

Effect of Tumor Infiltrating Lymphocyte on Local Control of Rectal Cancer after Preoperative Radiotherapy

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ABSTRACT

Objective: To study the effect of tumor infiltrating lymphocytes at cancer nest on local control of rectal cancer after preoperative radiotherapy. **Methods:** From Jan. 1999 to Oct. 2007, a total of 107 patients with rectal cancer were reviewed. They were treated by preoperative radiotherapy, 30 Gy/10 fractions/12 days. Two weeks later, the patient underwent a surgical operation. Their pathological samples were kept in our hospital before and after radiotherapy. Lymphocyte infiltration (LI) degree, pathologic degradation and fibrosis degree after radiotherapy in paraffin section were evaluated under microscope. **Results:** After followed-up of 21 months (2–86 months), a total of 107 patients were reviewed. Univariate analysis showed that lymphocyte infiltration (LI), fibrosis and pathologic changes after radiotherapy were significant factors on local control. Logistic regression analysis showed that LI after radiotherapy was a significant effect factor on local control. **Conclusion:** LI, fibrosis and pathologic degradation after radiotherapy are significant for local control of rectal cancer after preoperative radiotherapy. LI after radiotherapy was a significantly prognostic index for local control of rectal cancer after preoperative radiotherapy.

Key words: Rectal cancer; Tumor infiltrating lymphocyte; Preoperative radiotherapy; local control; Prognosis; Immunohistochemistry; Downstaging

Preoperative radiotherapy (RT) has recently been approved as the new standard treatment for rectal cancer. However there was still some controversial topic about local control, including the role of lymphocyte infiltration (LI) on response of rectal cancer after preoperative radiotherapy^[1]. Tumor infiltrating lymphocytes (TIL) was a group cells mainly infiltrating in tumor nest and around tumor mass. Almost 30 years ago, the identification of tumor infiltrating lymphocytes was reported^[1, 2], and represented as a new hope in cancer treatment. At that time, it was thought that patients whose tumor had high numbers of TIL had a good prognosis, while patients with few or no TIL had a poor prognosis. Some reports indicated that this viewpoint is simplistic. While infiltration of the tumor with lymphocytes may be one factor

associated with a positive outcome. In this study, the prognostic significance of LI was examined while close attention was paid to the therapeutic effect of preoperative radiotherapy in patient with rectal cancer. Furthermore, the effect of local radiotherapy on LI was also evaluated. Lymphocytes infiltration around cancerous lesion is an important immune response. Tumor responses to preoperative RT were assessed in terms of tumor downstaging and tumor regression. The purpose of this study was to evaluate the prognostic significance of LI after preoperative radiotherapy for rectal cancer.

MATERIALS AND METHODS

Patient Characteristics

Between January, 1999 and August, 2007, a total of 107 patients with locally advanced mid- and low-rectal adenocarcinoma were enrolled in

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our study of preoperative radiotherapy and were eligible for this retrospective analysis. All had clinical stage T2, T3 to T4 tumors or regional lymph nodes enlargement but had not distant metastasis, except one with liver metastasis. There were 61 males (57%) and 46 females (43.0%), with a mean age of 57 years old (ranged 27–86 y).

Clinical TNM Stage

Clinical TNM stage was defined by intracavity B ultrasound and pelvic MR. It included T1:0 case, T2:2 cases, T3:32 cases, T4:73 cases; N0:8 cases, N1:22 cases, N2: 77 cases; M0:106 cases, and M1:1 case.

Tumor Mass

The pathologic samples of all 107 patients before and after radiotherapy were kept in our hospital. The rates of intestine circumference involved by tumor mass were: 1/4 circle involved in 15 cases, 2/4 in 62 cases, 3/4 in 22 cases, and 4/4 in 81 cases. The median distance from the edge of tumor mass to anus was 5 (ranged 2–12) cm, the median diameter of tumor mass was 5 (range 1–11) cm.

Research Methods

All patient clinical data were collected, and tumor nests TIL were observed under microscope. In order to investigate the relationship between TIL number and local control of tumor, 30 pairs of patients with rectal cancer were chosen randomly, and themselves contrast were performed before and after radiotherapy.

Radiotherapy (RT)

Radiotherapy was delivered to the pelvis through three fields (posterior to anterior and 2 lateral fields with 30 degree wedge on lateral fields) using an energy of 10 MV from a Siemens linear accelerator (Siemens Co.), while the patient was in the prone position. The total dose was 30 Gy, with a daily dose of 3 Gy administered 5 d each week (30 Gy/10 f/12 d), the superior border of the pelvic field was the bottom of S1, and the inferior border was 3 cm distal to the tumor. The anterior border was located 3 cm anterior to the tumor and the posterior margin was 1 cm behind the posterior margin of the sacrum. The target volume included the primary tumor, perirectal fat tissue, and the internal iliac and presacral lymph nodes.

Surgery

Surgical resection was performed 2 w after completion of preoperative radiotherapy. Total mesorectal excision and autonomic nerve preservation were in accordance with the standard procedures. All surgeries were carried out by qualified colorectal surgeons. The surgery doctor decided Miles or Dixon.

Degree Evaluation of Tumor Regression and Lymphocyte Infiltration after RT

Before preoperative RT, patients underwent preoperative diagnostic and staging work-ups, including digital rectal examination, full blood counts and a biochemical profile, serum carcinoembryonic antigen (CEA) level, colonoscopy with biopsy, chest radiography, abdomino-pelvic CT, pelvic MRI, and/or transrectal ultrasonography. The cross-sectional areas of the primary tumors were measured using axial T2-weighted images by tracing the lesion boundary. On T2-weighted images, the cross-sectional lesion areas were defined as intermediate signal intensity areas that had the different signal intensity and contoured from the normal rectal wall. The lesion volumes were displayed automatically in a three-dimensional format and were calculated by summing each of the cross-sectional volumes of the entire lesion. Positive lymph node involvement was defined as a lymph node ≥ 5 mm in the smallest diameter observed on CT or MRI.

After radical surgery, tumor specimens were reviewed and the post-RT pathologic stage (pTNM) was determined according to the TNM classification system recommended by the American Joint Committee on Cancer. Tumor downstaging was determined by comparing pretreatment clinical and postoperative pathologic T classifications, and downstaging was defined as pT2 or lower. Tumors were also assessed using Wheeler's tumor regression grading system. Semiquantitative evaluation of histopathologic tumor regression was performed according to Wheeler stage in 2002^[3]. There are 3 grades of Rectal Cancer Regression Grade (RCRG), that is RCRG Grade 1: no tumor cells or few viable cancer cells and fibrotic mass; RCRG grade 2: obvious fibrosis and some viable cancer cells; RCRG grade 3: no regression with many viable cancer cells. All paraffin section was observed by one group pathologist.

Lymphocyte Infiltration Degree