Tumor Response and Negative Distal Resection Margins of Rectal Cancer after Hyperthermochemoradiation Therapy

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Abstract. *Background: The safety of regional hyperthermia has been tested in locally advanced rectal cancer. The aim of this study was to assess the effects of shorter distal margins on local control and survival in rectal cancer patients who were treated with preoperative hyperthermochemoradiation therapy (HCRT) and underwent rectal resection by using the total mesorectal excision (TME) method. Patients and Methods: Ninety-three patients with rectal adenocarcinoma who received neoadjuvant HCRT (total radiation: 50 Gy) were included in this study. Surgery was performed 8 weeks after HCRT, and each resected specimen was evaluated histologically. Length of distal surgical margins, status of circumferential margins, pathological response, and tumor node metastasis stage were examined for their effects on recurrence and survival. Results: Fifty-eight (62.4%) patients had tumor regression, and 20 (21.5%) had a pathological complete response. Distal margin length ranged from 1 to 55 mm (median, 21 mm) and did not correlate with local recurrence (p=0.57) or survival (p=0.75) by univariate analysis. Kaplan-Meier estimates of recurrence-free survival and local recurrence for the <10 mm versus ≥10 mm groups were not significantly different. Positive circumferential margins and failure of tumors to respond were unfavorable factors in survival. Conclusion: Distal resection margins that are shorter than 10 mm but are not positive appear to be equivalent to longer margins in patients who undergo HCRT followed by rectal resection with TME. To improve the down-staging rate, additional studies are needed.*

Cancer of the lung and bronchus, prostate, and colorectum in men and of the lung and bronchus, breast, and colorectum in women continue to be the most common fatal type of cancer (1). Colorectal cancer alone is expected to account for 9% (26,580) of all male and 9% (24,790) of all female cancer deaths in 2010. More than one-third of colorectal carcinomas occur in the rectum. An important concern in rectal cancer is a high local recurrence rate, as opposed to that in colon cancer. Current guidelines from the National Comprehensive Cancer Network (2) recommend that all patients with clinical stage II/III rectal cancer should be treated with preoperative chemoradiation followed by total mesorectal excision (TME). In locally advanced rectal cancer, the addition of 5-fluorouracil (5-FU) to preoperative radiotherapy has been shown to improve the pathological complete response rate, tumor down-staging, and locoregional control compared with radiotherapy alone (3). Hyperthermia is a procedure that involves heating tissues to a high temperature ranging from 41 to 43˚C. This therapy has been combined with radiotherapy and/or chemotherapy for many years, with remarkable success in treating advanced and recurrent cancer. Hyperthermia affects cells in the S phase, inhibits sub-lethal damage repair, and improves oxygenation, making it an attractive therapy to combine with radiation and/or chemotherapy in the hopes of synergy (4). A previous study reported the additional effect of hyperthermia over preoperative radiation alone without any increase in adverse effects (5). Local hyperthermic therapy in combination with radiation has been shown to be less invasive; therefore, the use of local hyperthermia with radiation for local advanced rectal cancer has been recommended as a preoperative therapy.

Sphincter-preserving ultra-low anterior resection (LAR) is preferred to abdominoperitoneal resection (APR) with permanent colostomy for tumors located at least 2 cm proximal of the anal sphincter complex. Previous studies have shown that close distal margins are associated with an increased risk of mucosal recurrence and overall cancer recurrence (6). We have been conducting a clinical trial of regional hyperthermia in

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combination with chemoradiotherapy (hyperthermochemo-radiation therapy; HCRT) by using chronochemotherapy (7) for locally advanced rectal cancer (8). The advantages of preoperative HCRT include tumor down-staging, improved resectability, overall survival, and increased anal sphincter preservation (9). The aim of this study was to assess the effects of shorter distal margins on local control and survival in rectal cancer patients who were treated with preoperative HCRT and underwent rectal resection by using the TME method.

Patients and Methods

Patients and therapeutic strategy. Between January 2004 and March 2011, 93 patients with proven rectal adenocarcinoma who underwent HCRT followed by surgery were included in this study. During the diagnostic work-up, all patients underwent staging for distant metastases with computed tomography of the abdomen and thorax. T Stage was determined by magnetic resonance imaging, especially T2-weighted imaging before and after HCRT. The extent and location of the tumor were classified according to the TNM (10).

Preoperative HCRT. All patients in this study underwent preoperative HCRT at the Department of Radiology and Radiation Oncology, Gunma University Hospital. The radiation treatment was delivered by 10-MV x-rays through a three-field box technique. The clinical target volume encompassed the primary tumor and the entire mesorectal tissue. The total radiation dose was 50 Gy, with daily fractions of 2.0 Gy on 5 consecutive days per week. Chemotherapy consisted of 5-FU (250 mg/m^2 per day) and levofolinate calcium (25 mg/m^2 per day) administered by continuous infusion at night for 5 days a week in the 1st, 3rd, and 5th weeks of radiation. Two to five hyperthermia sessions were performed once a week with 8 MHz radiofrequency capacitive heating equipment (Thermotron-RF 8, Yamamoto Vinita Co., Ltd., Japan).

Surgery and postoperative therapy. Rectal resection was performed using the principles of TME 8 weeks after the completion of HCRT. A complete 6-month course of adjuvant 5-FU-based chemotherapy was typically recommended for all medically fit patients completing HCRT and curative surgery. The majority of the patients received oral 5-FU/leucovorin.

Pathology. Each resected specimen was examined for histological changes after HCRT according to the histological criteria of the Japanese Classification of Colorectal Carcinoma (11). Grades were assigned according to the amount of necrosis, degeneration, and lytic change of the tumor in the estimated total amount of the lesion (12). Grading of the histopathological response was performed by pathologists. The distal margin was defined as the gross distance between the distal edge of the tumor or post-treatment fibrosis, if present, and the distal mucosal resection margin.

Results

Patients' characteristics. Ninety-three patients with lower third rectal cancer were included in this study; the median age was 64 years. Sixty-eight patients were males, and 25 patients were females, with a male-to-female ratio of 2.7: 1. Patient characteristics are shown in Table I. All patients tolerated this regimen without hematological toxicity. The non-hematological toxicities observed were diarrhea in one patient and anorexia in one patient, both with grade 3 cancer. When the clinical pretreatment stage was compared with the pathologic results, down-staging of the T and N stages was possible in 51 (45.2%) and 54 patients (58.1%), respectively. The overall down-staging rate, including both the T and N stages, was 63.4% (59/93). Significant down-staging estimated in the primary lesion, in which tumors were undetectable by MRI and colonoscopy and negative results were obtained from biopsies, occurred in 47 patients (50.5%). Anterior resection was performed with colorectal anastomosis using a double-stapler device in 55 (59.1%) patients and with coloanal anastomosis using the hand-sewn technique in 21 (22.6%) patients. Abdominoperineal resection was performed in 17 (18.3%) patients. The overall sphincter preservation rate in the present study was 81.7% (76 out of 93 patients).

Table I. *Patients' characteristics.*

Characteristic	No. of cases (%)
Age, years	
Median (range)	64 (43-85)
Gender	
Male	68 (73.1)
Female	25 (26.9)
Stage	
II	39 (41.9)
III	50 (53.8)
IV	4 (4.3)
Surgical technique	
APR	17 (18.3)
LAR	76 (81.7)
Sphincter-preserving rate	81.7%

APR, Abdominoperitoneal resection; LAR, low anterior resection.

The pathological diagnoses obtained from surgical specimens are shown in Table II. Pathological complete response (pCR) of the primary tumor (Figure 1) and lymph nodes on the pathological specimen was observed in 20 patients (21.5%), and one patient showed pCR of the primary tumor but had residual tumor cells in the regional node. All patients had pathologically negative distal resection margins. Patients with pCR after HCRT had no better outcome than did those without pCR (Table II). pCR after HCRT might not be indicative of a prognostically favorable biological tumor profile. For the LAR specimen, the distal resection margins ranged from 1 to 55 mm (median 21 mm), not including the anastomotic staple rings. Fourteen (15.1%) patients who underwent LAR had distal resection margins of <10 mm. Seven (7.5%) patients were found to have positive circumferential margins with the pelvic side wall.

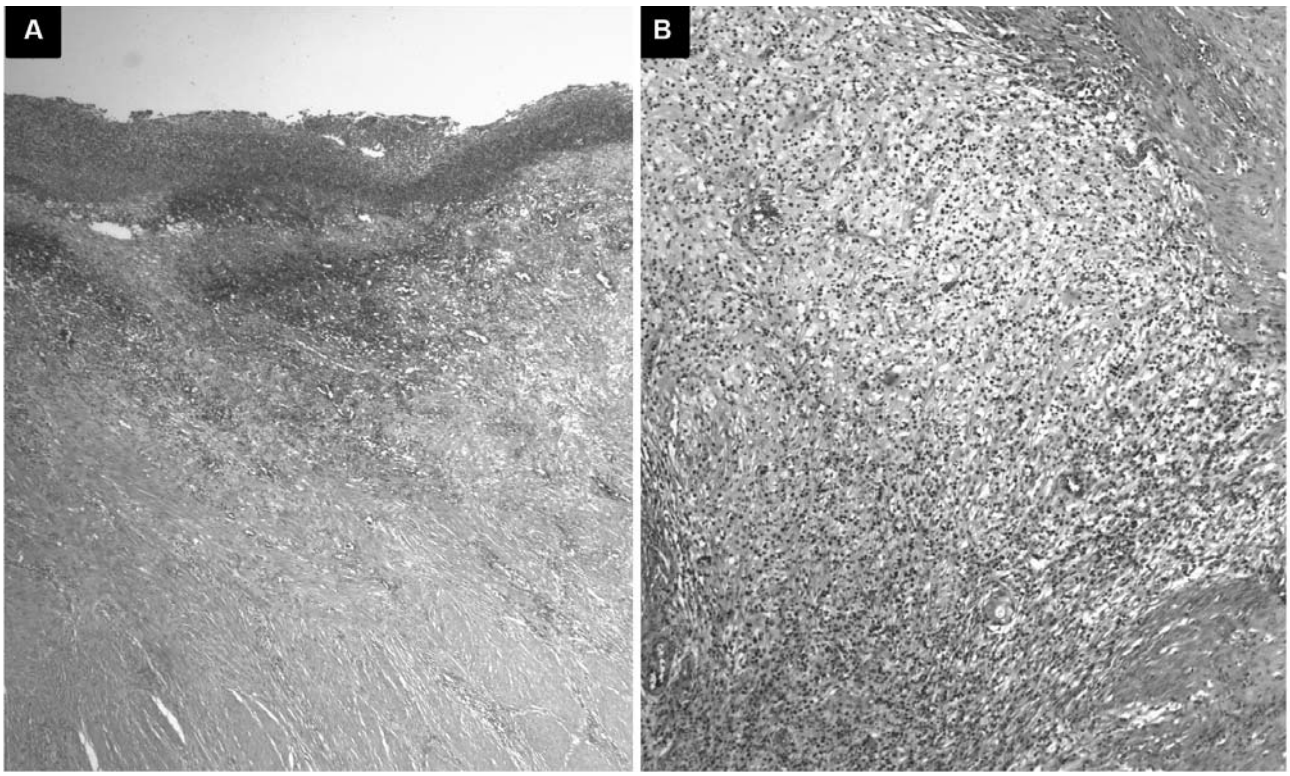

Figure 1. *Microscopic evaluation of tumor response. A: Low magnification (×25) image showing the ulcer at the tumor bed site. B: Higher magnification (×100) image deep in the wall of the fibrosis shows a high number of lymphocytes and fibroblasts scattered throughout the scar tissue.*

The median follow-up was 37 months (range 4-81 months) for all patients, and 84 patients were still alive at the time of writing. A distal margin length shorter than 10 mm did not correlate with local recurrence (p=0.57) or survival (p=0.73) by univariate analysis. Kaplan-Meier estimates of recurrence-free survival and local recurrence for the <10 mm *versus* >10 mm groups were not significantly different (Figure 2). However, positive circumferential margin and down-staging were related to overall survival (Figures 3 and 4).

Discussion

Whether LAR or APR is performed, ensuring that the intact rectum and mesorectum are removed with clear surgical margins is immensely important to prevent the local recurrence of rectal cancer. Preoperative chemoradiation can potentially increase the feasibility of sphincter-preserving resections by reducing the tumor volume and by defending against local tumor extensions (13). Given the additional effects of hyperthermia on chemoradiation therapy, HCRT may compensate for the narrow circumference and distal resection margins. The rate of

Table II. *Comparison of clinicopathologic variables.*

Distal resection margin	<10 mm n=14	≥10 mm n=79	*p*-value
Local recurrence	1 (7.1%)	3 (3.8%)	0.5745
Survival	13 (92.9%)	71 (89.9%)	0.7313
Pathologic circumferential resection margin	– n=86	+ n=7	*p*-value
Local recurrence	3 (3.5%)	1 (14.3%)	0.1795
Survival	79 (91.9%)	5 (71.4%)	0.029
Pathologic complete response	pCR (–) n=73	pCR (+) n=20	*p*-value
Local recurrence	4 (2.3%)	0 (0%)	0.2896
Survival	70 (91.9%)	20 (71.4%)	0.1006
Down-staging	– n=34	+ n=59	*p*-value
Local recurrence	3 (8.8%)	1 (1.7%)	0.1049
Survival	27 (79.4%)	57 (96.6%)	0.0187

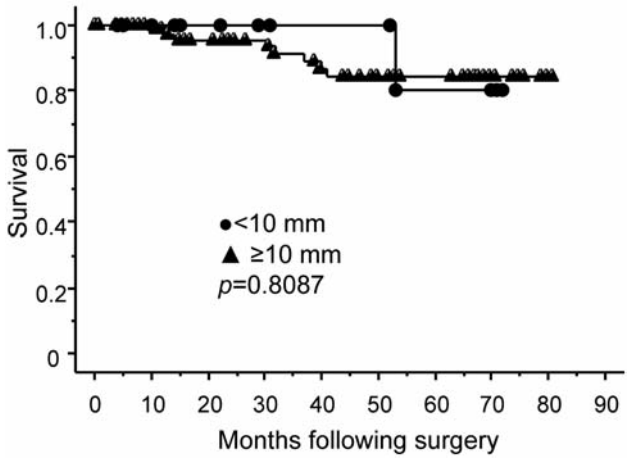

Figure 2. *Kaplan-Meier distribution of overall survival for patients with <10 mm distal margins versus those with ≥10 mm distal margins.*

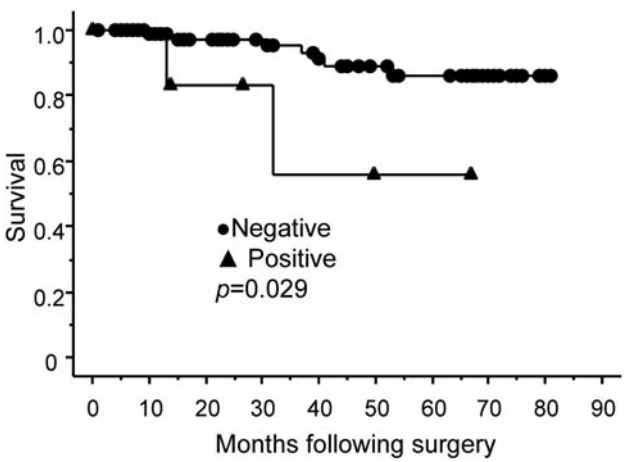

Figure 3. *Kaplan-Meier distribution of overall survival for patients with negative circumferential margins versus those with positive circumferential margin.*

pCR after neoadjuvant chemoradiation therapy ranged from 10 to 16% in various series examined in a review (14). Recent efforts incorporating newer cytotoxic and molecularly targeted agents into chemoradiation therapy regimens have been reported. Large randomized trials showed that the addition of weekly oxaliplatin to fluoropyrimidine-based chemoradiation led to an increase in grade 3/4 toxicity but no difference in pCR rates. Early phase trials evaluating the anti-epidermal growth factor receptor antibody cetuximab in combination with chemoradiation reported modest pCR rates of 5 to 12%. In this study, the pCR rate was 21.5%, which compares favorably with that observed in the other reports. Moreover, our study showed a greater reduction of adverse effects through the use of chronochemotherapy (8).

Tumor distance from the anal verge was significantly greater after HCRT, thus it was possible to carry out sphincter-preserving surgery in a larger proportion of the patients. The close distal resection margin, even if it was shorter than 10 mm, was not related to local recurrence and survival in this study. A positive circumferential margin was also not related to local failure (Table II). Obtaining negative distal and circumferential margins remains a goal of rectal cancer surgery after HCRT. The malignant potential and behavior of tumor after HCRT might be different from the pretreatment status. Further investigations are needed in order to archive better individual oncologic results.

Down-staging in this study was a good predictor of outcome. Down-staging oncological treatment has not been viewed as an additional therapy, and there is no evidence-based protocol to follow if the tumor fails to regress or increases in size after HCRT. Trials of chemotherapy with

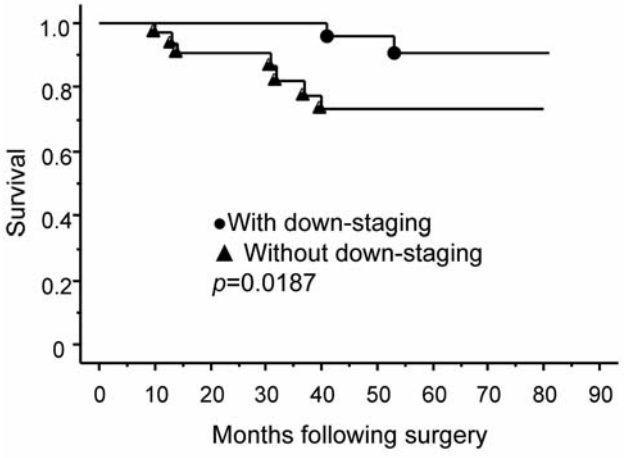

Figure 4. *Kaplan-Meier distribution of overall survival for patients with down-staging versus those without down-staging.*

new biologic agents in a preoperative setting for patients whose disease fails to down-stage after HCRT are needed. New techniques for rectal cancer surgery also need to be investigated. However, a prospective randomized study that inspects the adequacy and safety of the distal and circumferential resection margins would be difficult to set up. The limitations of our study include the small number of patients and the short follow-up period. The results of our study are encouraging in terms of the rate of down-staging, pCR, and sphincter-preserving surgery. The favorable results of our study might be due to additional hyperthermia with chemoradiation therapy. Further investigations to improve the down-staging rate of HCRT for rectal cancer are required.

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