Original Study

Pattern and Management of Recurrence of Mid-Low Rectal Cancer After Neoadjuvant Intensity-Modulated Radiotherapy: Single-Center Results of 687 Cases

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Abstract

We retrospectively analyzed 687 patients with rectal cancer treated with 50.6 Gy/22-fraction intensity-modulated radiation therapy and rectal resection. The 5-year local recurrence-free survival and cancer-specific survival rates were 94.4% and 77.5%, respectively. Overall, 33.3% of patients (9of 27) with local recurrences, 35.8% of patients (19 of 53) with lung metastases, and 60% of patients (15 of 25) with liver metastases received curative treatment, and these patients achieved a 3-year survival rate of 87.8% after recurrence.

Background: The purpose of this study was to retrospectively analyze the pattern and the management of recurrence of rectal cancer treated with 22-fraction intensity-modulated radiation therapy (IMRT). **Patients and Methods:** This study included patients who underwent IMRT with gross tumor volume of 50.6 Gy in 22 fractions with concurrent capecitabine treatment over a period of 30 days, after which the patients underwent total mesorectal excision at Peking University Cancer Hospital (2007-2015). Study end points were local recurrence-free survival (LRFS), local disease-free survival (LDFS), disease-free survival (DFS), and cancer-specific survival (CSS). **Results:** A total of 687 patients were included in our analysis. The median age was 57 years (range, 21-87 years), and 66.4% of the patients were male. The estimated 5-year LRFS and 5-year LDFS rates were 94.4% (95% confidence interval [CI], 92.1%-96.7%) and 96.1% (95% CI, 94.1%-98.1%), respectively. The estimated 3-year DFS and 5-year CSS rates were 77.5% (95% CI, 74.1%-80.9%) and 84.7% (95% CI, 80.9%-88.4%), respectively. Overall, 33.3% of patients (9 of 27) who developed local recurrence, 35.8% of patients (19 of 53) who developed lung metastasis, and 60% of patients (15 of 25) who developed liver metastasis received curative treatment after recurrence. The estimated 3-year survival after recurrence rates of patients who received curative versus palliative treatment were significantly different (87.8% vs. 15.3%, $P = .000$). **Conclusion:** Rectal cancer treated with the 22-fraction IMRT regimen provides good local control. More than one-fourth of patients who develop recurrence have the chance to receive curative treatment with the incorporation of a multidisciplinary team and achieves excellent survival after recurrence.

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Introduction

Total mesorectal excision with neoadjuvant chemoradiotherapy (nCRT) has significantly improved the outcome for rectal cancer patients, and it has became the gold standard for locally advanced rectal cancer.[1,2] Generally, nCRT includes traditional 50 Gy in 25 fractions or 50.4 Gy in 28 fractions. The 22-fraction intensity-modulated radiation therapy (IMRT) was designed to shorten the treatment course and decrease radiation-related toxicity. For its higher biological equivalent dose (BED), good down-staging, and low toxicity, this unique neoadjuvant

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regimen has been approved by the ethics committee and has been used as routine practice at Peking University Cancer Hospital since 2007. We previously reported the efficacy and safety data of the 22-fraction IMRT for rectal cancer.[3] In the present study, we report the pattern and the management of recurrences of rectal cancer treated with this unique modality; the long-term survival data are also analyzed.

Patients and Methods

Patient Selection

Data were collected on patients who received IMRT with concurrent capecitabine treatment followed by surgery at Peking University Cancer Hospital from September 2007 to February 2015. Each patient enrolled in our study satisfied the following criteria: (1) rectal adenocarcinoma located within 10 cm to the anal verge and pathologically diagnosed using biopsy; and (2) clinical tumor stage T3 to 4 or any T stage, N+ as determined using endorectal ultrasound, pelvic magnetic resonance imaging (MRI), or computed tomography (CT). A positive lymph node was defined as $>$ 5 mm in diameter or indistinct border and mottled heterogeneous appearance upon imaging.[4] Patients with the following characteristics were excluded: (1) history of chemotherapy or pelvic radiation; (2) history (within 5 years) of malignant tumor; (3) inflammatory bowel disease; (4) the presence of acute obstructive symptoms or serious comorbidities deemed unsuitable for neoadjuvant radiation; or (5) post-IMRT assessment and surgery conducted at another hospital. Informed consent was obtained from all participants before treatment.

Neoadjuvant and Surgical Treatment

The IMRT regimen consisted of 22 fractions of 2.3 Gy (gross tumor volume [GTV]) and 1.9 Gy (clinical target volume [CTV]). The total dose of 50.6 Gy (GTV)/41.8 Gy (CTV) was administered 5 times per week over a period of 30 days. IMRT treatment was performed using a Varian RapidArc system (Varian Medical Systems, Palo Alto, CA). GTV was defined as the primary tumor including the mesorectum. CTV was defined as the primary tumor, mesorectal region, presacral region, mesorectal lymph nodes, lateral lymph nodes, internal iliac lymph node chain, and pelvic wall area. Capecitabine treatment was administered concurrently with IMRT at a dose of 825 mg/m^2 orally twice per day. Dose reduction recommendations were conducted in accordance with the protocol described in our previous report.[3,5] Surgery on the basis of the principle of total mesorectal excision was recommended 8 weeks or more after the completion of radiation. Adjuvant chemotherapy was routinely recommended to patients. Capecitabine alone, Oxaliplatin, Leucovorin and 5-FU (mFOLFOX6), or Oxaliplatin and Capecitabine (CapeOX) were prescribed at the discretion of the physician.

Pathologic Assessment

The seventh edition of the American Joint Committee on Cancer Tumor, Node, Metastases (TNM) system was used for pathological staging.[6] Histopathological results were reviewed by 2 pathologists. The status of the circumferential resection margin (CRM) was assessed following the protocol described by Quirke.[7]

End Points

The primary end points were cancer-specific survival (CSS), local disease-free survival (LDFS), and survival after recurrence (SAR). CSS was defined as the time from the date of completion of neoadjuvant treatment to the date of death from the same cancer or other related causes. LDFS was defined as the time from the date of completion of neoadjuvant treatment to the date of diagnosis of incurable local recurrence (LR). SAR was defined as the time from the date of diagnosis of local or distant recurrence to the date of death from the same cancer or other related causes. Secondary end points included LR-free survival (LRFS) and disease-free survival (DFS). LRFS was defined as the time from the date of completion of neoadjuvant treatment to the date of LR. DFS was defined as the time from the date of completion of neoadjuvant treatment to the date of any type of recurrence.

Follow-up

Patients were followed at 3-month intervals for the first 2 years after treatment, then at 6-month intervals for the next 3 years, and then annually or biannually. Evaluations consisted of physical examination, serum carcino-embryonic antigen levels, a complete blood count, and blood chemical analysis. Proctoscopy, abdominal ultrasonography, CT imaging of the abdomen and pelvis, and chest radiography were also routinely performed every 6 to 12 months after treatment.

Statistical Analysis

IBM SPSS Statistics for Macintosh, Version 20.0 (IBM Corp, Armonk, NY) software was used for all analyses. Kaplan–Meier survival curves were used to depict time-to-event parameters. The log rank test was used to compare factors that affect survival. Because of the single-arm nature of this retrospective study, most data were descriptive.

Results

Patient Demographic Characteristics

A total of 687 consecutive patients were included. The median patient age was 57 years (range, 21-87 years), and 66.4% of patients (456 of 687) were male. The median tumor height was 5 cm (range, 1-10 cm). The proportion of patients with prestaging MRI was 88.2%. Initial lymph node status was cN+ in 82.8% of patients (569 of 687). Patient characteristics and prestaging methods are listed in Table 1.

Acute Toxicity

In total, 4.7% of patients (32 of 687) developed grade 3 toxicity, which included the following: diarrhea (1.7%; 12 of 687), neutropenia (1.5%; 10 of 687), anemia (0.7%; 5 of 687), radiation dermatitis (0.4%; 3 of 687), and thrombocytopenia (0.4%; 3 of 687). No patients developed grade 4 toxicity.

Surgery and Pathological Findings

The median interval from neoadjuvant IMRT to surgery was 8 weeks (range, 4-74 weeks). A total of 55.5% of patients (381 of 687) underwent low anterior resection (LAR), 41.0% underwent abdominoperineal resection (282 of 687), 3.3% underwent a