Accelerated hyperfractionation field-involved re-irradiation combined with concurrent capecitabine chemotherapy for locally recurrent and irresectable rectal cancer

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Objectives: To evaluate the efficacy and treatment-related toxicity of accelerated hyperfractionation field-involved re-irradiation combined with concurrent capecitabine chemotherapy for locally recurrent and irresectable rectal cancer (LRIRC).

Methods: 72 patients with LRIRC who underwent the treatment were studied. Three-dimensional conformal accelerated hyperfractionation radiotherapy (3D-CAHRT) was performed and the dose was delivered with a schedule of 1.2 Gy twice daily, with an interval of at least 6 h between fractions, 5 days a week. Concurrent capecitabine chemotherapy was administered twice daily. After 36 Gy in 30 fractions over 3 weeks, patients were evaluated to define the resectability of the disease. If resection was not feasible irradiation was resumed until the total dose administered to the tumour reached 51.6–56.4 Gy.

Results: Two patients temporarily interrupted concurrent chemoradiation because of Grade IV diarrhoea. The remaining 70 patients completed the planned concurrent chemoradiation. In all patients, the complete response rate was 8.3% and the partial response rate was 51.4%. The overall response rate was 59.7% and clinical benefit rate was 93.1%. Symptomatic responses proved to be obvious and tumour resection was performed in 18 patients. The overall median survival time and median progression-free survival time were 32 and 17 months, respectively. 3 year overall survival and progression-free survival were 45.12% and 31.19%, respectively. Severely acute toxicities included Grade III–IV diarrhoea and granulocytopenia with 9.7% and 8.3% incidence respectively. Small bowel obstruction was severely late toxicity, and the incidence was 1.4%.

Conclusion: Three-dimensional conformal accelerated hyperfractionation field-involved re-irradiation combined with concurrent capecitabine chemotherapy might be an effective and well-tolerated regimen for patients with LRIRC.

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Local recurrence (LR) represents the most frequent relapse of disease after conventional treatment of rectal cancer. LR incidence is less than 15% for Stage I rectal cancer with curative resection and long-term survival is possible without adjuvant treatment. But for Stage II/III rectal cancer, LR incidence will reach 16–65% [1], and even if adjuvant treatment has been taken actively there is still a LR incidence of 5–20% [2, 3], which will lead to treatment failure. Without treatment, overall survival is only 3.5–13.0 months for patients with locally recurrent disease [4], and quality of life is seriously compromised due to clinical symptoms such as local pain, tenesmus, etc. Treatment options for these patients include radical resection, radiation therapy alone, chemotherapy alone, and a combined modality treatment with all of these

measures. Radical resection is the most significant measure to improve survival in patients with locally recurrent rectal cancer (LRRC) [5–13]; re-irradiation can further boost local control and survival [6], and the addition of chemotherapy can also bring a survival benefit [7, 14]. Radical resection is feasible for non-fixed recurrent tumours, but the majority of LRRCs appear in the form of a fixed tumour in the narrow pelvis. The pelvic wall can be easily invaded and complete resection is usually not feasible. For locally recurrent and irresectable rectal cancer (LRIRC) the combination of re-irradiation and chemotherapy is an ideal treatment modality that can result in a considerable survival benefit [6]. But because of fear of re-irradiation toxicities, the radiation dose is often limited to 30–40 Gy [7, 15]. At this dose, an antitumour effect that might achieve complete response or survival cannot be expected. There have been reports that the combination of external beam irradiation (EBRT) with intra-operative radiotherapy (IORT) allowed local delivery of a tumoricidal

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biological dose of up to 80–90 Gy [16, 17]. This strategy, however, is difficult to apply in practice because of the complexity of the technique and operation.

Three-dimensional conformal accelerated hyperfractionation radiotherapy (3D-CAHRT) can boost the local dose of radiation delivered to the tumour, maximally protect normal tissue adjacent to the tumour, relieve radiotherapy-related complications and hopefully promote survival for patients with LRIRC. Here we report some of the research in this field that might offer guidance for clinical treatment of these patients.

Materials and methods

The inclusion criteria of the patients

(1) All the patients included had experienced a curative resection, histologically confirmed as rectal adenocarcinoma, and had received adjuvant chemoradiotherapy or radiotherapy alone after primary surgery. There was an interval of more than 12 months from the completion of initial radiation therapy to the initiation of re-irradiation therapy. The previous irradiation field was a standard pelvic irradiation field (anteroposterior–posteroanterior field extended inferiorly to cover perineal tissue and scar after combined abdominoperineal resection. In the lateral field with inclusion of internal iliac and pre-sacral nodes, the posterior portion of the field is altered after combined abdominoperineal resection. Lateral field with anterior modification to include external iliac nodes). The previous dose of radiotherapy was less than 50 Gy. No late toxicity presented in either the small bowel or bladder. (2) There was obvious clinical and image evidence [including CT, MRI, positron emission tomography (PET)/CT, etc.] demonstrating that the disease was limited to the pelvis without defined distant metastases at the time of diagnosis. Lesions were measurable and irresectable as evaluated by the surgeon (lesions deemed irresectable were fixed lesions in the narrow pelvis, or the extent of infiltration on the pelvic side-wall through CT or the involvement of pelvic structures etc.). (3) Important organal (including heart, liver, lung, kidney etc.) functions are all normal and there was no accompanying severe comorbidity. (4) Karnofsky performance status ≥ 60 ; expected survival > 3 months. (5) Written informed consent was obtained from all patients before they were admitted into the study.

Patient characteristics

72 consecutive patients with LRIRC who underwent treatment between June 2004 and June 2008 were studied. There were 45 males and 27 females. The median age of the patients was 59 years (range 29–78 years). Pathological records of primary surgery were obtained for all patients and the primary surgical margins were all negative. The median time interval from the end of initial radiation therapy to the time of re-irradiation therapy was 25 months (range 13–77 months). The post-operation stage was defined according to the 2002 American Joint Committee on Cancer (AJCC) classification system [18], and patients seen before 2002

were restaged according to the current system. Other patient characteristics are listed in Tables 1 and 2.

Treatment

Radiation therapy

3D-CAHRT was taken and the dose was delivered with a schedule of 1.2 Gy twice daily, with an interval of at least 6 h between fractions, 5 days a week.

In the first preparation for radiation therapy, patients fasted with full bladders. They were then immobilized in the supine position. This was followed by a planning CT scan in the treatment position. The thickness of the scan was 2.5–5 mm for each slice. After the digital image data were transferred into a treatment planning system, the target volumes and normal structures (including bilateral femur neck, bladder, small bowel involved in irradiation field) were outlined on each slice by a radiation oncologist.

The gross target volume (GTV) included the recurrent tumours and local lymph nodes exceeding 1 cm (internal iliac nodes and external iliac nodes might be involved). The clinical target volume (CTV) was delineated with a 1 cm margin around the GTV. The planning target volume (PTV) was delineated with a 1 cm margin around the CTV, and the margin was further adjusted by checking organ movements with fluoroscopy.

The beam's-eye view (BEV) technique was used to find beam pathways that could wrap around the target volume adequately and thus decrease normal tissue damage. The number of irradiated fields ranged from five to eight. The dose was referred to a normalisation point inside the PTV to obtain a homogeneity of prescribed dose $\pm 5\%$.

Table 1. The characteristics of patients with primary surgery

	<i>n</i>	%
Type of primary surgery		
Dixon resection	43	59.7
Miles resection	29	40.3
Stage		
T3N0M0	10	13.9
T4N0M0	19	26.4
T14N1M0	35	48.6
T14N2M0	8	11.1
Adjuvant treatment		
Adjuvant chemoradiotherapy	65	90.3
Adjuvant radiotherapy alone	7	9.7
Pathological type		
Poor differentiated adenocarcinoma	19	26.4
Moderate differentiated adenocarcinoma	38	52.8
Well-differentiated adenocarcinoma	15	20.8
Number of evaluated lymph node		
≥ 12	56	77.8
< 12	16	22.2

Table 2. The characteristics of patients with local recurrence

	n	%
Karnofsky performance status		
≥90	9	12.5
80	29	40.3
70	23	31.9
60	11	15.3
Diagnosis		
Pathological ^a diagnosis*	23	31.9
Imaging	49	68.1
Number		
1	50	69.4
≥2	22	30.6
Size		
≤5 cm	25	34.7
>5 cm	47	65.3
Patterns ^b		
Anastomotic	5	6.9
Presacral	27	37.5
Lateral	26	36.1
Perineal	4	5.6
Anterior	10	13.9
F-stage ^c		
0	22	30.6
1	23	31.9
2	20	27.8
3	7	9.7
CEA test		
Increase	45	62.5
No increase	27	37.5
Clinical symptoms		
Local pain	31	43.1
Tenesmus	28	38.9

CEA, carcinoembryonic antigen.

^aIncluding 18 patients confirmed by subsequent resection.^bPre-sacral: predominantly midline, in contact with the sacral bone; lateral: laterally located, near to or invading the piriform muscle, in contact with the sacral bone or in association with anterior organs or along the iliac vessels or in the obturator lymph node compartment; anterior: predominantly midline, involving bladder, uterus, vagina, seminal vesicles, or prostate; anastomotic: midline, after low anterior resection, low Hartmann procedure, or local excision, at the staple line; perineal: midline, perineum, or anal sphincter complex with surrounding perianal and ischioanal space.^cA evaluation of the extent of infiltration on the pelvic side-wall through staging CT. Five groups were defined: F0: no evidence of contact with the pelvic side-wall; F1, extent of contact less than a quarter of pelvic side-wall; F2, contact was less than half circumference of side-wall; F3, contact more than half circumference; F4, involvement of bony structures or small bowel.

Owing to fear of re-irradiation toxicities, dose limitation to the bilateral femur neck was 30 Gy for less than 5% volume, to the bladder was 30 Gy for less than 50% volume, and to the small bowel involved in the irradiation field was 10 Gy for less than 50% volume. A dose-volume histogram (DVH) was produced with a

review of the CTV, PTV, bilateral femur neck, bladder, small bowel, etc.

Radiation therapy was delivered with a 6 MV photon beam. After the initial 36 Gy in 30 fractions over 3 weeks, patients were evaluated by abdominal and pelvic CT scan to define the resectability of the disease. If unfeasible, the GTV was redrawn in accordance with tumour shrinkage, and irradiation was continued until the dose to the tumour reached 51.6–56.4 Gy.

Chemotherapy

Concurrent capecitabine chemotherapy was administered with 850 mg m⁻² twice daily from the 1st day to the 14th day and from the 22nd day to the 35th day. After concurrent chemoradiation, patients continuously received two to four cycles of chemotherapy with the combination of capecitabine (2 × 1000 mg m⁻² day⁻¹ on days 1–14) and oxaliplatin (130 mg m⁻² on day 1) for 3 weeks or capecitabine (2 × 1000 mg m⁻² day⁻¹ on days 1–14) and irinotecan (CPT-11, 200–250 mg m⁻² on day 1) for 3 weeks. Best supportive care was given during chemotherapy or chemoradiation.

Surgery

After 36 Gy in 30 fractions over 3 weeks patients were evaluated by abdominal and pelvic CT scan to define resectability of the disease. If feasible, surgery was performed 6–7 weeks after chemoradiation. After the operation, patients continuously received two to four cycles of combined chemotherapy as described above, and radiation therapy was not delivered.

Evaluation methods

During concurrent chemoradiation treatment and adjuvant chemotherapy patients were evaluated weekly with physical examination and complete blood count. 4–6 weeks after completing chemoradiation, patients were re-evaluated for changes in their lesions, and carcinoembryonic antigen (CEA) levels were tested. Efficacy was evaluated according to World Health Organization (WHO) criteria, which include complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). The overall response rate (RR) was calculated as the sum of CR and PR and the clinical benefit rate was calculated as the sum of CR, PR and SD. Radicality of resection was defined as an R0 resection with microscopically free surgical margins (the tumour did not go out to the edge of the specimen), whereas a R1 resection had focally microscopically involved margins. The attempted resection included anterior resection and combined abdominoperineal resection. Toxicities were graded based on the European Organization for Research and Treatment of Cancer/Radiation Therapy Oncology Group or WHO criteria. Comprehensive pain was assessed and rated as no pain (0), mild pain (1–3), moderate pain (4–6) and severe pain (7–10) according to the visual analogue scale/score (VAS). Objective responses were divided into four levels according to symptomatic changes: symptoms either disappeared, were alleviated, remained or were exacerbated.

Statistics methods

Rates were calculated directly. Overall survival (OS) was calculated from the LRIRC concurrent chemoradiation date until the last follow-up or death, and progression-free survival (PFS) was calculated from the first day of treatment to the detection of local progression or distant metastasis. Both were calculated with the Life Tables method. Statistical analyses were performed using the SPSS statistical software program (SPSS for Windows Release 12.0; SPSS Inc., Chicago, IL).

Results

Follow-up

Two patients temporarily interrupted concurrent chemoradiation because of Grade IV diarrhoea and subsequently refused to resume radiotherapy. The other 70 patients completed the planned concurrent chemoradiation without interruption. Follow-up was performed every 3–6 months after the completion of the entire treatment. Physical examination, complete blood count, CEA levels and liver ultrasound were performed at each follow-up; chest radiograph and pelvic CT scan were performed periodically. Median duration of follow-up for surviving patients was 24 months (range 10–57 months). All patients with PD during evaluation or follow-up received combined chemotherapy or best supportive care.

Acute and late toxicity

In all patients, acute toxicities mainly included haematological toxicity, gastrointestinal toxicity, radiocystitis, radiodermatitis, fatigue, infective fever, hand and foot syndrome, and hepatic injury (Table 3). Severely acute toxicities included Grade III–IV diarrhoea and granulocytopenia, and the incidences were 9.7% and 8.3%, respectively. Two patients temporarily interrupted concurrent chemoradiation because of Grade IV diarrhoea and subsequently refused to resume radiotherapy. Patients with Grade III–IV granulocytopenia were treated with granulocyte colony-stimulating factor (G-CSF),

Table 3. Acute toxicities

	<i>n</i>	%
Diarrhoea		
Grade I–II	24	33.3
Grade III–IV ^a	7	9.7
Nausea and vomit	19	26.4
Fatigue	67	93.1
Acute radiocystitis	8	11.1
Acute radiodermatitis	31	43.1
Hand and foot syndrome	9	12.5
Hepatic injury	4	5.6
Granulocytopenia		
Grade I–II	29	40.3
Grade III–IV	6	8.3
Thrombocytopenia	2	2.8
Anaemia	43	59.7
Infective fever	5	6.9

^aIncluding two patients temporarily interrupted concurrent chemoradiation because of Grade IV diarrhoea.

Table 4. Late toxicities

	<i>n</i>	%
Skin fibrosis	4	5.6
Urinary incontinence	2	2.8
Dysuria	2	2.8
Small bowel obstruction ^a	1	1.4

^aRequiring surgery.

which did not influence the treatment. Other toxicities were all Grade I–II and well tolerated. Notably, five patients presented with infective fever, accompanied by Grade III–IV diarrhoea and granulocytopenia. They all received antibiotics and G-CSF, and treatment and survival were not influenced.

Late toxicities mainly included skin fibrosis, urinary incontinence, dysuria and small bowel obstruction with differing incidence (Table 4). Except for one patient with small bowel obstruction who required re-operation, other late toxicities were generally mild and needed no special treatments.

Efficacy of treatment

All patients were evaluated for efficacy and considerable responses were observed. 6 patients acquired clinical CR and 37 patients acquired clinical PR. The overall response rate and clinical benefit rate were estimated as 59.7% and 93.1% respectively. 18 patients deemed irresectable in previous evaluation were available for resection; 16 of these patients received R0 resection. Symptomatic responses proved to be obvious, with 29 of 31 patients presenting local pain relief and 23 of 28 patients presenting tenesmus relief (including clinical symptom disappearance or alleviation). After concurrent chemoradiation CEA levels were obviously decreased in 40 patients who had high CEA levels before the treatment (Table 5.)

Survival analysis

Survival time was calculated from the LRIRC concurrent radiotherapy date until the last follow-up attendance or until death. The overall median survival time and median progression-free survival time were 32 months and 17 months, respectively. The 3 year overall survival rate and progression-free survival rate were 45.12% and 31.19%, respectively (Figures 1 and 2).

Discussion

Radical resection is the most significant measure used to improve survival in patients with LRRC, and the 5 year survival rate after resection can reach 50% (R0 resection) [5–8]. However, only 40–60% of LRRCs are resectable [5, 6, 19]. The patients with irresectable LRRC generally develop a metastasis quickly, which reduces their 5 year survival rate to 0–20% [5, 20]. Currently, chemoradiation-based synthetic treatment is the most important treatment modality. This study was therefore designed to improve the efficacy of chemoradiation, which would finally bring a survival benefit to patients with LRIRC.

Table 5. Efficacy of treatment

	<i>n</i>	%
Response (<i>n</i> =72)		
CR	6	8.3
PR ^a	37	51.4
SD	24	33.3
PD	5	6.9
RR	43	59.7
Clinical benefit	67	93.1
Surgery (<i>n</i> =72)		
R0 resection	16	22.2
R1 resection	2	2.8
Relief of clinical symptoms		
Pain relief (<i>n</i> =31)	29	93.5
Tenesmus relief (<i>n</i> =28)	23	82.1
Decrease of CEA (<i>n</i> =45)	40	88.9

CEA, carcinoembryonic antigen; CR, complete response; PD, progressive disease; PR, partial response; RR, overall response rate; SD, stable disease.

^aIncluding 18 patients who received resection.

The majority of LRRC lesions are located in a previously irradiated field of the pelvis. Among the in-field recurrences, 56% occurred in the low pelvis and 22% in the pre-sacral region [21]. In our study, the majority of the in-field recurrences occurred in the lateral pelvis (36.1%) and the pre-sacral region (37.5%); few occurred in the anastomotic (6.9%) or perineal regions (5.6%). Re-irradiation of the in-field recurrences can aggravate the late irradiation toxicities of adjacent tissue (including small bowel, bladder etc.) and limits the increase of tumour dose. 3D-CAHRT can suppress accelerated proliferation, prevent the repair of sublethal damage by cancer cells, reduce the fractional dose and shorten the treatment time, which in combination can relieve late toxicity and decrease tumour proliferation. Therefore, it can protect normal tissue adjacent to tumour and maximally increase the dose received by the tumour. Capecitabine is the first of a new class of

Figure 1. Life Tables 3 year overall survival curve for locally recurrent and irresectable rectal cancer. The median overall survival was 32 months. The 3 year overall survival rate was 45.12%.

Figure 2. Life Tables 3 year progression-free survival curve for locally recurrent and irresectable rectal cancer. The median progression-free survival was 17 months. The 3 year progression-free survival rate was 31.19%.

fluoropyrimidines rationally designed to be taken orally. The efficacy, safety and feasibility for its combination with accelerated intensity-modulated radiotherapy in locally advanced rectal cancer had been proved in Phase II trials [22, 23]. In our study, 3D-CAHRT was taken to deliver field-involved re-irradiation and the shrinking field technique was performed after 36 Gy was given in 30 fractions over 3 weeks. The doses received by the bladder and small bowel were controlled effectively, but the dose received by the tumour finally reached 51.6–56.4 Gy. This is higher than the 30–40 Gy, which was reported as a limited dose for EBRT [7, 15]. At this dose, an antitumour effect that might achieve complete response or survival benefit can be expected.

Concurrent capecitabine chemotherapy not only enhanced the efficacy of re-irradiation, but also prolonged distant metastasis. In fact, our results showed that except for two patients who temporarily interrupted concurrent chemoradiation because of Grade IV diarrhoea and subsequently refused to resume radiotherapy, the remaining 70 patients tolerated the modality of treatment well. Although there were high incidences of Grade III–IV diarrhoea and granulocytopenia, the incidences were consistent with previous reports [20, 24]. Other toxicities such as radiodermatitis, hand and foot syndrome, etc., were Grade I–II and well tolerated. Notably, a few patients presented with infective fever, which was accompanied by Grade III–IV diarrhoea and granulocytopenia. They all received antibiotics and G-CSF, and treatment and survival were not influenced.

Regarding the efficacy of this multimodality treatment, 18 patients with tumours deemed irresectable in previous evaluations were resected. 16 of them received R0 resection. In our study, the overall response rate and clinical benefit rate reached 59.7% and 93.1%, respectively. We simultaneously observed 93.5% of patients presenting pain relief, 82.1% presenting tenesmus relief and 88.9% presenting decrease in CEA. Our results were better than those from a similar study performed in Italy [20], which reported an overall response rate and pain relief rate of 44.1% and 83.3% respectively in a Phase II

multicentric study of 59 patients with LRRC. The advantage was mainly because we instituted 5-fluorouracil for capecitabine and greatly boosted the local dose to the tumour. The former helped us to administer high-dose capecitabine with few toxicities, and the dose to the tumour in our study reached 51.6–56.4 Gy, which was higher than the 40.8 Gy used in the Italian study. All these made it possible to improve the local control rate and overall survival rate [9].

Finally, as the follow-up time was short, only 3 year overall survival and progression-free survival were available in our study. Overall median survival time and median progression-free survival time were 32 months and 17 months respectively. According to reports [5, 6, 20], overall median survival time for patients with LRRC was about 24–40 months; 5 year overall survival and progression-free survival were about 30–40% and 30% respectively; 3 year overall survival and progression-free survival were 58.9% and 46.6% [20]. These reported results were better than our results, perhaps because these studies included all patients with LRRC, whereas we excluded resectable patients before treatment. Since radical resection is the most significant predictor of improved survival in patients with LRRC, the relative low survival rates in our study were understandable.

Conclusions

Taken together, our data suggest that three-dimensional conformal accelerated hyperfractionation field-involved re-irradiation combined with concurrent capecitabine chemotherapy might boost the local dose to the tumour, make irresectable patients available for resection; it was also well tolerated. All of these benefits render this an option for patients with LRRC.

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