Long-course neoadjuvant chemoradiotherapy with versus without a concomitant boost in locally advanced rectal cancer: a randomized, multicenter, phase II trial (FDRT-002)

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Abstract

Background: This study was designed to explore whether an intensified chemoradiotherapy (CRT) led to a better clinical outcome in locally advanced rectal cancer.

Methods: Patients with stage II/III rectal cancer were randomly allocated to receive either pelvic intensity-modulated radiation therapy (IMRT) of 50 Gy/25Fx concurrently with capecitabine and oxaliplatin (Arm A), or pelvic radiation of 50 Gy/25Fx with a concomitant boost of 5 Gy to the primary lesion, followed by a cycle of XELOX 2 weeks after the end of CRT (Arm B). All patients were planned to receive a definitive operation 8 weeks after the completion of CRT and a total of six perioperative chemotherapy cycles of capecitabine and oxaliplatin regardless of pathological result. Pathological complete response (ypCR) was the primary endpoint.

Results: From February 2010 to December 2011, 120 patients from three centers were enrolled in this study. Ninety-five percent patients completed a full-dose chemoradiotherapy as planned. Then 53 and 57 patients received a radical surgery, and 8 and 14 cases were confirmed as ypCR in two groups (P = 0.157). The other 10 patients failed to receive a definitive resection because of unresectable disease. Similar toxicities were observed between two groups and more incision healing delay were found in Arm B (3 vs. 13, P = 0.011). No statistical differences were observed in local-regional control (P = 0.856), disease-free survival (P = 0.349) and overall survival (P = 0.553). Mesorectal fascia (MRF) involvement was an independent prognostic factor for survival in multivariate analysis.

Conclusions: A concomitant boost to oxalipatin-combined preoperative chemoradiotherapy demonstrated a slightly higher pCR rate but delayed incision healing after surgery. The impact of MRF involvement on survival merits further investigations.

Trial registration: NCT01064999 (ClinicalTrials.gov).

Keywords: Rectal cancer, Neoadjuvant chemoradiotherapy, Intensity-modulated radiation therapy
Introduction
With report of results from a series of large randomized clinical trials comparing neoadjuvant pelvic radiotherapy (RT) alone versus RT plus concurrent 5-fluorouracil (5-FU), the standard modality for stage II/III rectal cancer has shifted to preoperative chemoradiotherapy (CRT), followed by total mesorectal excision (TME) and postoperative chemotherapy, which leads to preservation of normal tissue, improvement of tumor regression and excellent local control [1].

The German CAO/ARO/AIO-94 study is the milestone of preoperative CRT [2]. Patients who received preoperative RT in the study had superior local control and reduced toxicity compared with patients in the postoperative group. Subsequently, the EORTC 22921 trial [3] and FFCD9203 trial [4] suggested 5-FU-based CRT resulted in a lower local recurrence rate compared with long-course RT alone, in spite of similar long-term survival. Furthermore, in EORTC 22921 trial, the ypT0–2 group had a significant better OS and DFS than the ypT3–4 group [5]. Similar results were also observed in MDACC’s retrospective study, where tumor regression could be converted to a better long-term prognosis [6]. Moreover, in a pooled analysis [7], it was reported that patients with pCR after CRT have better long-term outcome than those without pCR (5-year crude DFS: 83.3% vs 65.6%). Therefore, in some views, tumor downstaging, especially pCR, was regarded as a goal in neoadjuvant treatment of locally advanced rectal cancer, which motivated the combination of systemic chemotherapy and advanced RT technique in this approaches.

In our center, previous phase II studies reported that oxaliplatin plus 5-FU-based CRT showed good tumor responses and tolerable toxicities [8–10]. Higher radiation dose was reported to contribute to tumor downstaging in literatures [11–13]. Therefore, we designed this randomized trial to explore whether a combined regimen of oxaliplatin-added chemoradiotherapy and a concomitant boost to the primary tumor would further lead to a better clinical outcome.

Patients and methods
Patient eligibility
The main inclusion criteria of this study were as follows: (1) newly diagnosed rectal adenocarcinoma; (2) aged between 18 and 75 years old; (3) tumor located within 12 cm from anal verge; (4) clinically staged T3–4 and/or N+; (5) no evidence of distant metastases; (6) had Karnofsky Performance Status score of 60 or more; and (7) had adequate hematologic, renal and hepatic function.

Patients were excluded if they had history of malignant tumor but not including cured skin cancer or cervical cancer in situ, had inflammatory bowel disease, ischemic heart disease, peripheral neuropathy, or psychological disorders. Informed consent must be obtained from every patient before randomization. The procedure of random assignment was performed centrally at the Fudan University Shanghai Cancer Center.

Treatment schedule
The IMRT technique and tumor volumes definition has been described in our previous trial [9]. For Arm A, the planning dose to the PTV2 (pelvis) were 50 Gy in 25 fractions, five times per week (Monday through Friday) over 5 weeks. For Arm B, the planning doses to the PTV1 (primary tumor) and PTV2 were 55 Gy and 50 Gy in 25 fractions. Electronic portal imaging device (EPID) films were used to verify the isocenter and positioning of each patient for the anterior and lateral gantry positions.

Capecitabine and oxaliplatin were given in combination with pelvic radiotherapy. The concurrent chemotherapy regimen was same in both Arms. Capecitabine of 625 mg/m² was given twice daily from Monday to Friday, and oxaliplatin was administered at a fix dose of 50 mg/m²/week throughout the entire course of CRT. Two weeks after the end of CRT, one additional cycle of XELOX (capecitabine 1000 mg/m² twice daily on day 1–14 and oxaliplatin 130 mg/m² on day 1) was scheduled for patients in Arm B (Fig. 1).

After the completion of CRT, patients were planned to undergo TME 8 weeks later, while the operation type, such as abdominal-perineal resection (APR) or low anterior resection (LAR), and whether to perform a temporary colostomy, were left to the surgeon to decide. All patients were recommended to receive a total of six cycles of XELOX in perioperative period, regardless of their pathological features.

Treatment evaluation and follow-up
Baseline evaluation included a comprehensive medical history collection, digital examination, colonoscopy and biopsy, computed tomography (CT) scanning of chest and abdomen, and magnetic resonance imaging (MRI) of pelvis. Endorectal ultrasound (EUS) and positron emission tomography (PET) were not routinely recommended.

Pathologic examination of surgical specimens was performed in accordance with the American Joint Committee on Cancer (AJCC, Version 7) [14]. If less than 12 lymph nodes were found during standard examination for resected lymph nodes, two pathologists needed to double check to verify the number of lymph nodes. The tumor regression grade (TRG) after chemoradiotherapy was recorded according to the AJCC TRG system. TRG 0: Complete tumor response-no viable cancer cells; TRG 1: Moderate response-single or small groups of tumor cells; TRG 2: Minimal response-residual cancer outgrown by fibrosis; TRG 3: Poor
response-minimal or no tumor cells killed. PCR was defined as the absence of viable tumor cells in the resection specimens including the primary tumor and lymph nodes (ypT0N0), and near-pCR was defined as ypT0N1a or TRG1 in our study. Those with a margin of circumferential rectal margin (CRM) < 1 mm were marked in positive status [15].

Acute toxicities were defined as toxicities occurred during the entire course of CRT and were evaluated weekly according to the National Cancer Institute Common Toxicity Criteria (CTCAE 4.0). Follow-up was scheduled every 3 months during the first 2 years after surgery, and then every 6 months over the next 3 years. After 5 years, the frequency of follow-up was extended to once each year.

Endpoints and statistics
An intention-to-treat (ITT) dataset including all eligible patients were used in the analysis procedure. The hypothesis was to increase the ypCR rate from 10% in the Arm A to 25% in the Arm B. A total of 120 patients were required to detect such a difference, with α = 0.20 (two tailed) and power = 0.80. Secondary endpoints were listed as follows: toxicities, sphincter preservation rate, local failure (LF), disease-free survival (DFS) and overall survival (OS).

All features were listed by mean and standard deviations for normal distributional data, by median and interquartile range (IQR) for non-normal distributional data, and by frequency for categorical variables. Comparisons between two groups were performed using χ² tests for categorical variable. Survival curves were estimated using the Kaplan-Meier method and compared with Log-rank test. Cox proportional hazards regression was used for univariate and multivariate modeling and for examining the prognostic significance of the variables identified in the model. P values of less than 0.05 were taken to indicate statistically significant differences.

Results
Baseline characteristics
From February 2010 to December 2011, 120 eligible patients in three centers (Fudan University Shanghai Cancer Center, Shanghai, China; The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, China; The First Affiliated Hospital of Suzhou University, Suzhou, China) were randomly assigned in the trial, and the final analysis was performed in ITT set including all 120 cases (Fig. 2).

Patient characteristics were presented in Table 1. Eighty-four were male and 36 were female, and the median age was 56 (range 22–75). More cases were diagnosed with cT3, cN+, negative mesorectal fascia (MRF) and with the distance from anal verge less than 5 cm. No statistical differences were observed between two groups in the baseline characteristics (Table 1).

Compliance and toxicities
Full-dose radiotherapy was given in 98.3% patients in both groups. One case in Arm B received single drug
during the whole course of CRT for the reason that he refused intravenous chemotherapy. Almost all patients completed five cycles of weekly oxaliplatin, except that one and four patients terminated oxaliplatin in the second and fourth cycles, respectively. No further chemotherapy dose modification was recorded.

The overall acute grade 3–4 toxicities were 18.3 and 25.0% in the two groups, Arm A and Arm B, respectively. Diarrhea, radiation dermatitis and nausea were the three most common toxicities in both groups, though a slightly higher number of above cases were found in Arm B without significant difference (Table 2).

Surgical procedures and pathological outcome
Radical surgery was performed in 53 (88.3%) patients in arm A and 57 (95.0%) in arm B after a median interval between CRT and surgery of 51 and 58 days, respectively. The other ten patients failed to undergo a surgery due to unresectable diseases. Anterior resection procedure was performed in 13 and 22 patients (24.5 and 38.6% of the patients who underwent surgery in arms A and arm B), respectively (Table 3). Arm B demonstrated a slightly better ypCR, ypT and ypN stage. PCR were found in 22 cases, 8 in Arm A and 14 in Arm B. There were 45.3 and 31.6% patients demonstrating positive lymph nodes in two groups, respectively. The rate of anastomotic fistula and low anterior resection syndrome were equally low in both arms, but more delayed incision healing were observed in Arm B (Table 4).

In additional analysis for tumor response, good response was defined as pCR plus near-pCR, the others...
were marked as poor response, including those who could not receive surgery for unresectable lesion. A higher good response rate was observed in Arm B (30% vs. 55%, \(P = 0.006\)) (Table 5). Two patients in Arm A received additional postoperative radiotherapy of 10–15 Gy because of a positive margin.

**Long-term prognosis**
A total of 49 patients in Arm A and 51 in Arm B received adjuvant CT. The most frequent regimen was XELOX, with median of three cycles.

With a median follow-up of 42 months (range 3.2–80.7 months), ten patients were confirmed with local recurrence and 26 patients were diagnosed with distant metastases. A total of 20 patients died, 17 of cancer-related disease, 3 of other reasons. There were no significant differences in 3-year local-regional failure (10.9% vs. 9.4%, \(P = 0.856\)), 3-year DFS (56.0% vs. 68.8%, \(P = 0.349\)) and 3-year OS (75.3% vs. 88.5%, \(P = 0.553\)) between two groups (Fig. 3).

**Univariate and multivariate analysis of OS, DFS and LC**
All potential prognostic factors, including demographic and clinical features were evaluated using Kaplan-Meier and Cox model (Table 6). Positive MRF was associated with poorer local control, DFS and OS; ypN and tumor response were correlated with DFS and OS; pCR was in favor of longer DFS. In the multivariate Cox model, ypT, ypN and pCR were excluded because they exhibited a strong correlation with tumor response. MRF was the only independent prognostic factor for local control, DFS and OS simultaneously. Tumor response was also an independent risk factor for DFS (Table 7).

**Discussion**
This phase II randomized trial was designed to compare two different dose-intensified regimens in neoadjuvant therapy. With the preset alpha of 0.20, the primary end-point reached an expected higher pCR rate (13.3% vs. 9.4%).

### Table 2
Acute toxicity according to CTCAE 4.0, on all patients receiving treatment

| Adverse Event          | Grade 1–2 |                      | Grade 3–4 |                      |
|------------------------|-----------|----------------------|-----------|----------------------|
|                        | Arm A (N = 60) | Arm B (N = 60) | Arm A (N = 60) | Arm B (N = 60) |
|                        | No. %      | No. %                | No. %      | No. %                |
| Diarrhea               | 21 35.0%  | 16 26.7%             | 4 6.7%     | 6 10.0%              |
| Nausea                 | 35 58.3%  | 3 51.7%              | 2 3.3%     | 3 5.0%               |
| Vomiting               | 5 8.3%    | 7 11.7%              | 2 3.3%     | 2 3.3%               |
| Anorexia               | 13 21.7%  | 18 30.0%             | 0 0.0%     | 1 1.7%               |
| Radiodermatitis        | 27 45.0%  | 22 36.7%             | 8 13.3%    | 10 16.7%             |
| Anemia                 | 37 61.7%  | 34 56.7%             | 0 0.0%     | 0 0.0%               |
| Leukopenia             | 27 56.7%  | 21 35.0%             | 2 3.3%     | 3 3.3%               |
| Neutropenia            | 20 33.3%  | 20 33.3%             | 2 3.3%     | 3 3.3%               |
| Thrombopenia           | 15 25.0%  | 15 25.0%             | 1 1.7%     | 2 3.3%               |
| Overall                | 40 66.7%  | 43 71.7%             | 11 18.3%   | 15 25.0%             |

*All \(P\) values are comparison of grade 3 and 4 adverse events between the two arms

### Table 3
Pathologic characteristics of the operative specimen from patients (N = 110a)

| Type of surgery | Arm A | Arm B | Total | \(P\) value |
|-----------------|-------|-------|-------|-------------|
| Malign       |       |       |       |             |
| Miles          | 36    | 32    | 68    | 61.80%      |
| Anterior resection | 13 | 22 | 35 | 31.80% |
| Hartmann       | 4     | 3     | 7     | 6.40%       |
| ypT stage     |       |       |       |             |
| ypT0           | 10    | 16    | 26    | 23.60%      |
| ypT1–2         | 16    | 24    | 40    | 36.40%      |
| ypT3–4         | 27    | 17    | 44    | 40.00%      |
| ypN stage     |       |       |       |             |
| N0             | 29    | 39    | 68    | 61.80%      |
| N+             | 24    | 18    | 42    | 38.20%      |
| pCR            | 8     | 14    | 22    | 20.00%      |
| non-pCR        | 45    | 43    | 88    | 80.00%      |
| Total          | 53    | 57    | 110   |             |

**Abbreviations:** MRF Mesorectal fascia

*a Patients who did not undergo surgery excluded*
Furthermore, the intensified dose regimen was associated with better tumor response but more delayed incision healing after surgery in the experimental arm (Arm B). Therefore, our results suggested that the enhanced dose regimen with a concomitant boost to the primary tumor in oxaliplatin-added neoadjuvant chemoradiotherapy warrant more attentions.

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enhanced treatment dose intensity was regarded as an
effective method, including both radiotherapy and
chemotherapy dose. Plenty of early phase II trials indi-
cated that it was beneficial to add oxaliplatin to standard
FU-based CRT [16], and several continuous small sam-
ple size studies in our center also showed similar results
[8, 9]. Therefore, based on literature review at that time,
oxaliplatin was administered in both two arms in this
trial. Additionally, our previous study reported that
23.7% patients were evaluated as pCR, who received
IMRT to the pelvis of 50 Gy and a concomitant boost of
5 Gy to the primary tumor, in combination with oxali-
platin and capecitabine, followed by a cycle of XELOX
before surgery [8]. Therefore, a concomitant boost to
the primary tumor was regarded as an efficient supple-
mentary to the approach and this regimen was recom-
manded as the experimental arm in this trial.
Noticed the rate of pCR was 23.3% in the experimen-
tal arm compared with 13.3% in the controlled arm in
the present study, it may be resulted from both

Table 6 Results of the univariate analysis of prognostic factors on overall survival, disease-free survival, local control

| Factor               | Overall Survival | Disease-free Survival | Local Control |
|----------------------|------------------|-----------------------|---------------|
|                      | HR    | 95% CI | p   | HR    | 95% CI | p   | HR    | 95% CI | p   |
| Gender               |       |        |     |       |        |     |       |        |     |
| male / female        | 0.849 | 0.334–2.160 | 0.731 | 1.280 | 0.674–2.434 | 0.451 | 0.588 | 0.125–2.771 | 0.502 |
| Age                  |       |         |     |       |        |     |       |        |     |
| > 55 / <=55         | 0.737 | 0.325–1.672 | 0.465 | 0.872 | 0.476–1.599 | 0.658 | 2.002 | 0.518–7.742 | 0.315 |
| Treatment            |       |         |     |       |        |     |       |        |     |
| high-dose / low-dose | N/A   | N/A     | N/A | N/A   | N/A    | N/A | 0.892 | 0.258–3.082 | 0.856 |
| cT stage             |       |         |     |       |        |     |       |        |     |
| cT4 / cT3            | 1.319 | 0.542–3.209 | 0.542 | 1.166 | 0.596–2.278 | 0.654 | 0.318 | 0.040–2.511 | 0.277 |
| cN stage             |       |         |     |       |        |     |       |        |     |
| cN+ / cN0            | 1.051 | 0.390–2.835 | 0.921 | 1.036 | 0.496–2.166 | 0.925 | 2.678 | 0.339–21.146 | 0.350 |
| MRF                  |       |         |     |       |        |     |       |        |     |
| MRF+ / MRF-          | 2.971 | 1.297–6.802 | 0.010 | 2.485 | 1.351–4.572 | 0.003 | 4.802 | 1.240–18.590 | 0.023 |
| Location             |       |         |     |       |        |     |       |        |     |
| > 5 cm / <=5 cm      | 1.191 | 0.515–2.753 | 0.683 | 0.888 | 0.462–1.709 | 0.723 | 0.484 | 0.103–2.280 | 0.359 |
| Length               |       |         |     |       |        |     |       |        |     |
| > 5 cm / <=5 cm      | 1.563 | 0.662–3.693 | 0.308 | 1.219 | 0.658–2.260 | 0.528 | 2.059 | 0.532–7.965 | 0.296 |
| ypT stage            |       |         |     |       |        |     |       |        |     |
| ypT1–2/ypT0          | 1.047 | 0.294–3.734 | 0.944 | 1.672 | 0.641–4.363 | 0.294 | 1.797 | 0.187–17.278 | 0.612 |
| ypT3–4 / ypT0        | 1.238 | 0.372–4.114 | 0.728 | 2.116 | 0.838–5.339 | 0.113 | 3.620 | 0.436–30.808 | 0.234 |
| ypN stage            |       |         |     |       |        |     |       |        |     |
| ypN+ / ypN0          | 3.518 | 1.346–9.191 | 0.010 | 2.234 | 1.178–4.234 | 0.014 | 0.776 | 0.201–3.004 | 0.714 |
| pCR                  |       |         |     |       |        |     |       |        |     |
| non-pCR / pCR        | 2.728 | 0.639–11.646 | 0.175 | 2.656 | 0.946–7.459 | 0.064 | 2.058 | 0.261–16.257 | 0.494 |
| Response             |       |         |     |       |        |     |       |        |     |
| Poor / Good          | 2.574 | 1.013–6.544 | 0.047 | 2.228 | 1.156–4.297 | 0.017 | 1.224 | 0.345–4.339 | 0.755 |

Good response: pCR plus near pCR; Poor response: others
Abbreviations: HR Hazard ratio, pCR Pathological complete response, MRF Mesorectal fascia

Table 7 Results of the multivariate analysis of prognostic factors on overall survival, disease-free survival, local control

| Factor               | P value | 95% CI       | HR    |
|----------------------|---------|--------------|-------|
| Overall Survival     | 0.023   | 4.802–1.240  | 18.590 |
| Disease-free Survival| 0.011   | 2.231–1.203  | 4.136  |
| Local Control        | 0.047   | 1.959–1.007  | 3.808  |

Abbreviations: HR Hazard ratio, MRF Mesorectal fascia
chemotherapy and radiation dose escalation. Even though in the next six phase III trials, the mainstream view considered no significant benefit was brought by additional oxaliplatin [17–24], we still hold some different opinions as follows: the completion proportion of oxaliplatin during CRT ranges from 41 to 94.5% in these trials, which may be a leading cause of inconsistent results. It is worthy more attention that two trials having an enhanced pCR rate demonstrated a high completion proportion of oxaliplatin of 85% or more (CAO/ARO/AIO-04 and FORWARC trial) [19, 21]. Therefore, a pooled analysis including all above trials is expected to identify the subgroup population who can really benefit from additional oxaliplatin.

Furthermore, with the development of RT technique, such as IMRT and brachytherapy, higher preoperative pelvic irradiation dose was delivered in some studies. Radiation dose was regarded as a significant factor in the degree of tumor downstaging as reported by Mohiuddin et al. [11], whose study suggested that the rate of pCR was significantly correlated with RT dose, as patients treated to a dose of less than 50 Gy had a downstaging rate of 67% and a pCR rate of 3%, compared with a downstaging rate of 89% and a pCR rate of 45% at doses of more than 55 Gy \( (P = 0.05) \). What’s more, in The Radiation Oncology Group (RTOG) 0012 phase II trial [12], patients were randomly assigned to either hyperfractionated pelvic RT plus continuous infusion 5-FU or standard pelvic RT plus continuous infusion 5-FU and irinotecan, and both arms achieved very high pCR rates of 26% in each arm. So, the intensified RT dose plays a role in preoperative treatment of LARC.

In the uni- and multi-variate analysis of our study, we found that MRF status played as independent prognostic factors for long-term prognosis. As reported in the experience of MERCURY trial [25], MRI-defined involvement of CRM is an independent prognostic factor for 5-year overall survival \( (mCRM+ \text{ vs } mCRM-: \text{ 62.2% vs } 42.2\%) \), for DFS \( (67.2\% \text{ vs } 47.3\%) \) and for local recurrence with a hazard ratio of 3.5 \( (P < 0.05) \). In our study, the results was similar. Nevertheless, since the sample size was small, we couldn’t perform subgroup analysis to verify the conclusion.

However, this study had some limitations. Firstly, the control arm was not the current standard of care for locally advanced rectal cancer. As we stated previously, when we designed and conducted this study, oxaliplatin was still in high expectation in the neoadjuvant CRT phase. Secondly, it was indeed difficult to clarify which is the main reason for a better tumor response and more severe toxicities since radiation dose and consolidation chemotherapy were enhanced simultaneously in the experimental group. Thirdly, we didn’t notice any long-term benefit in the group with higher pCR rate. As it was common in most phase II trials in neoadjuvant treatment of LARC, the improvement of pCR rate was difficult to convert to a longer survival. Last but not the least, this study was originally designed as a two-stage trial with a total sample size of 240. But because of the disappointed results of several phase III trials about additional oxaliplatin in neoadjuvant CRT, we terminated this study after the completion of the first phase.

**Conclusion**

A concomitant boost to oxaliplatin-combined preoperative chemoradiotherapy demonstrated contribution to tumor regression with acceptable acute toxicity, but led to delayed incision healing after surgery. More data are needed to assess the impact of dose-intensified radiotherapy on long-term survival. The impact of MRF involvement on survival merits further investigation. Considered the experimental regimen was not compared to the standard of care, the conclusion should be interpreted cautiously.

**Abbreviations**

AJCC: American Joint Committee on Cancer; APR: Abdominal-perineal resection; CRM: Circumferential rectal margin; CRT: Chemoradiotherapy; CT: Computed tomography; CTCAE: National Cancer Institute Common Toxicity Criteria; DFS: Disease-free survival; EPID: Electronic portal imaging device; IMRT: Intensity-modulated radiation therapy; ITT: Intention-to-treat; LAR: Low anterior resection; LARC: Locally advanced rectal cancers; LR: Local control rate; MRI: Magnetic resonance imaging; OS: Overall survival; PET: Positron emission tomography; PTV: Planning target volume; TME: Total mesorectal excision; UICC: International Union against Cancer

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**Authors’ contributions**

JZ and ZZ designed the trial, JW and YG drafted and revised the manuscript, and all authors read and approved the final manuscript.

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**Availability of data and materials**

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Ethics approval and consent to participate**

This study was undertaken in accordance with the ethical standards of the World Medical Association Declaration of Helsinki. The trial protocol was approved by the Institutional Review Board on Medical Ethics at Fudan University Shanghai Cancer Center, and was registered at ClinicalTrials.gov (NCT 01064999). All study participants provided written informed consent prior to treatment.

**Consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.
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