Deep regional hyperthermia combined with modern concurrent chemoradiotherapy increases T-downstaging rate in locally advanced rectal cancer

Yuxia Wang a, Siyi Lu b, Yuxia Shao a, Ran Peng a, Xuemin Li a, Junjie Wang a and Hao Wang a, c

a Department of Radiation Oncology, Peking University Third Hospital, Beijing, PR China; b Department of General Surgery, Peking University Third Hospital, Beijing, PR China; c Cancer Center, Peking University Third Hospital, Beijing, PR China

ABSTRACT

Background: Deep regional hyperthermia might have an additional effect on radiotherapy in treating locally advanced rectal cancer (LARC). This study aimed to investigate the role of hyperthermia combined with modern preoperative concurrent chemoradiotherapy (CRT) for LARC.

Methods and materials: From 2012 to 2018, 152 consecutive patients with LARC treated with neoadjuvant chemoradiation were enrolled and analyzed retrospectively. Pelvic radiotherapy (45–50 Gy) was delivered as volumetric modulated arc therapy (VMAT), concurrently with capecitabine chemotherapy. Fifty patients received hyperthermia combined with CRT (HCRT group) twice a week. Treatment response and outcomes were compared between the two groups. Furthermore, the relationships between peripheral blood neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and lymphocyte-to-monocyte ratio (LMR) in response to hyperthermia were analyzed.

Results: Patients treated with hyperthermia had a significantly higher T-downstaging rate than those without hyperthermia (82.0 vs. 62.7%; p = .016). Hyperthermia was an independent favorable predictor of T-downstaging (odds ratio [OR] = 2.473; 95% confidence interval [CI] 1.050–5.826; p = .038). In the HCRT group, a pre-therapeutic elevated NLR (≥3) was associated with a higher T-downstaging rate (100.0 vs. 73.5%; p = .043). However, NLR was not associated with the T-downstaging rate in the CRT group. Five-year rates of locoregional recurrence-free survival (96.8 vs. 94.7%, p = .959), disease-free survival (DFS; 61.4 vs. 79.3%, p = .242), and overall survival (OS; 92.7 vs. 89.8%, p = .831) were not statistically different between the CRT and HCRT groups.

Conclusions: Hyperthermia can improve preoperative treatment response in LARC. Pretreatment NLR may be a predictive factor for hyperthermia.

Introduction

Preoperative chemoradiotherapy (CRT) followed by total mesorectal excision (TME) is the standard of care for locally advanced rectal cancer (LARC). Despite these treatments, pelvic recurrences occur in 10% of patients and distant metastasis develops in at least 20% of patients with LARC [1]. Hyperthermia (HT) has been demonstrated to enhance the tumor-killing effect of radiotherapy or chemotherapy by increasing blood flow in hypoxic areas or killing resistant tumor cells via direct cytotoxic effects [2]. For LARC, previous studies indicated that HT might increase the response rate or prolong overall survival (OS) in combination with CRT [3–6]. However, in most of these studies, radiotherapy and concurrent chemotherapy regimens were vastly different from the current standard regimens. Therefore, it is necessary to explore the role of HT under current standard preoperative concurrent chemoradiotherapy.

Predictive markers are needed to select appropriate patients for HT treatment. However, very few studies have reported the predictive markers for HT in rectal cancer [6]. HT can influence the immune system and mediate protective anti-tumor immune responses [7]. An increasing number of studies indicate that tumor-related inflammatory and immune markers, such as the lymphocyte-to-monocyte ratio (LMR), neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), are associated with tumor response and prognosis in rectal cancer [8–10]. Thus, these indexes might help predict the efficacy of HT in LARC. However, there have been few reports about the role of peripheral inflammatory markers in HT for LARC.

Therefore, our study aimed to evaluate the impact of deep regional HT combined with CRT for LARC. Moreover, we also investigated the role of inflammation-related parameters in predicting tumor response to HT treatment.
Materials and methods

Patients

This retrospective study included 152 consecutive patients with LARC at the Department of Radiation Oncology, Peking University Third Hospital, between October 2012 and November 2018 (Figure 1). Among these, 50 patients received HT combined with concurrent CRT before surgery (HCRT group), and 102 patients received CRT only as neoadjuvant therapy (CRT group). Ethical approval was obtained from the Ethics Committee of the Peking University Third Hospital (IRB00006761-M2020491). The research ethics committee waived the requirement for informed consent. The inclusion criteria were as follows: (1) histologically confirmed rectal adenocarcinoma; (2) clinical stage T3–4 or N+ (Union for International Cancer Control [UICC] Stage II or III); and (3) received complete neoadjuvant CRT followed by curative TME. The exclusion criteria were as follows: (1) patients who received immunosuppressive or anti-inflammatory treatments before CRT; (2) patients with autoimmune disease, hematological disease and acute infection; and (3) patients confirmed with other cancers before being diagnosed with rectal cancer. HT was indicated in all patients diagnosed with T3–4/N+ rectal cancer except (1) those who were reluctant to HT, (2) those who had a tendency to experience severe bleeding, (3) those who had severe infections and could not tolerate HT, (4) those with cardiac problems or (5) those who had metal implants or pacemakers that could cause heat accumulation (overheating).

Endorectal ultrasonography, pelvic magnetic resonance imaging and computed tomography were used for clinical staging according to the 8th edition of the American Joint Committee on Cancer.

Treatment

Preoperative radiotherapy with a dose ranging from 45 to 50 Gy was administered to the whole pelvis in 25 fractions over 5 weeks, and radiotherapy was delivered as VMAT for all patients. Concurrent chemotherapy with a daily dose of 1650 mg/m² capecitabine was administered orally and divided into two equal doses per day. Surgery was scheduled 5–14 weeks after completion of radiotherapy. Radical resection was performed according to the principle of TME by four experienced colorectal surgeons at the Peking University Third Hospital. The interval between radiation and surgery was 9.820 ± 2.103 weeks and 10.154 ± 2.362 weeks in the CRT and HCRT groups, respectively (Table 1). Four to six cycles of postoperative 5-fluorouracil-based chemotherapy were recommended to all patients after complete resection.

External heating was delivered once or twice weekly during radiotherapy with a radio frequency HT treatment system (SR1000, Xianke Medical Equipment, Shenzhen City, Guangdong Province, China) at a frequency of 40.68 MHz [11]. The therapeutic time was 40–60 min per treatment and at least 48 h between the two treatments. The target temperature was 40.5–43°C. The temperature was measured intrarectally on the surface of the tumor using a single flexible probe in 10 patients. The cumulative equivalent minutes at 43°C (CEM 43°C) were calculated according to a previously described method [12,13], and the mean CEM 43°C was 1.10 min (range 0.34–2.34 min). For the other 40 patients who refused intrarectal temperature measurement, HT parameters were set according to the doctor’s experience, and power outputs were increased up to patients’ tolerances. Local HT was performed within 1 h before or after radiotherapy. A water bolus was used for cooling and energy coupling. The median number of HT sessions was 7 (range, 2–10), and 96.0% (48/50) of patients received four or more HT sessions.

Approximately, 84.3% (86/102) and 74.0% (37/50) of patients received 4–6 cycles of XELOX or capecitabine for postoperative chemotherapy in the CRT and HCRT groups, respectively (p = .128).

Endpoints and statistical analysis

Pearson’s chi-squared or Fisher’s exact test and Student’s t-test were used to compare categorical and continuous variables, respectively. A logistic regression model was used to determine whether a factor was an independent predictor of pathological response in the multivariate analysis. For the survival analyses, OS was defined as the time from TME to death or last follow-up, and disease-free survival (DFS) was defined as the time from TME to the first event of recurrent disease, death, or last follow-up. Locoregional recurrence-free survival (LRFS) was measured from the date of TME to the date of first locoregional recurrence or last follow-up visit or death without recurrence. Survival curves were derived from Kaplan–Meier estimates and compared using log-rank tests. All blood specimens were tested in the laboratory of our hospital within one week before radiotherapy. The NLR was calculated as the absolute neutrophil count/absolute lymphocyte count. PLR was calculated as platelet count/absolute lymphocyte count. LMR was calculated as lymphocyte count/absolute monocyte count. The systemic immune-inflammation index (SII) was calculated as platelet count × neutrophil count/lymphocyte count. For NLR, the cutoff value was 3.0, which was derived from previous studies [9,14,15]. Other peripheral indexes that lacked previous reports about cutoff value, receiver-operating characteristic (ROC) analysis, relative area under the curve (AUC) statistics and Youden’s
test were used to determine the optimal cutoff value. All statistical analyses were performed using IBM SPSS software version 23 (IBM Corp., Armonk, NY), and a p value < .05 was considered statistically significant.

**Results**

**Patient and tumor characteristics**

According to the inclusion and exclusion criteria, 152 patients were included in the study. One hundred and two patients received CRT treatment, and 50 patients were treated with the same regimens plus deep regional HT. The patient characteristics are summarized in Table 1. The baseline characteristics of the two groups were comparable. No significant differences were found in age, sex, pretreatment clinical tumor stage or surgery type. Regarding the pathologic characteristics after neoadjuvant treatment, the proportion of ypT stage, ypN stage, tumor regression grade, lymphovascular space invasion, perineural invasion and resection margin did not differ significantly between the CRT and HCRT groups (Table 1).

**Treatment response**

In all patients, the rates of T-downstaging, N-downstaging and pathologic complete response were 69.1, 64.5 and 17.1%, respectively. Patients treated with HCRT had a significantly higher T-downstaging rate than those treated with CRT alone (82.0 vs. 62.7%, p = .016, Table 2). In univariate analysis, factors associated with T-downstaging rates were HT (OR = 2.705; p = .018), higher cT stage (OR = 7.537; 95% CI 1.461–38.880; p = .016), and NLR ≥ 3 (OR = 2.941; 95% CI 1.195–7.238; p = .019, Table 3). In the multivariate analyses, HT (OR = 2.473; 95% CI 1.050–5.826; p = .038) and NLR ≥ 3 (OR = 3.324; 95% CI 1.262–8.751; p = .015) remained as independent significant predictors for T-downstaging (Table 4). Among the patients who underwent intra-rectal temperature measurement, the T-downstaging rate was 70.0% (7/10), and the mean CEM 43°C showed no difference in downstaging and non-downstaging patients (1.23 vs. 0.81, p = .413).

Among the patients treated with HCRT, the T-downstaging rate was significantly higher in patients with baseline NLR ≥ 3 than in those with baseline NLR < 3 (100.0 vs. 73.5%, p = .043; Table 5). In patients with baseline NLR < 3, the T-downstaging rate in the two treatment groups was similar (75.0 vs. 58.1%, p = .115; Table 5). As for PLR, LMR and SII, the ROC analysis showed that all AUCs were less than 0.6; therefore, no optimal cutoff value was derived for these indexes (data not shown).

The pCR rates for the CRT and HCRT groups were 14.7 and 22.0%, respectively (p = .262). The R0 resection rates were 99.0 and 100.0% for the CRT and HCRT groups, respectively (p = 1.000).

| Table 1. Patients and tumor characteristics. |
|----------------------------------------------|
| **CRT group** | **HCRT group** | **p Value** |
| Age (year) | 59.2 ± 12.5 | 60.6 ± 11.6 | .496 |
| Sex | | | .112 |
| Male | 69 (67.6%) | 40 (80.0%) | – |
| Female | 33 (32.4%) | 10 (20.0%) | – |
| Tumor distance from the anal verge | | | .112 |
| <5 cm | 26 (25.5%) | 19 (38.0%) | – |
| 5–10 cm | 76 (74.5%) | 31 (62.0%) | – |
| cT | | | .125 |
| 2 | 7 (6.8%) | 1 (2.0%) | – |
| 3 | 79 (77.5%) | 35 (70.0%) | – |
| 4 | 16 (15.7%) | 14 (28.0%) | – |
| cN | | | .452 |
| N0 | 21 (20.6%) | 13 (26.0%) | – |
| N+ | 81 (79.4%) | 37 (74.0%) | – |
| Interval between CRT and surgery | 9.820 ± 2.103 | 10.154 ± 2.362 | .379 |
| Type of resection | | | .850 |
| Miles | 32 (31.4%) | 18 (36.0%) | – |
| Dixon | 59 (57.8%) | 27 (54.0%) | – |
| Hartmann | 11 (10.8%) | 5 (10.0%) | – |
| ypT | | | .732 |
| 0 | 16 (15.7%) | 12 (24.0%) | – |
| 1 | 10 (9.8%) | 5 (10.0%) | – |
| 2 | 35 (34.3%) | 15 (30.0%) | – |
| 3 | 39 (38.2%) | 18 (36.0%) | – |
| 4 | 2 (2.0%) | 0 (0%) | – |
| ypN | | | .601 |
| 0 | 87 (85.3%) | 41 (82.0%) | – |
| + | 15 (14.7%) | 9 (18.0%) | – |
| Lymphovascular space invasion | | | .273 |
| Yes | 7 (6.9%) | 1 (2.0%) | – |
| No | 95 (93.1%) | 49 (98.0%) | – |
| Perineural invasion | | | .746 |
| Yes | 12 (11.8%) | 5 (10.0%) | – |
| No | 90 (88.2%) | 45 (90.0%) | – |
| Resection margin | | | 1.000 |
| Positive | 1 (1.0%) | 0 (0%) | – |
| Negative | 101 (99.0%) | 50 (100.0%) | – |

CRT: concurrent chemoradiotherapy; HCRT: hyperthermia plus concurrent chemoradiotherapy.
chemoradiotherapy.

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### Table 2. Relationship between the tumor response and hyperthermia.

| Variable | CRT (%) | HCRT (%) | p Value |
|----------|---------|----------|---------|
| T-downstaging | .016 | | |
| No | 38 (37.3) | 9 (18.0) | – |
| Yes | 64 (62.7) | 41 (82.0) | – |
| N-Change | .761 | | |
| cNO – pN0 | 19 (18.6) | 11 (22.0) | – |
| cNO – pN+ | 2 (2.0) | 2 (4.0) | – |
| cN ± pN0 | 68 (66.7) | 30 (60.0) | – |
| cN ± pN+ | 13 (12.7) | 7 (14.0) | – |
| pCR | .262 | | |
| Yes | 15 (14.7) | 11 (22.0) | – |
| No | 87 (85.3) | 39 (78.0) | – |

CRT: concurrent chemoradiotherapy; HCRT: hyperthermia plus concurrent chemoradiotherapy.

### Table 3. Univariate analysis of T-downstaging rates by clinical characteristics in all patients.

| Characteristic | No. of patients | T-downstaging |
|----------------|-----------------|---------------|
| No. | % | OR | 95% CI | p Value |
| Age, years | | | | | |
| ≤50 | 32 | 22 | 68.8 | – | – |
| >50 | 120 | 83 | 69.2 | 1.020 | 0.439–2.366 | .964 |
| Gender | | | | | |
| Female | 43 | 31 | 72.1 | 1.222 | 0.561–2.661 | .614 |
| Male | 109 | 74 | 67.9 | – | – |
| Distance | | | | | |
| ≤50 | 45 | 34 | 75.6 | 1.567 | 0.712–3.451 | .265 |
| >50 | 107 | 71 | 66.4 | – | – |
| Hyperthermia | | | | | |
| Yes | 50 | 41 | 82.0 | 2.705 | 1.185–6.176 | .018 |
| No | 102 | 64 | 62.7 | – | – |
| cT | | | | | |
| T2 | 8 | 2 | 25.0 | – | – |
| T3/T4 | 144 | 103 | 71.5 | 7.537 | 1.461–38.880 | .016 |
| cN | | | | | |
| N0 | 34 | 28 | 82.4 | 2.485 | 0.952–6.488 | .063 |
| N+ | 118 | 77 | 65.3 | – | – |
| NLR | | | | | |
| ≥3 | 42 | 35 | 83.3 | 2.941 | 1.195–7.238 | .019 |
| <3 | 108 | 68 | 63.0 | – | – |

### Table 4. Multivariate analysis of T-downstaging.

| Variable | OR | 95% CI | p Values |
|----------|----|--------|----------|
| Hyperthermia | | | .038 |
| Yes vs. No | 2.473 | 1.050–5.826 | – |
| cT | | | .064 |
| T3/T4 vs. T2 | 4.868 | 0.913–25.940 | – |
| NLR | | | .015 |
| ≥3 vs. <3 | 3.324 | 1.262–8.751 | – |

### Table 5. Treatment response according to NLR level before neoadjuvant chemoradiotherapy.

| NLR ≥ 3 (%) | NLR <3 (%) | p Value |
|-------------|------------|---------|
| HCRT | T-downstaging | .043 |
| No | 0 (0) | 9 (26.5) | – |
| Yes | 14 (100.0) | 25 (73.5) | – |
| CRT | T-downstaging | | |
| No | 7 (25.0) | 31 (41.9) | .115 |
| Yes | 21 (75.0) | 43 (58.1) | – |

CRT: concurrent chemoradiotherapy; HCRT: hyperthermia plus concurrent chemoradiotherapy; NLR: neutrophil-to-lymphocyte ratio.

### Treatment toxicity

The treatment toxicity information of five patients (three in the CRT group and two in the HCRT group) was incomplete. For the remaining 147 patients, there was no grade 4 toxicity observed (Table 6). Grade 3 toxicity was noted in 4.1% (6/147) of the patients. The frequency of toxic effects did not differ between the treatment groups, except for bone marrow suppression. The rate of G2–G3 bone marrow suppression in the HCRT group was lower than that in the CRT group (4.2 vs. 17.1%, p = .041).

### Discussion

In this study, we found that patients who received neoadjuvant deep regional HT combined with modern concurrent CRT had a significantly higher T-downstaging rate than patients who received CRT alone. Moreover, HT remained a favorable independent predictor of T-downstaging rate in the multivariate analysis. Among patients who received HT, patients with a baseline NLR ≥ 3.0 had a significantly higher T-downstaging rate than those with NLR < 3.0. Furthermore, HT did not increase the toxicity of LARC treatment in our study. However, our study indicates that HT might not provide survival benefits for LARC.

The role of HT in combination with radiotherapy and chemotherapy for rectal cancer is still conflicting and remains controversial [3–6,16–19]. Several studies have suggested that HT combined with radiotherapy could significantly improve the pCR rate, LRFS and OS [3,4,6,16]. However, most of these studies were conducted before the establishment of standard preoperative CRT for LARC. First, the radiotherapy dose was approximately 40 Gy [3,4], which is much lower than the 45–50 Gy applied nowadays. Second, the radiotherapy techniques used in these studies were not uniform, although 3D-CRT and IMRT/VMAT are both standard recommendations [4,6,16–19]. Third, several studies also included patients with recurrent or metastatic diseases [16]. Therefore, there is still a lack of evidence regarding the role of HT under the condition of standard CRT for LARC. The main advantage of our study was that radiotherapy was administered according to the modern strategy (45–50/1.8–2.0 Gy) using VMAT, and the concurrent chemotherapy was uniformly using capecitabine. Moreover, all the patients included were stage II/III, which is in line with the recommendation for neoadjuvant CRT in the guidelines.

### Survival

The median follow-up times in the HCRT and CRT groups were 30 months (range, 6–79 months) and 49 months (range, 4–87 months), respectively. The 5-year LRFS rates for the patients in the CRT and HCRT groups were 94.7 and 96.8%, respectively; the 5-year DFS rates in the CRT and HCRT groups were 79.3 and 61.4%, respectively. The 5-year OS rates in the CRT and HCRT groups were 89.8 and 92.7%, respectively. The LRFS, DFS and OS did not differ significantly between the CRT and HCRT groups (Figure 2). Patients who received HT were stratified into two groups using a cutoff value of 3.0, to assess the significance of NLR in HT treatment. The LRFS, DFS and OS did not differ significantly between the two groups (data not shown).
TME surgery significantly reduces the recurrence rate of rectal cancer [20]. As the surgery was conducted in the narrow pelvis, we speculated that the downstaging of the primary tumor might provide a larger space for operation. Thus, it is much easier for surgeons to obtain a wider resection margin. Therefore, HT is one of the options for large tumor volume or lower rectal cancer, especially for male patients whose pelvis is much narrower than that of females. Furthermore, Yasui et al. reported that tumor size (>4 cm) and tumor category (T4) were independent risk factors for postoperative complications [21]. Therefore, HT may reduce the incidence of surgical complications through tumor downstaging.

Accumulating evidence has indicated that the circulating NLR is a negative prognostic indicator in colorectal cancer [9,14,15,22]. It has been demonstrated that circulating lymphocytes can induce cytotoxic cell death and produce cytokines that inhibit cancer proliferation and metastasis [23]. In contrast, circulating neutrophils induce angiogenesis and promote tumor growth by releasing inflammatory cytokines [24,25]. Elevated NLR, caused by a low lymphocyte count or a high neutrophil count, may lead to an inadequate anti-tumor immune response and an increased potential for tumor progression [26]. Jeon et al. [22] reported that an elevated NLR before CRT was a negative predictive marker for pCR and was independently associated with decreased RFS. However, in our study, patients with a baseline of high NLR (≥3) had a significantly higher T-downstaging rate (100.0 vs. 70.6%) in the HT group, while NLR was not associated with T-downstaging rate in patients without HT. Rectal cancer with an elevated NLR may be more sensitive to HT. Considering that T-downstaging may be related to the treatment delivered (thermal dose interval between CRT and surgery, tolerance of capecitabine, etc.), these conclusions need a well-controlled large-scale study for further confirmation.

Four limitations must be considered when interpreting the results of our study. First, this was a retrospective analysis conducted at a single institution. Second, the sample size in the HCRT group was relatively small compared with that in the CRT group. Third, the cutoff values for NLR were chosen based on the most commonly used values identified in previous reports, but the optimal cutoff values for NLR are not known and vary widely between studies. Fourth, not all patients in this study underwent an intrarectal temperature measurement.

In summary, our study indicated that deep regional HT could improve tumor response in LARC, especially in patients with a baseline NLR ≥3. However, HT could not improve local-regional control or survival in these patients. The results of this study need to be confirmed with well-designed, large-scale, prospective randomized trials.

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No potential conflict of interest was reported by the author(s).
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Data availability statement
Data available on request from the authors.

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