

RESEARCH ARTICLE

Preoperative Radiotherapy and Chemotherapy for Rectal Cancer

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Abstract: The objective of this study is to investigate the complete pathological reaction of preoperative radiotherapy and chemotherapy for rectal cancer. We conducted a retrospective and explanatory study to evaluate the reaction to preoperative radiotherapy and chemotherapy in 46 patients of stage I, II and III rectal adenocarcinoma from 2006 to 2014. These patients were divided into four groups, in which 52.17% complete remission (24 cases), 15.21% moderate remission (7 cases), 6.53% minimum remission (3 cases) and 26.09% adverse reactions (12 cases). In this study, more than 50% of patients with preoperative radiotherapy and chemotherapy show complete pathological response, which may provide the possibility for patients with rectal adenocarcinoma to receive this treatment in the future, and a carefully selected group among the patients will enter the observation period.

Keywords: Rectal cancer, Adenocarcinoma, Treatment, Preoperative, Radiotherapy, Chemotherapy, Curative effect

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1. Introduction

Colorectal cancer is one of the most common malignant tumors in Venezuela, which poses a significant burden on the mortality and morbidity of the patients. In 2011, the incidence was 1604 males and 1612 females. A total of 822 men and 812 women died of colon, rectal and anal cancer. At present, it ranks fourth in tumor pathology in China^[1]. Tremendous efforts have been made in the past decade for the treatment of rectal cancer. Until recently, surgery remains the main treatment, but the proportion of patients with local recurrence after surgery was 20% to 50%^[2].

Although preoperative and postoperative adjuvant therapy may be effective, there has been an important recent trend to increase the use of neoadjuvant radiotherapy^[2].

Patients with early diseases have a good prognosis after surgical treatment, but many patients are diagnosed with advanced local diseases. For these patients, the established treatment mode in western countries is to carry out radiotherapy and neoadjuvant chemotherapy at the same time to improve local control and increase the chance of cure and resection. Unless all patients do not meet the criteria of this treatment protocol, all patients can receive surgery after concurrent radiotherapy^[3].

Clinical studies have shown that nearly 30% of patients may have complete clinical response after preoperative radiotherapy and chemotherapy.

This was defined as the absence of clinically detectable residual tumors. Therapeutic surgery before and after treatment and analysis of samples show that

complete pathological reactions may occur in some patients without tumor cell evidence^[3].

In western countries, preoperative radiotherapy and chemotherapy combined with surgery is the standard care of treatment. Surgery for rectal cancer may be responsible for high morbidity and mortality, especially in elderly patients. For those patients who have a sufficient clinical response to this preoperative treatment, it seems reasonable to request whether surgery is really necessary^[3].

Considering these observations, preoperative radiotherapy and chemotherapy can prolong the survival of patients with rectal cancer. Based on the experience of other researchers using this therapy, this paper raises the question of determining the complete pathological response of rectal cancer patients treated with preoperative radiotherapy and chemotherapy.

The use of preoperative chemoradiotherapy will be a very useful contribution, which will not only help to improve the survival rate of these patients, but also serve as a tool for further research, so as to promote the use of radical preoperative methods in the treatment of this disease, and determine the possibility of this combination treatment by avoiding surgery in highly selected cases.

1.1. Background

In a study, the authors Mak *et al.*^[4] evaluated the use of preoperative radiotherapy after introduction of the results from German study, and discussed the impact of tumor and social demographic factors on the acceptance rate of preoperative radiotherapy. Between 2000 and 2006, a total of 20,982 cases of T3-T4 tumors and lymph node positive rectal adenocarcinoma were surgically removed. The trend of preoperative radiotherapy before and after publication of German research results was analyzed. Logistic regression was also used to identify factors associated with preoperative radiotherapy. Among patients receiving radiotherapy, the proportion of patients receiving preoperative treatment increased from 33.3% in 2000 to 63.8% in 2006, which was adjusted according to age, gender, race, marital status, education, tumor stage, lymph nodes, tumor size and degree. One year after diagnosis was significantly correlated with the increase of preoperative radiotherapy use (adjusted odds ratio, 1.26/y; 95% confidence interval, 1.23–1.29). When comparing the years before and after the publication of the German study (2000–2003 vs. 2004–2006), patients were more likely to receive preoperative radiotherapy than postoperative radiotherapy (adjusted odds ratio, 2.35; 95% confidence interval, 2.13–2.59). In multivariate analysis, elderly female patients living in countries with low education level were significantly less likely to receive preoperative radiotherapy. They

concluded that after the publication of the German reference study, the application of preoperative radiotherapy in locally advanced rectal cancer has expanded rapidly, but preoperative radiotherapy may not be fully utilized in some social population groups^[4].

Caluwe *et al.*^[5] pointed out that preoperative radiotherapy can reduce the local recurrence rate and improve the survival rate of stage II and III patients with rectal cancer. They searched through database that include 'register of controlled trials in *Webs of Science*, *embase.com* and *PubMed* from 1975 to June 2012. They also manually searched *Ann Surg*, *Arch Surg*, *Cancer*, *J Clin Oncol*, *Int J Biol Phys Radiation Oncology* and *ASTRO* (American Society of Radiation Oncology), *ECCO* (European Cancer Organization) and *ASCO* (American Society of Clinical Oncology) from 1990 to June 2012. The main parameters were 5-year overall survival (OS) and 5-year local recurrence rate (LR). Secondary indicators included 5-year disease-free survival (DFS), metastasis rate, pathological complete remission rate, clinical remission rate, sphincter preservation rate, acute toxicity, mortality, postoperative morbidity and anastomotic leakage rate. The outcomes were summarized by odds ratio (or) and related 95% confidence interval (CI). Five trials were meta-analyzed. Only preliminary data were reported from one of the trials. Results show that preoperative radiotherapy plus chemotherapy could significantly increase grade III and IV acute toxicity (or 1.68–10, $p = 0.002$), but there was no difference in anastomotic leakage rate. Compared with preoperative radiotherapy alone (RT), preoperative concurrent radiotherapy and chemotherapy (CRT) significantly increased the complete pathological response rate of the upper sphincter (or 2.12–5.84, $p < 0.00001$), but did not affect the retention rate of the upper sphincter (or 0.92 – 1.30, $p = 0.32$). The 5-year local recurrence rate in CRT group was significantly lower than that in RT group (or 0.39–0.72, $p < 0.001$). SSE (or 0.92–1.34, $p = 0.27$) or OS (or 0.79–1.14, $p = 0.58$) was not statistically significant within 5 years. They concluded that by comparing preoperative RT with preoperative CRT, the pathological response and local control of stage II and III rectal cancer can be improved, but it is not beneficial to DFS or OS. Sauer *et al.*^[6] about “preoperative chemoradiotherapy and postoperative radiotherapy for locally advanced rectal cancer: results of the German phase iii randomized trial CAO/ARO/AIO-94, after a median follow-up of 11 years” pointed out that after the release of results from the CAO/ARO/AIO-94 working group in the tumor group, CRT has been determined as the standard treatment for locally advanced rectal cancer. Meanwhile, a study published by German Society for Cancer Surgery and Radiotherapy in 2004 showed a better local control rates. However, after a

median follow-up of 46 months, there was no survival benefit. In this study, they reported long-term results with an average follow-up of 134 months. A total of 823 patients with stage II to III rectal cancer were evaluated. They were randomly divided into 5-fluorouracil (5-fu) based preoperative CRT, 5-fu adjuvant chemotherapy or the same postoperative CRT regimen. Secondary targets were local recurrence, distant recurrence, and the cumulative incidence of DFS. Of the 799 patients, 404 were randomly divided into preoperative radiotherapy and chemotherapy group and 395 were in postoperative radiotherapy and chemotherapy group. The OS was 59.6% 10 years before operation and 59.9% after operation ($p = 0.85$). The local recurrence rates before and 10 years after operation were 7.1% and 10.1%, respectively ($p = 0.048$). There was no significant difference between 10-year distant metastasis (29.8% and 29.6%, $p = 0.9$) and DFS. Overall, the local control of preoperative radiotherapy and chemotherapy is significantly improved. However, there is no significant difference in OS.

1.2. Overall objective

This study aims to evaluate the complete pathological response of preoperative radiotherapy and chemotherapy in the treatment of stage I, II and III rectal cancer. In addition, the response was assessed according to the stage of manifestation of the disease.

1.3. Specific objectives

The response was assessed according to the stage of manifestation of the disease, and it was also evaluated according to the total dose of radiotherapy. The curative effect was evaluated according to the preoperative treatment time and the final operation time.

2. Method

This study is a retrospective and explanatory cohort study of preoperative radiotherapy for patients with stage I, II and III rectal cancer in the radiotherapy service of Caracas Hospital Of Clinics.

The study sample included 51 patients with stage I, II and III rectal cancer who received radiotherapy at the Caracas Hospital of Clinics between 2006 and 2014. The selected samples were 46 patients who met the inclusion criteria.

The subjects included patients with stage I-III rectal cancer with chemotherapy confirmed by histological examination and diagnostic study. Informed consent was obtained from patients. Patients with previous surgery and those with a history of remote disease or pelvic radiotherapy were excluded.

2.1. Program

The patient was treated with linear accelerator *Trilogy de Varian*® through three-dimensional conformal therapy (3D) or intensity modulated radiotherapy (IMRT). After the completion of CT, 120 multi leaf collimators are used for positioning and simulation on special tablet equipment and special laser system. *Eclipse de Varian* system® was executed to perform daily examination of patients by portal vein vision and OBI (on-board image) methods that reached a dose of 4500 cGy in the pelvis, followed by a reduction of 5040–5400 cGy or more in the dose range of 180 to 200 cGy.

2.2. Record data

One of the data recording tools of this study is the medical history of patients found in the radiotherapy service of Caracas Hospital of Clinics. This tool collects data on medical history, reason of visit, current disease, functional physical examination, instruments and systems, clinicopathological staging and extended research, including lower gastrointestinal endoscopy, transrectal ultrasonography, abdominal and pelvic CT scans, chest X-rays, hematological examination and post-treatment biopsy.

The pathoanatomical specimens were collected from the Department of Pathoanatomy of Caracas Hospital of Clinics. The collected specimens were studied macroscopically and microscopically, and the treatment response was determined according to the improved classification by Ryan *et al.*^[7] All patients were evaluated by pathoanatomists.

2.3. Statistical processing

Study variables were assessed in percentage.

2.4. Resources

This work was carried out in cooperation with the Department of Radiotherapy and the Department of Pathological Anatomy of Caracas Hospital of Clinics. The following material resources are provided: linear accelerator *Trilogy de Varian*®.

3. Result

A total of 51 patients with stage I, II and III rectal cancer were studied, of which 46 received preoperative radiotherapy and chemotherapy during the study period (December 2006 to June 2014). There was 1 case in 2006, 5 cases in 2007, 9 cases in 2008, 9 cases in 2009, 8 cases in 2010, 3 cases in 2011, 5 cases in 2012, 5 cases in 2013 and 1 case in 2014. The age ranges from 61 to 80. Male accounted for 65.21% (30 cases) and female accounted for 34.79% (16 cases).

Preoperative evaluation showed that oxaliplatin combined with capecitabine accounted for 78.26% (36 cases), followed by cetuximab 10.88% (5 cases), capecitabine 8.69% (4 cases), cetuximab, oxaliplatin and capecitabine combined therapy 2.17% (1 case).

According to the improved classification by Ryan *et al.*^[7], they were divided into four pathological response groups according to the pathological results. 52.17% had complete response (24 cases), while 15.21% (7 cases) had moderate response, 6.53% (3 cases) had minimum response and 26.09% (12 cases) had poor response. Pathological complete remission was obtained according to the stage: 3 cases in stage I, 3 cases in pathological complete remission, accounting for 100%; 8 cases in stage IIA, 7 cases in pathological complete remission, accounting for 87.5%. Among the 12 patients with stage IIIA, 8 patients had complete pathological remission, accounting for 66.6%; among the 15 patients with stage IIIB, 6 patients had complete pathological remission, accounting for 40%. For stage IIIC, 8 patients had no complete pathological reaction, accounting for 0%. If we included all stage III, we would have 35 patients, of which 14 showed 40% complete pathological response.

In evaluating the response to the total dose of radiotherapy, 9 cases (19.57%) used 5040 cGy, 36 cases (78.26%) used 5400 cGy, and 1 case (2.17%) used 5400 cGy. Among the 9 patients treated with 5040 cGy, 4 patients achieved complete remission, accounting for 44.44%. Among the 36 patients treated with 5400 cGy, 19 cases had complete pathological reaction, accounting for 52.77%. For patients receiving 5880 cGy, 100% of the response was complete. All patients evaluated in this study underwent surgery. We calculated the operation weeks and pathological reactions of 46 patients. It was observed that 11 patients (23.9%) operated from the 4th to 8th weeks after radiotherapy, of which 11 patients had complete pathological reactions, up to 100%. 10 cases were intervened from the 9th week to the 12th week, of which 7 cases had complete pathological reaction, accounting for 70%. 15 cases (32.6%) were intervened from week 13 to week 17, and 6 cases (35.2%) were completely relieved. After 18 weeks, 10 cases (21.7%) underwent surgery. None of the patients showed a complete pathological response.

4. Discussion

The purpose of this study was to evaluate the complete pathological response of preoperative radiotherapy to stage II and III rectal adenocarcinoma.

During the periods of 7 years and 6 months (December 2006 to June 2014), 51 patients with stage I, II and III rectal cancer were recruited, of which 46 patients were included in the study. There was 1 case in 2006, 5 cases in 2007, 9 cases in 2008, 9 cases in 2009,

8 cases in 2010, 3 cases in 2011, 5 cases in 2012, 5 cases in 2013 and 1 case in 2014. The age range is 61–80. Male accounted for 65.2% (30 cases) and female accounted for 34.7% (16 cases).

Preoperative evaluation mainly involve oxaliplatin plus capecitabine combined chemotherapy was found in 36 cases (78.2%), followed by cetuximab was found in 5 cases (10.8%), capecitabine 4 cases (8.6%), and cetuximab, oxaliplatin and capecitabine combined chemotherapy in 1 case (2.1%).

Garajová *et al.*^[8] depicted that neoadjuvant chemotherapy combined with radiotherapy has become the standard treatment for locally advanced rectal adenocarcinoma, which is more effective than adjuvant therapy in reducing local recurrence and minimizing toxicity. For stage II and III patients, neoadjuvant therapy, including 5-FU based radiotherapy and chemotherapy, is recommended. However, new chemotherapeutic drugs such as oxaliplatin have been integrated. These were two randomized phase III studies comparing the addition of oxaliplatin (star-01), 5-FU or capecitabine. Weekly addition of oxaliplatin significantly increased toxicity without improving complete pathological response or DFS. Originally designed as a two-arm study comparing capecitabine and 5-FU, oxaliplatin was added to the study protocol (called NSABP r-04). Although oxaliplatin has theoretical advantages as a radiosensitizer, no difference was observed in patients receiving capecitabine with or without oxaliplatin, 5-FU with or without oxaliplatin, and the toxicity of oxaliplatin was higher in both groups.

According to the improved classification by Ryan *et al.*^[7], this study was divided into four groups according to the pathological results, of which 52.17% of patients had complete remission (24 cases), 15.21% had moderate remission (7 cases), 6.53% had the lowest remission (3 cases), and 26.09% had poor response (12 cases). This is different from other series, as shown by Benzoni and his colleagues^[9]. Based on the pathological results of rectal cancer patients receiving radiotherapy combined with chemotherapy and surgery, they assessed the predictive value of clinical response to neoadjuvant therapy. They studied 58 patients with rectal cancer between 1994 and 2003, and recorded patients receiving neoadjuvant chemotherapy radiotherapy regimen and then underwent surgery. The clinical complete remission rate corresponds to the pathological complete remission rate, while the clinical evaluation overestimates the partial remission rate and disease stability. The positive rate of some clinical reactions was 92.8%, the positive rate of stable diseases was 90.9%, and the negative rate of advanced diseases was 20%. They concluded that the positive and negative predictive values of clinical evaluation of chemotherapy radiotherapy response, especially for partial response

and stable disease, were not sufficient to consider clinical evaluation and make treatment decisions.

Habr-Gama *et al.*^[10] evaluated the clinical response after neoadjuvant chemotherapy radiotherapy for distal rectal cancer. They believe that multimodal treatment of rectal cancer combined with radiotherapy, chemotherapy and surgery has become the preferred method for locally advanced rectal cancer. The application of neoadjuvant radiotherapy and chemotherapy reduces the toxicity and degree of tumor, increases the possibility of retaining sphincter, and improves the functional prognosis. They commented that some patients receiving neoadjuvant therapy may eventually have a complete clinical response. The complete clinical response of these patients is still controversial. Several methods have been proposed, including radical resection, local transanal resection and separate observation without immediate surgery. Recurrence is diagnosed through clinical evaluation and can usually be carried out through rescue procedures.

In this study, complete pathological response was obtained by stages: 3 cases in phase I, and 3 cases in pathological complete response, accounting for 100%; 8 cases in phase IIA, and 7 cases in pathological complete response, accounting for 87.5%. Among the 12 patients with stage IIIA, 8 patients had complete pathological remission, accounting for 66.6%; among the 15 patients with stage IIIB, 6 patients had complete pathological remission, accounting for 40%. For stage IIIC, 8 patients had no complete pathological reaction, accounting for 0%. If we put all stage III together, we will have 35 patients, of which 14 cases have 40% complete pathological reaction.

Habr-Gama *et al.*^[11] assessed the correlation between end-stage and survival in patients with distal rectal cancer, regardless of the initial stage of the disease. 260 cases of resectable rectal adenocarcinoma from distal rectal cancer (0–7 cm from the anal margin) were treated with 5-FU, folic acid and 5040cGy neoadjuvant CRT. Radical resection was performed on patients with incomplete clinical response 8 weeks after CRT. Patients with complete clinical remission were observed. SG and DFS were compared according to Kaplan Meier curve and log rank test in the final stage. 71 patients (28%) showed a complete clinical response (clinical stage 0). 179 patients with incomplete clinical response received surgical treatment. Among them, 22 cases (9%) were pathologically confirmed as pT0 N0 M0 (p0 stage), 59 cases (22%) as stage I, 68 cases (26%) as stage II and 40 (15%) as stage III. The survival rate in c0 stage was significantly higher than that in p0 stage ($p = 0.01$). The disease-free survival rate in c0 stage was better, but there was no significant difference. The incidence of DFS in 5 years was 97.7% and 84% (stage 0), 94% and 74% (phase I), 83% and 50% (phase II), 56%

and 28% respectively (phase III). Stage 0 was significantly associated with better outcomes.

In this study, 9 cases (19.57%) used 5040 cGy, 36 cases (78.26%) used 5400 cGy, and 1 case (2.17%) used cGy greater than 5400 cGy. Among the 9 patients treated with 5040 cGy, 4 patients achieved complete remission, accounting for 44.44%. Among the 36 patients treated with 5400 cGy, 19 cases had complete pathological reaction, accounting for 52.77%. For patients receiving 5880 cGy, 100% of the response was complete.

Habr Gama *et al.* conducted a retrospective analysis entitled “local recurrence after complete clinical response of rectal cancer, observation and waiting after neoadjuvant chemotherapy radiotherapy: the impact of rescue treatment on local disease control”, including cT2-4N0-2M0 in patients with distal rectal cancer treated with chemotherapy radiotherapy (CRT), the dose was between 50.4-54Gy + 5-FU chemotherapy and complete clinical response (CCR) at 8 weeks. RCC patients received a strict follow-up plan without immediate surgery (observation and waiting). The recurrence free survival rates of patients with local recurrence who were simply waiting for observation and waiting for rescue treatment were compared. Of the 183 patients, 90 (49%) underwent a preliminary evaluation after CRT. When considering early tumor recurrence (including follow-up in the first 12 months) and late recurrence, 28 patients (31%) had local recurrence (mean follow-up time of 60 months). Among them, 26 cases received rescue treatment, and 2 cases could not be rescued. Local recurrence occurred in 4 patients after observation and rescue treatment. The total cure rate of local recurrence was 93%.

The 5-year local recurrence free survival rates were 69% (all local recurrence) and 94% (after rescue) respectively. Systemic recurrence occurred in 13 cases (14%). The 5-year OS and DFS (including all recurrences) of all patients were 91% and 68% respectively. All patients evaluated in this study underwent surgery. We calculated the operation weeks and pathological reactions of 46 patients. It was observed that 11 patients (23.9%) operated from the 4th to the 8th weeks after radiotherapy, of which 11 patients had complete pathological reactions, up to 100%. 10 cases (21.7%) underwent surgery from 9 to 12 weeks after operation, of which 7 cases were completely relieved, accounting for 70%. 15 cases (32.6%) were intervened from week 13 to week 17, and 6 cases (35.2%) were completely relieved. After 18 weeks, 10 cases (21.7%) underwent surgery. None of the patients showed a complete pathological response.

Damin *et al.*^[13] published a critical review of current strategies and the most controversial issues in the treatment of rectal cancer. They mentioned that the new

technology makes the definition of tumor scope more precise. The improvement of surgical concept and technology leads to the improvement of sphincter preservation rate and better functional results of patients. Although preoperative chemotherapy, radiotherapy and total mesorectal excision have become the standard treatment for locally advanced tumors, there are still many problems to be solved in the treatment of rectal cancer, including the feasibility of non-surgical treatment after good response to neoadjuvant therapy, the ideal edge of surgical resection is the preservation of sphincter and the adequacy of minimally invasive tumor resection technology. In contrast, Wang *et al.*^[14] suggested that in the treatment of locally advanced ultra-low rectal cancer (anal sphincter invasive lesion), neoadjuvant treatment strategy should be adopted, sphincter should be retained, followed by local resection and two-stage total mesorectal resection. From October 2010 to October 2011, a total of 9 patients were evaluated. The lesions were evaluated as T2 in 2 cases, T3 in 5 cases and T4 in 2 cases; lymph node metastasis was found in 5 cases. The average distance from the tumor to the anal edge was 2.5 cm (range: 1–3 cm). The median follow-up was 27 months (range: 24–34 months). No distant metastasis was found. Only 1 case (11.1%) had local recurrence 12 months after operation, and then underwent abdominal perineal resection. The remaining 8 patients remain control for a long time. Wexner score was used for fecal incontinence evaluation. It was shown that the score was 4 at 2 years after operation (score > 7 was considered fecal incontinence, and the score range was 2–6).

In this study, more than 50% of preoperative chemoradiotherapy patients showed complete pathological reactions, 52.17% (24 cases), 15.21% moderate reactions (7 cases), 6.53% minimum reactions (3 cases) and 26.09% adverse reactions (12 cases).

In phase I, the complete pathological response was 100% while in phase IIA was 87.5%. In stage III, for stage IIIA and stage IIIB, the complete pathological response was 66.6% and 40% respectively, but the complete pathological response in stage IIIC was 0%. Therefore, preoperative radiotherapy and chemotherapy alone might not enough for patients in stage IIIC.

The ideal dosage should be equal to or greater than 5400 cGy. Patients treated with 5400 cGy showed 52.77% complete pathological response in this study when evaluating the response according to the total dose of radiotherapy. Only 44.44% of the patients used 5040 cGy had complete pathological reaction.

In this study, 46 patients were operated, in which 11 (23.9%) were operated within the 4th to 8th week after radiotherapy, and the pathological complete remission rate was 100%. According to this result, the ideal time

for surgery is between the 4th week and the 8th week, but when reviewing the patient samples of this study, we found that the pathological response of 3 patients with stage I was 100% when they underwent surgery during this period, which indicates that this statistical result may be biased and therefore not completely decisive. The remaining 10 cases (21.7%) were intervened from the 9th week to the 12th week, of which 7 cases had complete pathological reaction, accounting for 70%. 15 cases (32.6%) were intervened from week 13 to week 17, and 6 cases (35.2%) had complete pathological reaction. After 18 weeks, 10 cases (21.7%) underwent surgery. None of the patients showed a complete pathological response.

This work envisages that in the future, patients with rectal adenocarcinoma may receive preoperative radiotherapy and chemotherapy, and one group of patients may enter an observation period during which they can be cured by surgery when they relapse, as described in aforementioned studies.

Conflict of interest

Authors declared no conflict of interest.

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