ORIGINAL ARTICLE

Role of Neo-Adjuvant Chemoradiation in Locally Advanced Rectal Cancers

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ABSTRACT

Objective: To determine the radiologic downstaging and histological response after neo-adjuvant concurrent chemoradiation in locally advanced rectal cancers.

Study Design: Case series.

Place and Duration of Study: Radiation Oncology department of Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, from December 2004 to November 2005.

Methodology: Thirty patients with histopathologically confirmed locally advanced carcinoma rectum who had not received any treatment (chemotherapy, radiotherapy or surgery) prior to presentation were enrolled. Radiation therapy was delivered with a three-field technique to a dose of 50.4 Gy over 5 weeks at the rate of 1.8 Gy/day. Two cycles of chemotherapy were given synchronously, which comprised of 5-fluorouracil 350 mg/m^2 and folinic acid 20 mg/m^2 continuous intravenous infusion over first five days and last five days of radiotherapy. Surgery was planned 4-6 weeks later to chemoradiation after radiologic post therapy staging. Viable specimens were identified and toxicity was observed.

Results: All patients completed treatment without modification. Radiologic downstaging was found in 56.7%, stable disease was seen in 30.0% and progressive disease was present in 13.3% of the patients. Radiologically complete resolution of tumour was not observed. Pathological complete resolution of tumour was achieved in 3.3% and near complete resolution was observed in 13.3% of the patients. In 86.6% cases, a total gross tumour resection with no macroscopic residual disease was possible. All the patients tolerated the treatment well.

Conclusion: Neo-adjuvant chemoradiation for locally advanced rectal cancers is associated with high resectability rate and is relatively safe with acceptable morbidity which favours its use in future.

Key words: *Neo-adjuvant. Chemoradiation. Rectal cancers. Resectability rate. Radiology. Pathology. Downstaging.*

INTRODUCTION

Rectal cancer is the most frequent gastrointestinal cancer and the second leading cause of death attributed to cancer. The disease is common and affects approximately 5% of the population at some time in their lives and associated mortality from advance cases is high.[1] It causes mortality of 500,000 cases annually in the world. In United States alone, rectal cancer affects approximately 40,000 people annually.[2] This is one of the most common neoplasms of Western countries. Overall 5 years mortality rate is about 40 %.[3]

Surgery is the conventional treatment modality and the only chance of cure for rectal cancers,[4,5] however, when it is used alone, it results into high incidence of local recurrence especially in locally advanced rectal cancers. This has led clinicians to increase use of chemoradiation either pre or post operatively in an attempt to improve local control and survival. The rate of local failure in the pelvis following surgery increases with increasing stage of disease, ranging between 20%-70%.[5] More recently total mesorectal excision (TME) and intraoperative radiotherapy have resulted in much lower local recurrence rates.[6] The Dutch Colorectal Cancer Group randomized trial has clearly demonstrated that even with TME surgery, pre-operative irradiation was useful to reduce the risk of local recurrence.[7]

Adjuvant radiotherapy with or without chemotherapy has been widely used to improve outcomes in patients with rectal cancers. For locally advanced disease, post-operative chemoradiotherapy significantly improves local control as compared with surgery alone or surgery plus irradiation.[8] The National Institutes of Health consensus conference in 1990 recommended pos-toperative adjuvant chemoradiotherapy as standard treatment for patients with rectal cancer classified as tumour–node–metastasis (TNM) stage II (i.e., a tumour penetrating the rectal wall, without regional lymph-node involvement) or stage III (i.e., any tumour with regional lymph-node involvement).[9]

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Received November 03, 2008; accepted October 27, 2009.

Later on trend forwarded towards pre-operative regimens for further improvement of local control and overall survivals.

Several randomized studies have found lower rates of local failure with pre-operative radiotherapy than with surgery alone. The authors of a subsequent meta-analysis also concluded that the combination of pre-operative radiotherapy and surgery, as compared to surgery alone, significantly improved local control, overall survival and disease-free survival.[10] The Dutch Colorectal Cancer Group reported that the addition of short-course pre-operative radiotherapy to optimal surgery with total mesorectal excision reduced the rate of local recurrence but did not improve two-year survival.[11] The addition of chemotherapy to pre-operative radiotherapy improves local control, disease-free survival and is associated with increased toxicity but does not improve overall survival.[12-14]

After the increasing use of pre-operative chemoradiation in locally advanced rectal cancers, the interests of different investigators were to document the improvement in resectability and the rate of complete resolution of tumour on operative specimens after using combined chemoradiation before surgery. Study objective was to determine the radiologic downstaging, histological response and toxicity of neo-adjuvant concurrent chemoradiation for locally advanced rectal cancers. This may improve the number of curable resections in this group of patients to achieve good local controls and survivals.

METHODOLOGY

The study was carried out at Radiation Oncology Department of Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan, from December 2004 to November 2005. Thirty patients with histopathologically confirmed locally advanced carcinoma rectum with good WHO performance status were enrolled in the study. Written informed consent forms were obtained from all patients.

The patients who had not received any treatment (chemotherapy, radiotherapy, or surgery) prior to presentation or developing severe toxicity during treatment or not completing their treatment were excluded from the study.

The pre-treatment work-up was based on history and physical examination including digital rectal examination and biopsy via endoscopy, proctosigmoidoscopy. Complete blood counts, blood electrolytes, blood chemistry profile including liver and renal function tests and ECG were done. Metastatic work-up included chest X-ray PA view, abdominopelvic CT/MRI. TNM staging system was used to stage the tumour on the basis of clinical and radiologic findings.

All the patients received external beam radiotherapy to the pelvis. Treatment planning and field positioning were performed with orthogonal film simulation and contrast barium in the rectum. We used a three-field wedge technique with the patient in prone position using a linear accelerator with a X-ray beam of 6 MV or Co60 gamma rays. The treated volume included the macroscopic tumour and its potential extensions within the rectum, the mesorectum, and the pelvic lymph nodes. All patients were treated each day and port films were obtained weekly. In AP simulation film (Figure 1), the lateral border was 1.5-2 cm lateral to widest bony margin of true pelvic side wall, distal border 3 cm below primary tumour or at inferior aspect of obturator foramen (if tumour involving the lower rectum and anal canal, then anal marker was used and the inferior border was moved down to include the anus). Superior border was at the junction of lumbar 5 and sacral 1 (L5-S1) vertebra.

In lateral simulation film (Figure 1), the posterior border was placed at-least 1 cm behind bony sacrum and anterior border was placed 2-2.5 cm anterior to sacral promontory. Superior and inferior borders were the same which were used for anteroposterior simulation film. Customized blocks were used to spare posterior muscle and tissues, and small bowel in anterior and lateral fields. Total dose was 5040 cGy at the rate of 180 cGy/day to the pelvis over 5 weeks. Initial 4500 cGy was given to the whole pelvis and remaining dose i.e. 540 cGy was delivered as a boost by reducing the portals size only to the rectum.

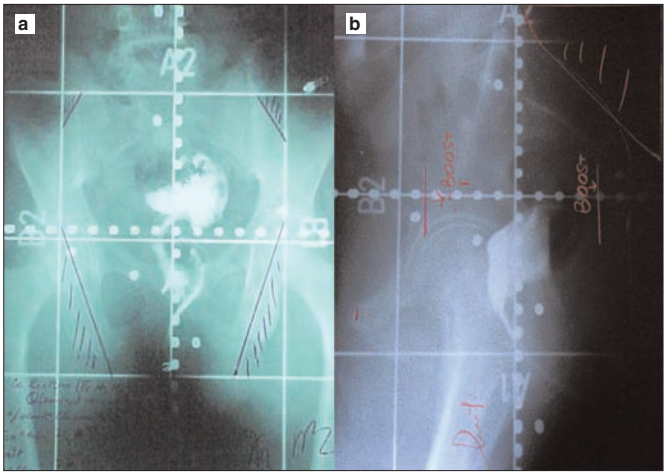

Figure 1: Simulation films **(a)** anteroposterior view **(b)** lateral view for rectal cancers, also showing the borders for the boost field.

For boost, superior border was placed at the level of S3, inferior border was unchanged in most of the cases. While lateral portals were reduced about 2-3 cm on each side in anteroposterior fields.

In lateral fields, superior and inferior borders were same as in boost AP film and posterior border same as in the initial treatment plan. While anterior border reduced to bring at 1-2 cm from sacrum as the arrow showing in the Figure 1.

Concurrent chemotherapy consisted of 5-fluorouracil 350 mg/m^2 and folinic acid 20 mg/m^2 continuous intravenous infusion in first 5 days and last 5 days of radiation therapy was given.

WHO response criteria was used to evaluate the radiologic response of the treatment by CT/MRI scan of the pelvis, which was carried out 4-6 weeks after chemoradiation. Surgery was carried out in 4-6 weeks after chemoradiation. Abdominoperineal resection (APR) was the surgical procedure to perform when the tumour was lower rectal, If the lesion was in the proximal rectum, then anterior resection (AR) was carried out. Total mesorectal excision (TME) was also carried out in few cases.

Pathologic complete response was defined as the absence of any residual tumour cells detected in the operative specimen including lymph nodes. Near complete response was defined as the presence of single microfocus of the tumor in the operative specimen including lymph nodes. Specimens were carefully examined by the pathologist to review any residual viable tumour or disease in the lymph nodes.

During the treatment, we monitored patients by weekly clinical examination with full hematology assessment. Blood chemistry profiles including liver function tests were performed before each cycle of chemotherapy. After surgery, all patients were followed-up with clinical examination every 6 weeks.

Computer based data analysis was carried out by using software SPSS version 11.00. Frequency and percentages of the following variables were described: WHO performance status, sex, presenting complaints, histological grade, pre-chemoradiation radiologic stage, radiological response, histological response, type of surgery, hematologic toxicities, gastrointestinal toxicities, genitourinary toxicities, skin toxicity, hand foot syndrome, and surgical complications. Continuous variable i.e. age of the patient has been summarized with mean and standard deviation, median and range.

RESULTS

Most patients were of good performance status and tolerated treatment very well. Majority of the patients were young. Male patients in the study were slightly higher in number than females. Bleeding was the most frequent presenting complaint either alone or in conjunction with other symptoms like pain or altered bowel habits. Initial biopsy specimen revealed the moderately differentiated tumours in most of the patients followed by well differentiated and poorly differentiated tumours. Pre-chemoradiation radiologic stage revealed that half of the patients were with organ invasion. Characteristics of the patients are described in Table I. Postchemoradiation radiologic downstaging is described in Table II.

Table I: Characteristics of the patients.

Total number of patients (N)	30
World Health Organization performance score	29 (96.7%) with 0 and 1 1 (3.3%) with 2
Age of the patients (years)	Mean age 37.4 standard deviation: 12.02 Median age: 38 (range:20-62)
Sex of the patients	18 (60%) Male 12 (40%) Female
Presenting complaints	Bleeding only 2 (6.7%) Bleeding and pain 16 (53.3%) Bleeding with altered bowel habits 12 (40%)
Histopathologic grade	Well differentiated: 5 (16.7%) Moderately differentiated: 13 (43.3%) Poorly differentiated: 6 (20%) Unknown: 6 (20%)
Pre-chemoradiation radiologic stage	T3 with N1 or N2 : 15 (50%) T4 organ invasion with N1 or N2:15 (50%)

Table II: Postchemoradiation radiologic responses.

Radiologic response	Number of patients	Percentage
Complete response	0	0.0%
Partial response	17	56.7%
Stable disease	10	33.3%
Progressive disease	3	10.0%

All patients completed chemoradiation without modification. Total gross tumor resection with no macroscopic residual disease was possible in 26 (86.6%) patients within 4-6 weeks after completion of chemoradiation. In 4 (13.3%) patients, no surgery was performed; 3 patients were in progression of disease and one patient refused surgery. Abdominoperineal resection (APR) was performed in 18 (60%) patients and anterior resection (AR) was carried out in 4 (13.3%) patients. TME and other surgical procedures were observed in 4 (13.3%) patients.

Postresection pathological responses are described in Table III. Pathological review of the specimen revealed a poor overall response.

Table III: Postresection pathological responses.

Pathological responses	Number of patients	Percentage
Complete response	1	3.3%
Near complete response (with microfocus of tumour)	3	10.0%
Overall response	4	13.30%
Node positive	13	43.30%
Node negative	11	36.70%
Nodal status undetermined	2	6.70%

Hematological toxicities were found in < 50% of the patients. Different degrees of leucopenia (30%), thrombocytopenia (6.7%) and anemia (3.3%) were observed. 6.7% of patients developed both leucopenia and anemia. Most toxicities were found to be grade-I and grade-II.

Gastrointestinal toxicities including grade-II vomiting (16.7%), grade-I nausea (13.3%), diarrhea grade-I, II and III (6.7%), and grade-II mucositis (6.7%) were observed in less than 50% of the patients. 3.3% patients developed both diarrhea and mucositis. No GI toxicity was observed in 53.3% of the patients.

Genitourinary, skin toxicities and hand foot syndrome were observed in, 20%, 46.7%, and 3.3% of the patients respectively.

There were no perioperative deaths. No fistula, abscess, or anastomotic leak was observed postoperatively. Notable postoperative complications are mentioned in Table IV.

Table IV: Notable postoperative complications.

Postoperative complications	Number of patients	Percentage
Bleeding	4	13.3%
Wound infection	2	6.7%
Delayed wound healing	1	3.3%

DISCUSSION

In the trial comparing pre-operative chemoradiation vs postoperative chemoradiation by German Rectal Cancer Study Group concluded in their results that the pre-operative chemoradiation is the preferred treatment for patients with locally advanced rectal cancer, given that it is associated with a superior overall compliance rate, an improved rate of local control, reduced toxicity, and an increased rate of sphincter preservation in patients with low-lying tumours.[14,15]

The rate of local recurrence with pre-operative chemoradiation and total mesorectal excision was only 6%; it is possible that further progress in the prevention of distant recurrences might be accomplished with more effective chemotherapy. Phase-I and II trials of pre-operative radiotherapy with concurrent capecitabine and oxaliplatin have been completed by German Rectal Cancer Study Group.[16] The advantages of this regimen include improved compliance with the chemoradiation when it is given before major surgery, as well as downstaging, which may enhance the rate of curative surgery and permit sphincter preservation in patients with low-lying tumors. In addition, because tumor oxygenation is better with pre-operative treatment than with postoperative treatment, irradiation seems to be more effective with the former approach.[17]

In this study, postchemoradiation radiologic down-staging was found in 56.7% of the patients which was very much comparable to the international studies: i.e. 58.3%.[18] Multivariate analysis of another study showed that neoadjuvant chemoradiation therapy resulted in 62% tumour downstaging and complete pathological response in 23% cases while 42% and 5% in neo-adjuvant XRT alone respectively.[19] Another study revealed tumour downstaging in 61.5% cases and complete pathological response in 24% following neo-adjuvant chemoradiation.[20] Similar results were drawn by Memorial Sloan-Kettering Cancer Centre, New York, USA.[21] The radiologic downstaging in this study was much encouraging by which we avail the opportunity to have the curative resections, but we couldn't get the benefit of sphincter preservation. The reason of more number of APRs may be that of the tumour location, most were very low-lying tumours and involving the lower most third of the rectum and anterior resections (ARs) were possible in only little number of patients contrary to our pre-treatment expectations.

As the pathologic responses can be analyzed on the operative specimen, which is a good end point to evaluate the efficacy of chemoradiation approach.[22] This end point heavily depends on the pathologic technique used to analyze the operative specimen. A careful analysis of the specimen was performed for all patients, and the distal and lateral circumferential margins were examined in all cases to assess the completeness of the surgery (R0 or R1 states of the surgical specimen). The rate of pathologic complete response also closely depends on the number of sections performed and the quality of search for residual cancer cells. In one American study about pre-operative chemoradiation,[23] the rate of pathologic complete response was only 8%. This lower than expected response rate may be due to a strict and careful search for residual viable cancer cells. In the literature, the rate of complete sterilization of the operative specimen varies between 5% and 32%.[24-26] The higher response rates are observed with protocols using higher radiation doses, longer intervals before surgery, concurrent chemotherapy, and rectal tumours of smaller size or lower stage. The rate of nearly complete sterilization or few residual cells is also often reported in the literature and varies between 15% and 48%.[24]

In this study, the rates of pathological complete resolution of tumour were below the range mentioned in above studies (3.3% vs. 5%). While patients having complete resolution with near complete resolution in this study are comparable at the lower range value with international studies, which is 13.3% vs. 15% respectively.

As a matter of fact, the role of adjuvant pelvic radiation therapy in rectal cancer has been confirmed in several randomized studies.[11,27-29] The data from international literature are in favour of a combined approach, both in pre-operative and postoperative treatment of advanced rectal cancers.[30] Pre-operative combined chemo-radiation proved to be a powerful means of downstaging the tumours to improve the resectability rates, controlling local failure, improving disease-free survival with reduced toxicity.[31, 32]

The discussion favours the pre-operative use of chemoradiation therapy in locally advanced rectal cancers. The results of our study also favour its use because of improved resectability rate by downstaging the tumour and reduced toxicity but the rate of sphincter sparing surgeries was low. Long-term follow-ups are required to document the local controls, disease-free survivals or overall survival rates. In future, more accurate mode of delivery of radiation therapy (IMRT

and IGRT) and novel chemotherapeutic agents can improve the results in this group of patients.

CONCLUSION

Neo-adjuvant chemoradiation for locally advanced rectal cancers is associated with high resectability rate and is relatively safe with acceptable morbidity, which favours its use in future. The above results in our population are similar to other reported series.

Acknowledgement: Many thanks to Dr. Mazhar Ali Shah for his sincere advice on various aspects of this study. We are thankful to the Physics, Radiology, Surgery and Pathology Department of the Shaukat Khanum Memorial Cancer Hospital and Research Centre for their cooperation in completion of this study.

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