rectal cancer: a randomised, multicentre, non-inferiority, phase 3 trial. *Lancet Oncol* 2012;13:579–588.
- 3 Shirasaka T, Shimamoto Y, Ohshimo H, Yamaguchi M, Kato T, Yonekura K, Fukushima M: Development of a novel form of an oral 5-fluorouracil derivative (S-1) directed to the potentiation of the tumor selective cytotoxicity of 5-fluorouracil by two biochemical modulators. *Anticancer Drugs* 1996;7:548–557.
- 4 Schoffski P: The modulated oral fluoropyrimidine prodrug S-1, and its use in gastrointestinal cancer and other solid tumors. *Anticancer Drugs* 2004;15:85–106.
- 5 Sadahiro S, Suzuki T, Tanaka A, Okada K, Kamijo A, Murayama C, Akiba T, Nakayama Y: Phase I/II study of preoperative concurrent chemoradiotherapy with S-1 for locally advanced, resectable rectal adenocarcinoma. *Oncology* 2011;81:306–311.
- 6 Gorski DH, Beckett MA, Jaskowiak NT, Calvin DP, Mauceri HJ, Salloum RM, Seetharam S, Koons A, Hari DM, Kufe DW, Weichselbaum RR: Blockade of the vascular endothelial growth factor stress response increases the anti-tumor effects of ionizing radiation. *Cancer Res* 1999;59:3374–3378.
- 7 Lee C-G, Heijn M, di Tomaso E, Griffon-Etienne G, Ancukiewicz M, Koike C, Park KR, Ferrara N, Jain RK, Suit HD, Boucher Y: Anti-vascular endothelial growth factor treatment augments tumor radiation response under normoxic or hypoxic conditions. *Cancer Res* 2000;60:5565–5570.
- 8 Marijnen CA, Rutten H, de Wilt H, Tesselaar ME, Nuyttens J, Remmelzwaal J, Punt CJ, Martijn H, Hospers GA, Cats A: Preoperative chemoradiotherapy regimen with capecitabine and bevacizumab in locally advanced rectal cancer: a feasibility study of the Dutch Colorectal Cancer Group (DCCG) (abstract). *J Clin Oncol* 2008;26(suppl):15040.
- 9 Willett CG, Duda DG, di Tomaso E, Boucher Y, Ancukiewicz M, Sahani DV, Lahdenranta J, Chung DC, Fischman AJ, Lauwers GY, Shellito P, Czito BG, Wong TZ, Paulson E, Poleski M, Vujaskovic Z, Bentley R, Chen HX, Clark JW, Jain RK: Efficacy, safety, and biomarkers of neoadjuvant bevacizumab, radiation therapy, and fluorouracil in rectal cancer: a multidisciplinary phase II study. *J Clin Oncol* 2009;27:3020–3026.
- 10 Crane CH, Eng C, Feig BW, Das P, Skibber JM, Chang GJ, Wolff RA, Krishnan S, Hamilton S, Janjan NA, Maru DM, Ellis LM, Rodriguez-Bigas MA: Phase II trial of neoadjuvant bevacizumab, capecitabine, and radiotherapy for locally advanced rectal cancer. *Int J Radiat Oncol Biol Phys* 2010;76:824–830.
- 11 Mandard A-M, Dalibard F, Mandard J-C, Marnay J, Henry-Amar M, Petiot J-F, Roussel A, Jacob J-H, Segol P, Samama G, Ollivier J-M, Bonvalot S, Gignoux M: Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. Clinicopathologic correlations. *Cancer* 1994;73:2680–2686.

- 12 Suzuki T, Sadahiro S, Fukasawa M, Ishikawa K, Kamijo A, Yasuda S, Makuuchi H, Ohizumi Y, Murayama C: Predictive factors of tumor shrinkage and histological regression in patients who received preoperative radiotherapy for rectal cancer. *Jpn J Clin Oncol* 2004;34:740–746.
- 13 Suzuki T, Sadahiro S, Tanaka A, Okada K, Kamata H, Kamijo A, Murayama C, Akiba T, Kawada S: Biopsy specimens obtained 7 days after starting chemoradiotherapy (CRT) provide reliable predictors of response to CRT for rectal cancer. *Int J Radiat Oncol Biol Phys* 2013;85:1232–1238.
- 14 Suzuki T, Sadahiro S, Tanaka A, Okada K, Saito G, Kamijo A, Akiba T, Kawada S: Relationship between histologic response and the degree of tumor shrinkage after chemoradiotherapy in patients with locally advanced rectal cancer. *J Surg Oncol* 2014;109:659–664.
- 15 The final results: bevacizumab safety post-marketing large cohort survey (PMS) in 2712 Japanese colorectal cancer patients. Chugai Pharmaceutical Co., Ltd. <http://chugai-pharm.jp/hc/ss/pr/safe/report/ava/index.html>.
- 16 Sanghera P, Wong DWY, McConkey CC, Geh JI, Hartley A: Chemoradiotherapy for rectal cancer: an updated analysis of factors affecting pathological response. *Clin Oncol* 2008;20:176–183.
- 17 Yerushalmi R, Idelevich E, Dror Y, Stemmer SM, Figer A, Sulkes A, Brenner B, Loven D, Dreznik Z, Nudelman I, Shani A, Fenig E: Preoperative chemoradiation in rectal cancer: retrospective comparison between capecitabine and continuous infusion of 5-fluorouracil. *J Surg Oncol* 2006;93:529–533.
- 18 Das P, Lin EH, Bhatia S, Skibber JM, Rodriguez-Bigas MA, Feig BW, Chang GJ, Hoff PM, Eng C, Wolff RA, Delclos ME, Krishnan S, Janjan NA, Crane CH: Preoperative chemoradiotherapy with capecitabine versus protracted infusion 5-fluorouracil for rectal cancer: a matched-pair analysis. *Int J Radiat Oncol Biol Phys* 2006;66:1378–1383.
- 19 Kim DY, Jung KH, Kim TH, Kim D-W, Chang HJ, Jeong JY, Kim YH, Son S-H, Yun T, Hong CW, Sohn DK, Lim S-B, Choi HS, Jeong S-Y, Park J-G: Comparison of 5-fluorouracil/leucovorin and capecitabine in preoperative chemoradiotherapy for locally advanced rectal cancer. *Int J Radiat Oncol Biol Phys* 2007;67:378–384.
- 20 Chan AK, Wong AO, Jenken DA: Preoperative capecitabine and pelvic radiation in locally advanced rectal cancer – is it equivalent to 5-FU infusion plus leucovorin and radiotherapy? *Int J Radiat Oncol Biol Phys* 2010;76:1413–1419.
- 21 Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, Berlin J, Baron A, Griffing S, Holmgren E, Ferrara N, Fyfe G, Rogers B, Ross R, Kabbinavar F: Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Eng J Med* 2004;350:2335–2342.
- 22 Willett CG, Boucher Y, di Tomaso E, Duda DG, Munn LL, Tong RT, Chung DC, Sahani DV, Kalva SP, Kozin SV, Mino M, Cohen KS, Scadden DT, Hartford AC, Fischman AJ, Clark JW, Ryan DP, Zhu AX, Blaszkowsky LS, Chen HX, Shellito PC, Lauwers GY, Jain RK: Direct evidence that the VEGF-specific antibody bevacizumab has anti-vascular effects in human rectal cancer. *Nat Med* 2004;10:145–147.
- 23 Spigel DR, Bendell JC, McCleod M, Shipley DL, Arrowsmith E, Barnes EK, Infante JR, Burris HA III, Greco FA, Hainsworth JD: Phase II study of bevacizumab and chemoradiation in the preoperative or adjuvant treatment of patients with stage II/III rectal cancer. *Clin Colorectal Cancer* 2012;11:45–52.
- 24 Velenik V, Ocivirk J, Music M, Bracko M, Anderluh F, Oblak I, Edhemovic I, Breclj E, Kropivnik M, Omejc M: Neoadjuvant capecitabine, radiotherapy, and bevacizumab (CRAB) in locally advanced rectal cancer: results of an open-label phase II study. *Radiat Oncol* 2011;6:105–112.
- 25 Gasparini G, Torino F, Ueno T, Cascinu S, Troiani T, Ballestrero A, Berardi R, Shishido J, Yoshizawa A, Mori Y, Nagayama S, Morosini P, Toi M: A phase II study of neoadjuvant bevacizumab plus capecitabine and concomitant radiotherapy in patients with locally advanced rectal cancer. *Angiogenesis* 2012;15:141–150.