

Postoperative Complications after Preoperative Chemoradiotherapy Combined with Hyperthermia in Locally Advanced Rectal Cancer

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We investigated whether regional hyperthermia (HT) increased post-surgical complications in patients with locally advanced rectal cancer treated with preoperative concurrent chemoradiotherapy (CCRT). Between 1996 and 2007, 205 patients treated with preoperative CCRT and curative surgery were evaluable for the analysis of acute and late toxicities. A total dose of 39.6 Gy or 45 Gy was delivered concurrently with one or two cycles of chemotherapy (5-fluorouracil, leucovorin). Eighty-eight patients received regional HT twice a week using an 8-MHz radiofrequency capacitive heating device. Surgery was performed 4~6 weeks after the completion of preoperative CCRT. The median age was 59 years (range, 18~83) and the median follow-up period was 61 months (range, 2~191). The 5-year overall survival and complication-free survival rate of all patients was 77.4% and 73.7%, respectively. Early leakage, delayed leakage, anastomotic stricture, fistula, and small bowel obstruction occurred in 1.0%, 2.9%, 1.5%, 5.9%, and 17.1%, respectively. HT did not increase all kinds of complications. The 5-year complication-free survival rate was 71.8% in the non-HT group and 76.3% in the HT group ($p=0.293$). Regional HT did not increase postoperative complications in patients with locally advanced rectal cancer treated with preoperative CCRT followed by curative surgery.

Key Words: Rectal Cancer, Preoperative, Chemoradiotherapy, Hyperthermia, Complication

Introduction

Locally advanced rectal cancer has been reported to have high rates of local recurrence after surgical resection alone.¹⁾ In 1990, a National Institutes of Health consensus conference recommended postoperative adjuvant chemoradiotherapy for patients with Stage II or III rectal cancer.²⁾ A large randomized control study showed that preoperative concurrent chemoradiotherapy (CCRT) was superior to postoperative CCRT in terms of local control and toxicities, although there was no difference in the disease-free and overall survival rate.³⁾ As a result, preope-

rative CCRT has become a standard component of multimodal treatment for patients with locally advanced rectal cancer.

Hyperthermia (HT), known as a potent radiosensitizer, has been shown to increase not only the response rates, but also clinical outcomes to radiotherapy (RT) in various cancers, including rectal cancer.⁴⁻⁶⁾ Two randomized trials comparing pre-operative RT to hyperthermoradiotherapy in locally advanced rectal cancer reported no significant difference of acute toxicity.^{7,8)} Recently HT has been combined with CCRT to increase the response and several pilot to phase II studies also reported that HT could be safely combined with preoperative CCRT in locally advanced rectal cancer.⁹⁻¹²⁾ However, there are few reports about the late complications after surgery following pre-operative hyperthermo(chemo)radiotherapy in locally advanced rectal cancer despite the long-term use of HT. In addition, most studies on complications were conducted using the BSD-2000 system (BSD Medical Corporation, Salt Lake City, Utah, USA); recently in Korea, capacitive type machines are being

This work was supported by a grant from the Chunma Medical Research Foundation, Korea (2013).

Received 30 April 2014, Revised 23 May 2014, Accepted 30 May 2014

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increasingly used.

Thus, we retrospectively analyzed the impact of HT using a capacitive type machine on postoperative complications in locally advanced rectal cancer treated with preoperative CCRT followed by curative surgery.

Materials and Methods

1. Patients

We previously reported the clinical outcomes of 235 patients with histologically-confirmed, locally advanced rectal adenocarcinoma (cT3-4 or N+), who completed preoperative CCRT with or without HT followed by curative resection from 1996 to 2007 [6]. Only tumors located within 10 cm from the anal verge were included. Patients with metachronous or synchronous double primary cancers, rectosigmoid or sigmoid tumors (above 10 cm from the anal verge), early distal rectal tumors (cT1-2N0), or distant metastasis at the time of diagnosis or at the time of surgery were excluded.

In this study, 205 patients who were evaluable for acute and late toxicities after surgery were analyzed. Patients with a follow-up period of less than 6 months after surgery (n=12) or who had previous abdominal surgery history (n=5) or who received postoperative RT (n=13) were excluded.

2. Treatment

Radiotherapy was delivered to the whole pelvis with three or four fields in a prone position. The total dose of RT was 39.6 Gy or 45 Gy with a daily dose of 1.8 Gy over 5 weeks.

Chemotherapy commenced concurrently with RT, and a total of 2~3 cycles of chemotherapy were administered before surgery. All patients received 5-fluorouracil and leucovorin; 5-fluorouracil ($425 \text{ mg/m}^2/\text{day}$) was continuously infused for 5 days during the first and last weeks of RT, and leucovorin (20 mg/kg) was infused on each day of chemotherapy. Mitomycin C (10 mg/m^2) was infused on day 1 in 161 patients.

Regional HT was delivered to the pelvis twice a week during preoperative CCRT using an 8-MHz radiofrequency capacitive heating device (Cancermia GHT-RF8; Green Cross Medical, Yongin). Each hyperthermic session began immediately after RT and continued for 40~60 minutes per session. The median number of HT treatments was eight (range, 1~

12). Intrarectal temperature was measured in 65 patients using a thermocouple. Temperature was measured 1~9 times in each patient; the highest temperatures were $39.7\sim0.8^\circ\text{C}$ (range, $37.9\sim42.4^\circ\text{C}$).

Surgery was performed 4~6 weeks after the completion of RT. The surgeon determined the type of surgery and total mesorectal excision was routinely performed. Adjuvant chemotherapy was administered in 198 patients. The same regimen as the preoperative treatment, except mitomycin C, was delivered to 164 patients for up to 12 cycles. Thirty-four patients received oral 5-fluorouracil agents.

3. Complications

Complications were evaluated through medical records, including physical examinations, colonofiberscopy and diagnostic images. Early leakage was defined as leakage that occurred within one month after surgery and delayed anastomotic leakage was defined as leakage thereafter. An anastomotic stricture was considered to be present when it was not possible to traverse the anastomosis site with a flexible colonofiberscope. As to small bowel obstruction, complications that required hospitalization or more serious ones were recorded regardless of the causes. Complication profiles of patients with locoregional failures were investigated during the disease-free period. The median follow-up period from the date of surgery to the last hospital follow-up was 59 months (range, 2~188 months) and 70.5 months (range, 10~179 months), respectively.

4. Statistics

Patients were classified into the non-HT or HT group according to the use of HT. Categorical variables were compared with the chi-square test or Fisher's exact test, and continuous ones with the student t-test for a comparison of the two groups. The survival rate was calculated from the first day of CCRT to the date of the event using the Kaplan-Meier method. The complication-free survival rate was calculated from the date of surgery. Log-rank test was used to test the significance of HT for survival. Statistical evaluations were performed using the SPSS statistics 20 software (SPSS, Chicago, IL). A p value <0.05 was considered as significant.

Results

The median age was 59 years (range, 18~83 years). The patient and tumor characteristics except gender distribution were not different in both groups (Table 1). The mean distance from anal verge to tumor was not different in both groups (6.3~2.9 cm in non-HT group vs. 6.4~2.8 cm in HT group, p=0.940).

The 5-year overall, disease free, locoregional relapse-free and distant metastasis-free survival rates of all patients was 77.4%, 75.2%, 93.8% and 78.8%, respectively (Fig. 1). Complications occurred in 52 (25.4%) of all patients until the last follow-up, and the complication-free survival rate was 73.7% at 5 years. Early leakage, delayed leakage and anastomotic stricture occurred in 2 (1.0%), 6 (2.9%) and 3 (1.5%) patients, respectively. Fistula developed in 12 (5.9%) patients; rectovaginal in 10, rectocutaneous in one, and enterorectal in one. Small bowel obstruction developed in 35 (17.1%) patients; 18 patients were treated conservatively, 15 required operation and

two died.

The details of complications according to the use of HT are summarized in Table 2. Complications occurred in 33 (28.2%) patients from non-HT group and 19 (21.6%) patients from HT group (p=0.281). The frequencies of early leakage, small bowel obstruction, and fistula formation were not different in both groups. The frequency of severe small bowel obstruction, requiring surgery or resulting in death, was 6.8% and 10.2% in the non-HT and HT groups (p=0.384). Delayed leakage occurred more in the non-HT group (5.1% vs. 0%, p=0.038). Complication-free survival curves of non-HT and HT groups (Fig. 2) were not different (71.8% vs. 76.3% at 5 years, p=0.293). In addition, the number of HT was not related to the incidence of complications.

In patients who received sphincter preservation surgery, the frequency of temporary diverting ileostomy or colostomy was similar in both groups (28.7% in non-HT group vs. 32.9% in

Table 1. Patient and tumor characteristics.

| | Patients (%) | | | p-value | |
|------------------------------|----------------|---------------|-------------------------------|---------|--|
| | Hyperthermia | | Hyperthermia (+) (n=88) | | |
| | (-) (n=117) | (+) (n=88) | | | |
| Age (y) | | | | | |
| Median (range) | 58 (18~81) | 60 (33~83) | | 0.304 | |
| Sex | | | | | |
| Male | 43 (36.8) | 73 (83.0) | | <0.001 | |
| Female | 74 (63.2) | 15 (17.1) | | | |
| Stage | | | | | |
| cT3 | 115 (98.3) | 85 (96.6) | | 0.653 | |
| cT4 | 2 (1.7) | 3 (3.4) | | | |
| N(−) | 77 (65.8) | 59 (67.0) | | 0.853 | |
| N(+) | 40 (34.2) | 29 (33.0) | | | |
| Radiation dose | | | | | |
| 39.6 Gy | 61 (52.1) | 37 (42.1) | | 0.152 | |
| 45.0 Gy | 56 (47.9) | 51 (57.9) | | | |
| Surgery | | | | | |
| Abdominoperineal resection | 16 (13.7) | 15 (17.0) | | <0.900 | |
| Ultra-low anterior resection | 27 (23.1) | 20 (22.7) | | | |
| Low anterior resection | 73 (62.4) | 53 (60.2) | | | |
| Transanal excision | 1 (0.9) | 0 | | | |

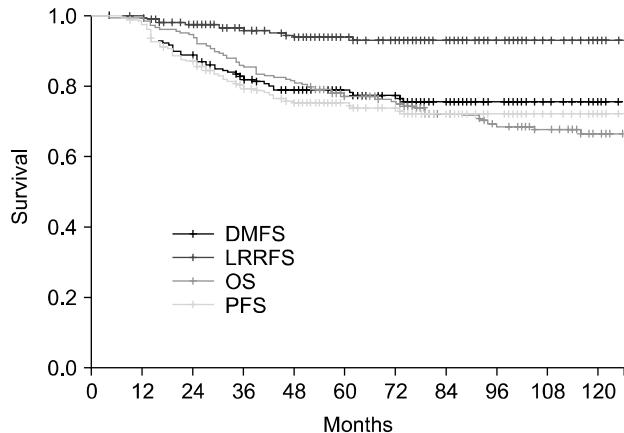


Fig. 1. Overall, disease-free, locoregional relapse-free, and distant metastasis-free survival rates of all patients.

Table 2. Complications after surgery.

| | Hyperthermia (-) (n=117) | Hyperthermia (+) (n=88) | p-value |
|-------------------------|--------------------------------|-------------------------------|---------|
| Early leakage | 2 (1.7%) | 0 | 0.508 |
| Delayed leakage | 6 (5.1%) | 0 | 0.038 |
| Small bowel obstruction | 20 (17.1%) | 15 (17.0%) | 0.993 |
| Anastomotic stricture | 1 (0.9%) | 2 (2.3%) | 0.578 |
| Fistula | 9 (7.7%) | 3 (3.4%) | 0.196 |

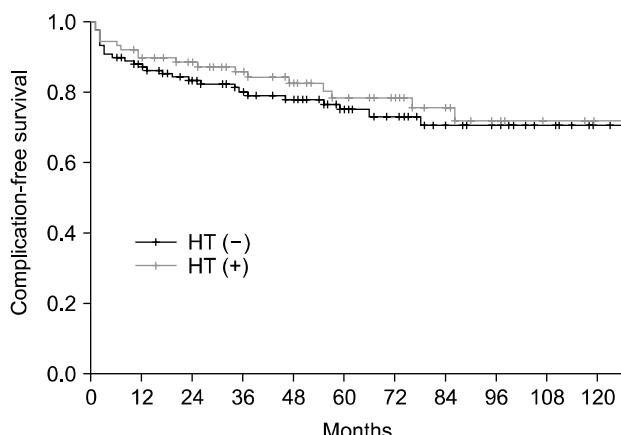


Fig. 2. Complication-free survival rates according to the use of hyperthermia ($p=0.293$).

HT group, $p=0.556$); of these, 25 patients received reduction surgery thereafter. Colostomy was performed newly on ten patients due to complications (8 in non-HT vs. 2 in HT group). Finally, the number of patients without ileostomy or colostomy was similar in both groups at the last follow-up (79.2% of non-HT group and 76.7% in HT group, $p=0.694$).

Discussion

Chemotherapy is concurrently used with radiotherapy in locally advanced rectal cancer because it could increase the response and local control rates without increasing postoperative morbidity and anastomotic leak rates.¹³⁾ Recently, HT has been attempted to be combined with CCRT in locally advanced rectal cancer; however there is little information about the potential postoperative complications after hyperthermochemoradiotherapy. However, this study showed that HT did not increase the postoperative complications after CCRT.

Van der Zee et al.⁸⁾ reported the results of the phase III study, comparing RT with and without HT in locally advanced cervical, rectal and bladder cancer. A total of 358 patients were enrolled. In primary or recurrent rectal cancer patients, a total dose of 46~50 Gy with or without a boost of 10~24 Gy was delivered. HT was given once weekly during the period of RT. In all patients, acute grade 3~4 radiation-related toxicities were seen in 4% of patients (2.2% in RT+HT group vs. 5.9% in RT group). The actuarial cumulative incidence of

Table 3. Ileostomy or colostomy status in patients who received sphincter preservation surgery.

| | Hyperthermia (-) (n=101) | Hyperthermia (+) (n=73) | p-value |
|----------------------------------|--------------------------------|-------------------------------|---------|
| Immediately after surgery | | | |
| Presence | 29 (28.7) | 24 (32.9) | 0.556 |
| No | 72 (71.3) | 49 (67.1) | |
| At the last follow-up | | | |
| Presence | 21 (20.8) | 17 (23.3) | 0.694 |
| No | 80 (79.2) | 56 (76.7) | |

grade 3~4 toxic effects at 2 years was 12% in each group. Although detailed toxicity profiles were not described, the acute and late toxicities did not differ according to the use of HT.

Schulze et al.¹⁴⁾ reported the toxicities in 43 rectal cancer patients who were enrolled in the phase II/III trial of preoperative CCRT with (19 patients) or without HT (27 patients). A total dose of 45 Gy was given concurrently with 5-fluorouracil and leucovorin. HT was given once weekly during the period of RT using the BSD-2000 system. Cutaneous or gastrointestinal side effects occurred slightly more frequently in the HT group during CCRT; however the differences were not statistically different. We analyzed the postoperative complications of 205 patients treated with preoperative CCRT±HT followed by surgery. The frequencies of early leakage, small bowel obstruction and fistula were similar between the non-HT and HT group. Also, delayed leakage was more frequent in the non-HT group.

The early anastomotic leakage rate after sphincter-saving resection has been reported as 3~20%.¹⁵⁻¹⁷⁾ Kim et al.¹⁸⁾ reported 3.4% of early leakage in 703 patients treated with preoperative or postoperative CCRT. In the current study, the early leakage rate after surgery occurred only in two (1.7%) patients treated with preoperative CCRT without HT. Patients treated with CCRT with HT had no early leakage. Schulze et al.¹⁴⁾ reported that the insufficiency of anastomosis occurred in 10% of patients and its development was not influenced by the use of HT in a phase II/III trial comparing preoperative CCRT alone to HT.

Small bowel obstruction is believed to occur less frequently

after preoperative RT when compared to postoperative RT. Kim et al.¹⁸⁾ reported that small bowel obstruction related to radiation enteritis was more frequent in patients treated with postoperative CCRT when compared to those treated with pre-operative CCRT (1.4% vs. 0%, p=0.042). In the current study, HT did not increase the frequency of small bowel obstruction with any causes when combined with preoperative CCRT (17.1% vs. 17%, p=993). Schulze et al.¹⁴⁾ reported that ileus occurred in 11% of patients, where HT also did not influence its development after surgery following preoperative CCRT.

Horie et al.¹⁹⁾ retrospectively compared the outcomes of 29 patients who underwent preoperative CCRT±HT followed by curative surgery for lower rectal cancer. A total dose of 40.5 Gy (1.5 Gy bid) with 5-fluorouracil, given as suppositories, was given. Sixteen patients received HT using an 8-MHz capacitive type machine (Thermotron RF-8, Yamamoto Vinita, Tokyo, Japan). The mean follow-up period was 4.9±2.8 years. Postoperative ileus occurred in 7% of patients. There was no anastomotic leakage after low anterior resection. Even though complications were not reported separately according to the use of HT, the frequencies of anastomotic leakage after a low anterior resection and postoperative ileus were not different from those of 48 patients who underwent surgical resection alone.

Recently, quality of life (QoL) as well as treatment outcome has been considered to be important in decision making. Schulze et al.¹⁴⁾ reported the quality of life as well as toxicities in locally advanced rectal cancer patients treated with preoperative CCRT with or without HT. QoL was assessed four times using the Gasrointestinal Quality-of-life Index²⁰⁾; before the start of preoperative CCRT (mean: 88±2 days before surgery), after the end of the CCRT (mean: 9±2 days before surgery), early after the surgery (mean: 53±4 days after surgery) and during the long-term follow-up (mean: 849±77 days after surgery). Although the domains ‘Symptoms’, ‘Physical functions’, ‘Social life’ and ‘Medical treatment’ at the end of the CCRT seemed to be worse in the HT group, HT did not result in a significant reduction of QoL. In the long-term follow-up, both groups reported equally good QoL scores.

Conclusions

Regional HT did not increase postoperative complications in locally advanced rectal cancer treated with preoperative CCRT. However, the retrospective nature of this study and the rarity of the results of large prospective studies limit the definite conclusions regarding the complications of HT combined with preoperative CCRT; hence a prospective randomized controlled trial is warranted.

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국소 진행성 직장암의 수술전 동시 항암방사선치료와 온열치료병합시 수술후 부작용

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예 지 원

국소 진행성 직장암 환자에서 수술 전 항암방사선동시요법으로 치료시 추가적인 고주파 온열치료 유무가 수술 후 부작용에 미치는 영향을 분석하였다. 1996년부터 2007년 사이, 본원에서 수술 전 항암방사선동시요법과 근치적 수술을 시행한 환자 205명을 대상으로 급, 만성부작용을 분석하였다. 총 방사선치료선량은 39.6 Gy에서 45 Gy였고 1회 내지 2회의 항암약물치료(5-fluorouracil, leucovorin)를 동시에 시행하였다. 88명의 환자가 주 2회, 8-MHz 고주파 온열치료기를 이용한 국소 온열치료를 시행하였다. 외과적 수술은 수술 전 치료 완결 후 4~6주 경과하여 시행하였다. 환자군의 나이 중앙값은 59세(18세~83세)이고 추적관찰기간 중앙값은 61개월(2개월~191개월)이었다. 전체 환자에서 5년 전체생존율과 무합병증 생존율은 77.4%와 73.7%였다. 각각의 조기 누출, 지연 누출, 연결부 협착, 누공, 소장폐쇄의 발생빈도는 1.0%, 2.9%, 1.5%, 5.9%, 그리고 17.1%였다. 온열치료는 모든 종류의 부작용을 증가시키지 않았다. 온열치료를 실시하지 않은 군과 온열치료군 간의 5년 무합병증 생존율은 71.8%와 76.3%였다($p=0.293$). 온열치료는 수술전 항암방사선동시요법 후 근치적 수술을 시행하는 국소 진행 직장암 환자의 수술후 부작용을 증가시키지 않는다.

중심단어: 직장암, 수술 전, 항암방사선치료, 온열치료, 부작용